# The Fundamentals of Clinical Discovery

Jonathan Rees

**ABSTRACT** There is a widespread view that clinical research is failing to advance appropriately, particularly in comparison with other aspects of biomedical science. I argue that this is due in part to an inadequate understanding of how medical advance occurs. The common usage of such terms as *basic* or *fundamental*, or the uncritical use of the term *model* is unhelpful—unhelpful, in that such terms tend to presuppose a certain model of clinical advance that is unusual, and furthermore, because they tend to exaggerate the importance of research in subjects such as biochemistry and genetics at the expense of other areas. I suggest that much medical research is best viewed as a form of engineering rather than science, and that the knowledge base and research funding for the amelioration of disease needs to be much more broadly based than at present.

A STEADY STREAM OF ARTICLES over the last 20 years has highlighted problems facing clinical research (Dieppe and Bachmann 2000; Goldstein and Brown 1997; Lenfant 2003; Rosenberg 1999; Snyderman 2004; Weatherall 1991). Most argue that undertaking clinical science is becoming more difficult, that funding is relatively harder to obtain, and that the career structures available for clinical researchers are inadequate. There is usually an implicit or explicit comparison with other forms of research which, for the moment, I will label as "basic" medical research. All these forms of research have as their principal justification the improvement of human health. Improvement in human health is

Grant Chair of Dermatology, University of Edinburgh, Room 4.018, First Floor, The Lauriston Building, Lauriston Place, Edinburgh, EH3 9HA, United Kingdom.
E-mail: jonathan.rees@ed.ac.uk.

The author would like to thank William Bains for helpful discussions.

*Perspectives in Biology and Medicine*, volume 47, number 4 (autumn 2004):597–607

for instance seen as the chief justification for funding of the Human Genome Project and for the enormous increase in biomedical funding over the last 30 to 40 years (Greenberg 2001). How well these areas of rational enquiry map onto those needed to solve disease is a theme I will return to later in this essay.

The concern about the role of clinical science and clinical scientists in medical discovery has not been lost on some funders of medical research. A number of initiatives on both sides of the Atlantic have been undertaken recently to try and expand the role of clinical scientists in the medical research enterprise (Academy of Medical Sciences 2000). In the United Kingdom for instance, the main government funder of medical research, the Medical Research Council (MRC), has for the last several years sent letters to clinicians reminding them that the MRC still funds clinical science, although the examples they quoted as clinical science hardly reassure that the Council has much expertise in this area (MRC 2003). Also, in the United Kingdom, national academies, such as the recently formed Academy of Medical Sciences, have produced reports on how to encourage and develop the funding streams necessary for successful clinical science (Academy of Medical Sciences 2000). These efforts, however worthwhile, are in my view unlikely to shape events significantly (Rees 2002b). As I will argue below, the chief issue surrounding clinical science lies in our failure to grasp the nature of much clinically important discovery and in the promulgation of a worldview of medical research and advance that is dysfunctional and increasingly not fit for purpose (Rees 2002a, 2002b). Clinical research is in trouble, not primarily because of any lack of funds, but rather because lack of funds is merely a symptom of an incomplete understanding of clinical advance. In order to improve clinical science, we need to ask how we can foster advance and remove incentive structures that frustrate many aspects of the discovery process necessary for improved health care.

In what follows I will try to sketch some of the issues that I believe are important. I will briefly refer to some examples from an earlier article in *Science* (on the role of the study of complex genetics in medical research; Rees 2002a), but I will also put some of the arguments in a broader epistemological perspective. The nature of most science has changed in the last half century. The scientific enterprise has expanded enormously, becoming more expensive and increasingly specialized and complex. Central control, in terms of peer review and funding mechanisms, has also increased. Science and scientists have also become more partisan, with the accompanying results of a more widespread exaggeration of the importance of discoveries and a more short-term duration of the indicators of success. With its increase in size, the research community has seen a fragmentation of activity and the need to invent proxy measures of success and advance, so that the enterprise can be managed and funded and those carrying it out deemed responsible for public funds. At the same time, those carrying out most medical research have become ever more distant from the practice and delivery of health care. As much medical science has become expropriated from the clinical con-

text, those undertaking it have frequently relied on secondhand and thirdhand descriptions of how health care is delivered and what represents genuine clinical advance. Finally, health care has become a major service sector in most Western economies, with both private companies and central governments becoming major players in providing technologies and the personnel involved in health care, parties that have obvious interests in the landscape of health delivery.

## THE CHANGING NATURE AND PRACTICE OF SCIENCE

Many of us have a romanticized (and beautiful) vision of scientific advance, a vision that might have been an accurate description of "revolutionary" science carried out by a small elite at a limited number of institutions half a century ago. My own favorite is in the celebrated account by Jim Watson (1999), in *The Double Helix*, of how he and Francis Crick reported (almost sadly it seems) getting only the occasional memo. Or think of Max Perutz's (1989) comments that he only had to start writing grant applications when he retired. How different that is from the everyday experiences of the present medical researcher. Grant applications are voluminous and increasingly—as Sydney Brenner (1996) points out—resemble documents that merely resemble flow diagrams of who reports to whom, with little room for science; ethics forms are subject to idiosyncratic criticism; and, in the United Kingdom at least, when you submit grant applications, it is unlikely that anybody around the grants committee table either knows you, has read your work at first hand, attends the same scientific meetings, or knows the views of your contemporaries in other countries. The community of peers has been replaced by a bureaucracy of proxy measures, such as grant income and impact factors.

Science has become more industrialized, with a rapid increase in the number of scientists and funding available to many individuals (Greenberg 2001; Ziman 1994, 2000). The size of many research groups has increased. In a wonderful obituary in *Nature* of Pat Wall (of the Melzack-Wall gate-theory fame), Clifford Woolf (2001) describes how modern lab heads are "really like chief executive officers of large multinational corporations, more involved in managing and delegating than in experimenting or thinking. Patrick David Wall, who died on 8 August aged 76, was the antithesis of this kind of scientist." There are very few persons who, like Fred Sanger, work literally with their own pair of hands. The increase in scale and cost of biological science has other implications. John Ziman, a former physicist, has chronicled the changing sociology of science (Ziman 1994, 1999, 2000). He points out that more and more science in universities has become "instrumental," undertaken as the production of knowledge with clearly foreseen or potential uses (Ziman 2002, 2003). Science is much less disinterested than it was: it has increasingly taken on many of the properties of commercial research and development activity—that is, it has become proprietary, more prosaic, pragmatic, and partisan. And I don't just mean that research

funding often comes from industrial sources, but that, rather than comprising curiosity-driven research, the research agenda is managed and directed at many levels. Some diseases are determined to be more important that than others diseases, more worthy of funds. Patient lobby groups influence funding and prestige, and pharmaceutical companies are aware that their markets are likely to be bigger in some disease areas than others, or that major markets may lie outside the boundaries of what has traditionally been considered disease (e.g., cosmetic surgery). These factors are in part external to science but can be courted by scientists and groups of scientists with particular backgrounds and interests.

The clearest example of this trend has been provided by genetics. The emergence of the new genetic technologies, the ability to undertake genetics on man rather than just model organisms, rightly revolutionized much biomedical work. However, what has followed, as I have argued elsewhere (Rees 2002a), has been a genocentric view of medicine that has sought to concentrate funding and interest for a particular group of diseases and persons. Thus, after the hopelessly naïve view that identifying genes for Mendelian disorders would lead to therapy over a short period of time (rather than developing useful tools that allow the study of biology), genetics funding has followed the mantra of the need to understand complex diseases and gene therapy. But any sense of proportion has been rapidly lost. Insofar as talking about genetic and environmental causes makes sense—for example, for most cancers and most inflammatory diseases—only a relatively small portion of the variation seen in human populations is accounted for by genetic factors; thus, the impact of genetics on, for instance, the prediction of disease status for the majority of common diseases is going to be at best marginal, and far less important than other factors relating to heath care delivery. (Hemminki et al. 2001; Lichtenstein et al. 2000). By contrast, changes in incidence point clearly to the overriding importance of environmental factors for most common diseases. Leading journals have published review papers pointing out these views, yet the message appears to fall on stony ground (Holtzman and Marteau 2000; Weiss and Terwilliger 2000). A large number of mapping studies and association studies on common complex diseases are still published, and large population studies on common inflammatory conditions are still planned with the aim of identifying important genetic health determinants of common diseases. Yet we remain ignorant of the natural history of some of the most common inflammatory diseases of man, such as atopic dermatitis or psoriasis.

There is, understandably, a rush to use new technologies. Unfortunately, however, the attraction seems to overcome a sense of prudence about the likely rewards. If the pool of biomedical investigators trained in genetics is expanded, this expanded pool will continue to find problems to occupy them. They are unlikely to retrain to use other approaches to solve clinical problems. If you have spent time mapping the rare genes accounting for some rare cases of obesity, you are more likely to want to study the complex genetics of obesity than you are to start to study economics and look at the use of pricing to influence supply and

demand of high calorie meals. When lobby groups launch a "Decade of the Brain" and train an increasing army of post-docs, are most of these scientists going to retrain in something else when the decade is over, or will the idea prevail that funding should be maintained or—better still—continually increased? A related problem is the way in which generic approaches appear to get adopted across whole swaths of medical research rather than in areas where they may be most useful. For instance, modern molecular technologies seem to hold out much hope for the diagnosis, management, and prevention of infectious disease. But the rises in obesity and type 2 diabetes are largely accounted for by changes in behavior: that we know, and the contribution of complex genetics would seem marginal to any sense of clinical reality.

Furthermore, there is often a general bias towards what sort of solution is to be sought. Here the increasing role of pharmaceutical industry in research goal setting and funding is important. Just as geneticists tend to do genetics, pharmaceutical companies sell drugs. They favor drug solutions for problems, as intellectual property is hard to obtain on other approaches to disease. And this bias affects not just directly funded work in universities but the tone of much medical research, where the promise of what may be patentable influences research direction. An example of this that I have used elsewhere is the case in which a genetic predictor of melanoma was favored over such easily observable markers of risk as skin color or freckles (Rees 2000).

## Biology versus Medicine, and Biomedicine versus Health

The distinction between the understanding of the biology of disease and the knowledge required to improve the health of the population is an important one. The primary rationale for much biomedical research is that the reductionist enterprise that I associate with cell biology or biochemistry is the best way to improve health care. This view is, I believe, increasingly insular, partisan, and subject to challenge. Science, rightly, gains respect from its championing of a worldview that demands an external test in reality, the dialectic of theory against data. It would be ironic if it failed to apply the same standards to its own activities.

To follow my argument, we need examine some of the terms used to describe various forms of rational enquiry. Much biomedical research is fond of the description *basic*, or *fundamental*. Understanding the pathways in the cell is seen as basic to understanding (say diabetes). I take a different view. Medicine is not science—at least, it is not science in the way that most engineering is not science. Medicine itself I think of as a form of engineering: the design of systems of intervention or artifacts, based on underlying principles. And as in the case of engineering, the approach we take in medicine should be defined by the problem and context. Basic knowledge is that theory which provides the solution. If understanding the psychological factors that determine why people walk or ride

by car a short distance influences body energy homeostasis, then that knowledge is basic.

Let me provide another topical example. In the United Kingdom, as in many other countries, there is a major shortage of cadaver kidneys for transplantation. One economist has suggested that providing a small tax incentive on everybody's tax return could save money by encouraging persons to register their organs, and by encouraging organ donation thus reduce the need for dialysis (Oswald 2001). Whether the idea will work, and the theory to test and experimentally resolve this issue, is basic knowledge: basic in the sense that we require it to solve the problem.

If we follow this argument through, we need to embrace a far wider range of academic disciplines as being relevant to medical care and to broaden the base of rational enquiry at the expense of the current staples. I have mentioned experimental economics, but critics will say that people already work in this area. In reality, the scale of activity is not commensurate with what is needed, nor is it commensurate with what is allocated to areas such as biochemistry.

One of the most important determinants of medical care is the doctor himself. The amount of work that examines the information processing and diagnostic skills of doctors is trivial compared with the funding made available for study of model organisms predicated on the assumption that this is the optimal way to improve health. Yet health informatics (including those relevant areas of biology and computing) is crucial to how medicine is practiced. And here I am making a plea not for pragmatic solutions to local issues, but for fundamental and theoretical work to underpin how those who diagnose are taught and kept competent. It is ironic that whereas disciplines such as informatics realize that study of both man and machine is necessary—that study of information handling by humans is relevant to how humans interact with machines and vice versa—medicine is still stuck in a Cartesian duality, believing that just delivering new drugs to the pharmaceutical salesman ensures improvement in health. Just as computing science embraces not just the physical world but the world of the human artifact, so should medicine (Simon 1969).

## WHAT SORT OF ACTIVITY IS CLINICAL SCIENCE?

So far in this essay I have skirted around any definition of clinical science, although the skeptical reader will already have a fair idea of what I label as biochemistry or genetics. There are many definitions of clinical science. I particularly like the handshake test proposed by Goldstein and Brown (1997) for patient-oriented research, as it describes most of what I do. Do you need to shake hands with your subjects? If you do, then you are likely to be engaged in patient-oriented research. Nonetheless, whatever the tactical merits of using such a definition (and I think there are many), it appears too facile to accept the "conventional wisdom" and imagine that much clinical research is translational

in nature, the mere testing of ideas developed in the laboratory. Clinical science is all too easily seen as journeyman work, unoriginal and merely applied. I think this view is mistaken. First, I would argue that the major direction of information flow is from patients to the laboratory. The wonderful unfolding of our knowledge about, say, structural proteins in skin has fed advance in cell biology far more than vice versa. Clinical science is, to put it slightly provocatively, more basic than cell biology. Mapping of a myriad of human disorders aids biology more than genetics has improved care. This is not to argue against the need for or the merits of much research activity, but rather to point out the inadequacy of the term *translation*. The idea of translation too often implies that the intellectual landscape has been defined in the "basic laboratory." Again, I disagree. The major issues facing medicine throughout much of the world relate to how we organize, deliver, and value the benefit health care provides. Skeptics should look at the work of psychologist Daniel Kahneman, the 2003 Nobel Prize winner in economics, to see how our worldview, or what I might call our standard operating models for assessing disease, needs revising (Kahneman 2003; Kahneman and Tversky 1996; Redelmeier and Kahneman 1996; Redelmeier, Katz, and Kahneman 2003). Kahneman's work, we can safely say, is not mere humdrum recording what people say, but, as the Nobel committee realized, theory driven and empirically tested science that changes the research landscape irrevocably. These fields of knowledge are not mere "bolt-on" activities that you dream up when you do a clinical trial but areas that require basic intellectual ideas—blue sky thinking. We need much more empirically tested theoretical work around health care delivery and how medicine works, not merely pragmatic trials of one drug versus another in terms of whether "quality of life" improves.

## REDUCTIONISM

A standard response to many of the issues I raise is, "But if we just knew in greater detail how the human genome worked (and while we are at it, the mouse, zebrafish, rat, worm, chimp genomes, too), and knew more cell biology, we could design rational therapies without all the waste and costs associated with conventional large pharmaceutical development (Glassman and Sun 2004). This is then followed by a request for large amounts of money for—depending on the time and audience—genomics, phenomics, systems biology, computational biology, or stem cell science. But clinical advance is not like this. Elsewhere I have documented how, over the space of 20 years, clinical science has dramatically changed the management of the major common dermatoses, acne, psoriasis and forms of dermatitis, and skin cancer (Rees 2002a). Most advances have involved the use of technologies developed without a clear purpose and the linking of these technologies to clinical problems. Often significant advance has come from one of a handful of individuals, sometimes over a short period of time of a year or two. A complete understanding of disease was not necessary—nor is it in any

logical sense ever attainable. Rather, advance requires investigational agents, usually drugs, assays that are close to the patient, and the ability to design proof of concept experiments (Rees 2002a). And here we must be aware that the sociology of clinical advance differs from that all too often projected as the way of doing successful science. Often the discoverers were isolated, without track records in the area of their discovery. What they do seem to have in common are powers of observation coupled with the ability to test ideas within a framework of clinical practice. It seems clear that this pattern of clinical discovery is the norm. David Healy (1996–2000), in a series of wonderful books of interviews, has documented how real therapeutic advance occurred in the golden age of clinical neuroscience. More recent examples, from sildenafil to botulinum, all suggest that this is the main route of clinical advance in medicine.

So does all this mean reductionism or biochemistry or genetics is not needed? Not at all, it is just not sufficient. It is far more dangerous not to be a reductionist than it is to be one—but one should accept reductionism's limitations. Neuroscience provides a good example in this regard. Studying the brain means working at different levels: molecules and populations, synapses and social groups. David Marr (1982), the late computational neuroscientist, said that trying to understand vision by studying only neurons was as futile as trying to understand bird flight by only studying feathers—it just can't be done. For medicine we need to be much more open to what sort of level of inquiry is needed in order to advance. The false dichotomy between basic (cell biology) and clinical science (translation) is unhelpful. Each level has to exist of itself, and the tools developed at one level may be useful to probe another, but often the attempt to map all down to the smallest scale will be unhelpful. Science is not a linear process from cell biology to population health but, by contrast, a series of activities and approaches, perhaps existing on the surface of a sphere as in non-Euclidian two-dimensional space, where the connotation of depth—implying deep or fundamental in a hierarchical sense—has no meaning.

## "BASIC" REVISITED, AND "BLUE SKIES" RESEARCH

Given the arguments I have made above, it is perhaps reasonable to ask whether I believe, or think it is sensible, to fund "blue-skies" research in the hope of promoting clinical care. If, as I have stated, *basic* is defined in terms of knowledge needed to solve a problem, is there still a space for disinterested work—curiosity-driven and perhaps playful intellectual activity? To answer this question, I need to return to some of the writings of John Ziman mentioned earlier, who has argued that academic science is increasingly partisan, pragmatic and less disinterested, and that it has taken on the properties of what was formerly described as industrial science (Ziman 2002).

There is, I believe, a confusion in the minds of many between *basic* (or *fundamental*) and *disinterested* research. It is too easy to say (for instance) that work on

one of numerous model organisms is basic, and to confuse this with work that is blue skies (because the chance of any clinical relevance seems small). In reality, the work may have merits, even if the potential for clinical application is finite. The problem may be the mere use of the word *model*: one seems able to justify the study of all God's creatures this way. Of course, the understanding of any organism may have relevance to human health, but how does this approach compare with others? Kahneman's work on the memory of pain and discomfort, and on how humans view and make choices, arose not from an attempt to solve medical problems, but from efforts to study (among other things) decision making and judgment. I doubt that application or clinical relevance were in the minds of those trying to expose the weaknesses of the classical economic model of "rational man" (Lovallo and Kahneman 2003).

Another example would be the widespread use of computing and imaging in clinical medicine. Many of the technologies necessary were developed not with the goal of improving human health but for other reasons, not least a sense of intellectual curiosity. To me, these cases persuade that biochemistry and genetics are all too often conflated with curiosity-driven research at the expense of a broader intellectual horizon. Too frequently a "consensus" appears in which those arguing for funding seek to benefit from such funding, but often with little perspective on either clinical practice or how advance has happened previously.

## A SENSE FOR THE FUTURE

Whether the worldwide medical research landscape is getting more homogenous, with less tolerance of alternative approaches, I do not know. In the United Kingdom, as a result of a large mismatch between funding and those applying for funding, there is a tendency to concentrate funding in fewer centers. It seems that the harder financially starved universities bid for central funds, the more homogeneity and straitjacketing of research strategy. The consensus feeds on itself, with those benefiting the most in turn influencing policy of the limited number of funding streams. This may be, as supporters would argue, a way to maximize benefit from scarce funds; alternatively, as some of us believe, it may be a way to constrain advance and preserve the status quo. Freeman Dyson (1998) tells the story of how John Randall, a famous if not first-rate physicist, set in motion the seeds of what would become a major strength of British science in the mid-20th century, namely molecular biology. Whatever his own skills as a physicist, Randall had great insight into future strategies for understanding biology. But his success, and those of his students, relied on a highly decentralized system of science with individual autonomous institutions (even department heads) making their own decisions, and with a vision over decades: some succeeded, most failed. Perversely, while there is more money available today, the room for maneuver seems less.

There is no one clinical science, merely many ways in which the burden of disease can be ameliorated. We have failed to capitalize on many of those ways.

A slight sense of dissatisfaction with the last quarter century of biomedical science is warranted. Medicine once again needs to redefine and broaden its intellectual heartlands (Rees 2002b).

## REFERENCES


Academy of Medical Sciences. 2000. The tenure-track clinician scientist: A new career pathway to promote recruitment into clinical academic medicine. http://www.acmedsci.ac.uk/Clinic.pdf.

Brenner, S. 1996. Loose ends. *Curr Biol* 6(1):98.

Dieppe, P., and M. Bachmann. 2000. Clinical research: Is the filling missing from the medical research sandwich? *J R Coll Physicians Lond* 34(3):282–84.

Dyson, F. J. 1998. *Imagined worlds*. Cambridge: Harvard Univ. Press.

Glassman, R. H., and A.Y. Sun. 2004. Biotechnology: Identifying advances from the hype. *Nature Reviews: Drug Discovery* 3:177–83.

Goldstein, J. L., and M. S. Brown. 1997. The clinical investigator: Bewitched, bothered, and bewildered—but still beloved. *J Clin Invest* (12):2803–12.

Greenberg, D. S. 2001. *Science, money, and politics: Political triumph and ethical erosion*. Chicago: Univ. of Chicago Press.

Healy, D. 1996–2000. *The psychopharmacologists: Interviews*. 3 vols. London: Arnold.

Hemminki, K., et al. 2001. Estimation of genetic and environmental components in colorectal and lung cancer and melanoma. *Gen Epidemiol* 20(1):107–16.

Holtzman, N. A., and T. M. Marteau. 2000. Will genetics revolutionize medicine? *N Engl J Med* 343(2):141–44.

Kahneman, D. 2003. A perspective on judgment and choice: Mapping bounded rationality. *Am Psychol* 58(9):697–720.

Kahneman, D., and A. Tversky. 1996. On the reality of cognitive illusions. *Psychol Rev* 103 (3):582–91.

Lenfant, C. 2003. Clinical research to clinical practice: Lost in translation? *N Engl J Med* 349(9):868–74.

Lichtenstein, P., et al. 2000. Environmental and heritable factors in the causation of cancer: Analyses of cohorts of twins from Sweden, Denmark, and Finland [see comments]. *N Engl J Med* 343(2):78–85.

Lovallo, D., and D. Kahneman. 2003. Delusions of success. How optimism undermines executives' decisions. *Harv Bus Rev* 81(7):56–63, 117.

Marr, D. 1982. *Vision: A computational investigation into the human representation and processing of visual information*. New York: W. H. Freeman.

MRC. 2003. MRC: Clinical research news. http://www.mrc.ac.uk/pdf-clinical_research_news_2003-2.pdf.

Oswald, A. J. 2001. Economics that matters: Using the tax system to solve the shortage of human organs. *Kyklos* 54:379–81.

Perutz, M. F. 1989. *Is science necessary?: Essays on science and scientists*. London: Barrie & Jenkins.

Redelmeier, D. A., and D. Kahneman. 1996. Patients' memories of painful medical treatments: Real-time and retrospective evaluations of two minimally invasive procedures. *Pain* 66(1):3–8.

Redelmeier, D. A., J. Katz, and D. Kahneman. 2003. Memories of colonoscopy: A randomized trial. *Pain* 104(1-2):187–94.

Rees, J. 2000. Patents and intellectual property: A salvation for patient-orientated research? *Lancet* 356:849–50.

Rees, J. 2002a. Complex disease and the new clinical sciences. *Science* 296(5568):698–700.

Rees, J. L. 2002b. Clinical Science: time for a new contract. *Clin Med* 2(5):423–25.

Rosenberg, L. E. 1999. The physician-scientist: An essential—and fragile—link in the medical research chain. *J Clin Invest* 103(12):1621–26.

Simon, H. A. 1969. *The sciences of the artificial*. Cambridge: MIT Press.

Snyderman, R. 2004. The clinical researcher: An "emerging" species. *JAMA* 291(7):882–83.

Watson, J. D. 1999. *The double helix*. Middlesex: Penguin.

Weatherall, D. J. 1991. The physician scientist: An endangered but far from extinct species. *BMJ* 302:1002–5.

Weiss, K. M., and J. D. Terwilliger. 2000. How many diseases does it take to map a gene with SNPs? *Nat Genet* 26(2):151–57.

Woolf, C. J. 2001. Patrick D. Wall (1925–2001). *Nature* 413(6854):378.

Ziman, J. 1994. *Prometheus bound: Science in a dynamic steady state*. Cambridge: Cambridge Univ. Press.

Ziman, J. 1999. Rules of the game of doing science. *Nature* 400:721.

Ziman, J. 2000. *Real science*. Cambridge: Cambridge Univ. Press.

Ziman, J. 2002. The continuing need for disinterested research. *Sci Eng Ethics* 8(3):397–99.

Ziman, J. 2003. Non-instrumental roles of science. *Sci Eng Ethics* 9(1):17–27.