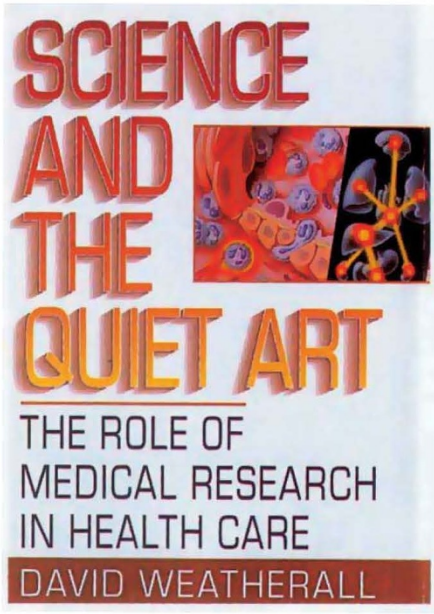

Science and the Quiet Art

THE ROLE OF MEDICAL RESEARCH IN MEDICAL CARE

BY DAVID WEATHERALL

W.W. Norton, New York & London, 1995

$25.00

REVIEWED BY JOHN A. BENSON JR

Why is the harvest of science so slow to reach the bedside? Professor Weatherall's concern about the public's increasing disillusion with modern medicine overcame his reluctance to write this book for the series sponsored by the Commonwealth Fund Book Program. The disillusion on the part of the public, media, politicians and doctors themselves was exacerbated by unsuccessful 'wars' against cancer, diabetes and heart disease; the media's inordinate appetite for 'breakthroughs'; medicine's growing reliance on high-tech treatment (Lewis Thomas's 'half-way technology'); the spiraling costs of health care; and the diminution of humanistic approaches to care. Weatherall is concerned that the public may become disengaged from supporting scientific research. Society must begin to understand the complex issues at stake, debate them realistically with an open scientific community, and painstakingly consider the ethical and societal questions posed by new knowledge.

Weatherall has sharpened the debate, working into carefully interdigitated chapters both iteration and reprise, hallmarks of accomplished lecturers. Some readers may deplore the redundancy. From the dogma of Galen through lucid progressions of scientific history to the ethical conundrums of the genetics revolution, he identifies slow cascades of discoveries whose relatedness was not apparent at first. In addition, the author defends the historical approach: public support of research for knowledge's sake — research with no predictable application in the clinic.

The appetite of the public and its politicians for supporting research was whetted by the virtual elimination of smallpox and polio through immunization, the discovery of antibiotics and the virtuosity of transplantation surgery. At the same time, high-tech medicine and specialization focused physicians more on understanding diseases than on the problems of sick people. Medical education founded on the basic sciences probably contributed to a concentration on diseases rather than the patient, particularly in "the overcharged atmosphere of the modern hospital". Faculty subspecialists dealt with one organ system, and "the boundaries between patient care and research became blurred." Recent emphases on community care, the preferences of patients, more holistic patient management and alternative medicine are changes for the better. Weatherall asks his readers to be patient and to appreciate that diseases have multiple causes, especially the more refractory degenerative ones, which are difficult to disassociate from the mysterious processes of ageing. He sees no fundamental contradiction between a scientific approach to managing disease and the 'pastoral aspects' of medical care.

Medicine is only slowly reaching the stage at which we recognize how little we know. Weatherall traces the fall of dogma from the mediaeval acceptance of authority to Vesalius's human anatomy, the observations of the surgeon Ambroise Paré and Paracelsus early in the 16th century, the discovery of circulation by Harvey and Willis and Linnaeus's classification of diseases in 1763. Pathology and the value of the autopsy were established, and advances like vaccination and bifocal lenses improved the quality of life.

Using coronary artery disease as an example, Weatherall notes that we have made less progress in understanding underlying causes and therefore learning how to prevent or cure important diseases than in controlling their symptoms and staying their ultimate conclusions. Intensive care units, clot busters and safer bypass surgery deal only with "the end results of a failing organ". Heart attacks, high blood pressure and cancer are seen by the author as the price for self-indulgence and affluence in modern humans poorly adapted over millennia to the environment of industrialized countries. To cope with prolonging life and the resulting cost, thinking has switched from more technology to community medicine and prevention.

Disenchantment with the slow progress of laboratory solutions to bedside dilemmas should be tempered by the knowledge that genetic adaptation has taken generations if not centuries. Using as evidence the evolution of the protective influence of symptom-free carriers of sickle-cell anaemia and thalassaemia against malaria, he counsels the frustrated and impatient. Another understanding of mutations is that we will never completely conquer infectious killers, new strains of resistant tuberculosis serving as a frightening example.

Variants of the genes that regulate the immune system may have been selected by previous exposure to infection and may be responsible for increased susceptibility to autoimmune diseases like type I diabetes and arthritis. Excessive Western diets may exaggerate the so-called 'thrifty genotype', which protected migraters during sporadic food availability. Weatherall notes the finding of Goldstein and Brown that genes controlling the activity of specific receptors that bind LDL cholesterol show remarkable variability, which leads to the suggestion that diets high in cholesterol and saturated fat stimulate defects in genetically normal persons by signaling cells to produce fewer LDL receptors. Even mutation of the histocompatibility genes responsible for presenting foreign proteins like viruses to the cells of the immune system may help explain the auto-destruction of the pancreatic islet cells in insulin-responsive diabetes.

Just as he elucidated the history of physiology, Weatherall treats us to a very clear exposition of the genetic revolution. Again disparate investigations added up to better understanding; Mendel began the process with peas, others discerned the cross-over or recombination of genetic material, and biometricians paved the way for more complex shuffling or mutations of genes during sexual reproduction. Eugenics, inborn

errors of metabolism, the knowledge that genes direct the production of specific enzymes and shrewd clinical observation followed. By 1950 the development of molecular biology enabled medical genetics to flourish. Here Weatherall, a participant in recent progress, stresses that curiosity-driven research was the major promoter.

Weatherall concludes with a return to the patient. He notes that despite the new biology, each of us is unique and influenced not only by ordinary heredity but also heredity mediated through tradition and the transfer of information through non-genetic routes from one generation to the next. Therefore, there is no reason why the new biology should have a dehumanizing effect on doctors of the future. Ethical issues rapidly accumulate because of scientific high-technology medicine. The definition of death, *in vitro* fertilization, and codes for organ transplantation must be founded on firm science, or "when this is not possible, on a consensus reached only after a completely open debate between doctors, courts, and public." Genetic manipulation makes the definition of the value of life even more difficult. Ethical questions arise with the 'selection' made possible by prenatal identification of genetic diseases. The transplantation effect of somatic gene therapy is less problematic than germ-line therapy that could pass a 'foreign' gene on to future generations. At the other end of life, public debate should help determine when and to what extent to apply the benefits of high-tech practice to ageing populations. In the end, "the sheer complexity and unpredictability of the manifestations of illness is responsible for the notion of medicine as an art." At that point "simple kindness and empiricism must take over." Weatherall predicts that "while there are still patients to treat, medicine is likely to remain very much an art."

This thesis and its annotated history rank with those of Rosemary Stevens and Paul Starr. Physicians, medical students, journalists, legislators and their health aides, anthropologists and biological scientists will appreciate its reasoned call for patience with 'the silent art'. The reviewer yearns for a broader dissemination of his instructive message through a televised series such as those by Lewis Thomas and David Attenborough.

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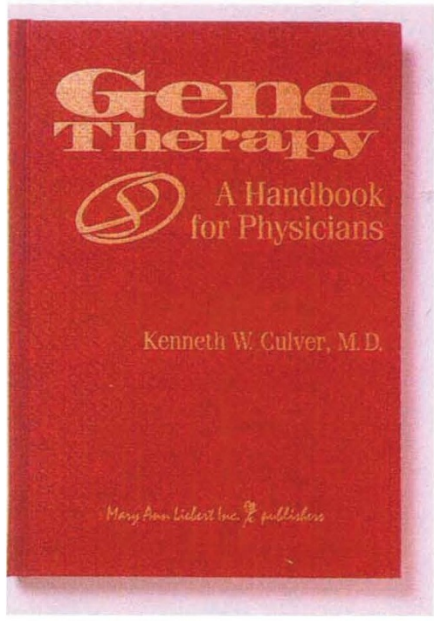

Gene Therapy:

A HANDBOOK FOR PHYSICIANS

BY KENNETH W. CULVER
Mary Ann Liebert Inc., 1994 $Price

REVIEWED BY JAMES J. FERGUSON JR

Some years ago Alvin Toffler, in his popular book *Future Shock*, offered the thesis that the social and technical complexities imposed by progress may be overwhelming our capacity to deal with them. Kenneth Culver's book helps us deal with such complexities of progress in the burgeoning field of gene therapy, and it does so with a flair. And Culver more than implies that we ain't seen nothin' yet! As a front-line participant in pioneering and continuing studies in gene therapy, Culver has the credentials to write on the subject. His efforts to this end are most welcome.

I'm reminded of a friend describing her first explorations on the Internet, chatting electronically with an unknown correspondent. When she typed "I've never done this before," the message purred back "I'll be gentle." Culver is mercifully gentle, leaving the unraveling of technical complexities to the extensive bibliography he provides. His overview of the background history and principles of the discipline is lucid, with special appeal to the novice reader. Its depth suffers only from the space limitations reasonably imposed by an overview of this type.

This is a 'niche' book, which targets the mid- and late-career physician whose every intuition insists there is something of overwhelming importance under way in medical science, but who isn't quite sure how even to frame a coherent question about it. The term 'Handbook' is something of a misnomer. Rather, *Gene Therapy* presents a concise vignette of an infant field that is progressing so rapidly that books can only describe its past rather than its present. The book was, in fact, published in 1994, probably with a publisher's deadline in late 1993. The intervening year surely has provided follow-up information on the provocative clinical initiatives mentioned in the book. New and equally tantalizing leads have obviously emerged since its publication. For example, recent progress in the application of gene therapy *in utero* begs timely updating, as does the inevitability of considering germ-line therapy. Will there be a sequel? We hope so.

The scope of this brief book (117 pages) is inviting. It effectively reviews the momentous developments that have made gene therapy technically possible and then explores and critiques the methodologies now used for the insertion of foreign genes into somatic cells. Culver appropriately points to the complexity and difficulty in effecting efficient gene transfer, currently the major impediment to progress in gene therapy. Starting with the pioneering treatment in 1990 of two desperately ill children with adenosine deaminase deficiency, his book recounts subsequent forays into this brave new world of somatic cell gene therapy in examples of familial hypercholesterolaemia and cystic fibrosis. There follows an outline of current, pending, and proposed applications of gene therapy to an extensive series of hereditary, immunological, hormonal and infectious disorders. Finally, in describing work in progress in the treatment and prevention of neoplastic diseases, the author displays the true promise and wonder of gene therapy in a dimension which wasn't even imagined a decade ago.

Does Culver's book have shortcomings? Certainly, but not many. Professionals in the field will not be sated by its content, but those of us on the sidelines have much to gain from reading it. *Gene Therapy* points to a future which may fall short of our expectations, or that may arrive too late for our needs, but nevertheless a future which we must comprehend and assimilate.

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