THE GENE WARS

SCIENCE, POLITICS, AND THE HUMAN GENOME

"A scrupulous . . . narrative of the genesis and opening years of the genome projects. . . . An essential history." —Horace Freeland Judson, *Nature*

ROBERT COOK-DEEGAN

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W · W · Norton & Company · New York · London

The text of this book is composed in Galliard with the display set in Garamond Old style and Stradivarius. Composition and manufacturing by the Maple-Vail Book Manufacturing Group. Book design by Marjorie J. Flock.

First published as a Norton paperback 1995

Library of Congress Cataloging-in-Publication Data

Cook-Deegan, Robert M.
The gene wars: science, politics, and the human genome / Robert Cook-Deegan.
p. cm.
Includes bibliographical references.
1. Human Genome Project. 2. Human gene mapping.
QH445.2.C66 1994
573.2'12—dc20 93-10762

ISBN 0-393-31399-9

W. W. Norton & Company, Inc., 500 Fifth Avenue, New York, N.Y. 10110
W. W. Norton & Company Ltd., 10 Coptic Street, London WC1A PU

2 3 4 5 6 7 8 9 0

To Kathryn, Patrick, and Maeve

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Preface

A CENTRAL TENET OF MODERN BIOLOGY holds that the long-chain organic molecule deoxyribonucleic acid (DNA) encodes all the instructions needed to create life. The recipe for making a human being is written out sequentially in a four-letter digital code, embodied in the six feet of DNA coiled inside virtually every human cell. Amassing the scientific tools to decode that instruction set has been a major preoccupation of molecular biology ever since 1953, when James D. Watson and Francis Crick first described DNA's double helical structure. The Human Genome Project is a natural outgrowth of this effort.

The genome project emerged from several independent sources in the mid-1980s. Once it welled up in the scientific community, the project quickly became a contentious political issue as well as a scientific one. Among its friends, enthusiasm for the project inspired rhetorical exuberance. The project became the "Holy Grail of biology" and a quest for the all-revealing "Book of Man." These sincere, but nonetheless hyperbolic, conceptions overshadowed what is, in essence, an extensive road-building project for genetic exploration.

One factor that incited passion about the genome project among scientists was its price tag. Very early in the project's evolution, the figure of $3 billion began to be bandied about. This estimate of the project's eventual cost was made long before any reliable projections could be made about its constituent parts; indeed, even the cost of getting started was highly uncertain. The $3 billion was to be spread out over ten or twenty years. If the National Institutes of Health continued spending at its current rate, however, it would expend a total of $150 to $200 billion during that time on all of its activities. In that case the genome project might account for between 1 and 2 percent of the total NIH expenditures for many years to come. But the larger debate was never cast in these terms. Rather the debate became one of "big" science versus "small" science. The reliance on systematic technology development and goal-directed gene-mapping efforts presaged a new style for biology, one that elicited excitement from those attracted to whiz-bang technologies but drew gasps of revulsion from those who aspired to cultivate biology on a more modest scale and with a decentralized organization. The battle was, among

other things, over whose vision would control the budget and which scientific aesthetic would prevail.

The purpose of the genome project is to explore the territory discovered in 1865, when Gregor Mendel first described hereditary "elements." The early genetic pioneers could only glimpse this new world indirectly, by studying how traits were inherited. They could not guess what the substance of genes might be. That awaited elucidation in 1944, when Oswald T. Avery, Colin McLeod, and Maclyn McCarty, working at the Rockefeller Institute in New York, demonstrated that DNA in bacteria contained the inherited genetic information. Subsequent biology showed that DNA is indeed the universal language of life. All organisms, with a few minor variations, use the same DNA code.

Maps of this biological frontier could be drawn only after the structural basis of inheritance had been worked out. The study of genetics was the study of how characters are inherited—how knowing something about parents tells us something about their children. In the 1950s and 1960s, molecular biology spawned molecular genetics. The central target of this new approach to genetics became explaining how DNA was copied so that it could be passed on to subsequent generations, on one hand, and how its instructions were translated into cellular function, on the other. The structural analysis of DNA function became a dominant theme of modern biology, including research aimed at conquering human diseases.

A somewhat separate science of human genetics developed in parallel. Human genetics long emphasized the study of pedigrees—the transmission of traits from one generation to another—and the genetic differences among human populations. Medical genetics, the study of how some diseases were passed on as genetic traits, constituted a once abstruse spinoff of human genetics. During the 1970s and 1980s, genetics was drawn out of the backwater and entered the mainstream of biomedical research, emerging as a dominant strategy to understand mysterious diseases. This development resulted from the confluence of this tradition of human genetics with the *molecular* genetics practiced in bacteria, yeast, fruit flies, nematodes, mice, and other organisms.

A revisionist history has already crept into the reconstruction of the genome project's genesis. Specialists in human and medical genetics have, in some quarters, attempted to claim the origin of the genome project as their own. This could well have occurred, indeed perhaps should have. It would have been logical for the Human Genome Project to emerge from within human genetics or medical genetics. The progression from gene mapping to the Human Genome Project is so natural that many within the field believe it must have arisen so. But that is not the way it happened.

None of the three main instigators of the Human Genome Project, as it actually developed, was a human geneticist. Each used genetic techniques and engaged in biomedical research on human diseases, but none was engaged in

studying human genetic disease or human pedigrees as a primary focus. The genome project began, instead, as a technological vision. Its name came from thinking about systematically applying the tools of molecular genetics to the entire genome—the full complement of DNA in human cells. In this view, gene mapping was a subsidiary step, with determination of the complete DNA code as the primary goal. Human genetics later recaptured some pieces of the genome project by redefining its goals, but the genome project clearly began outside of the mainstream in human genetics.

Advances in methods for analyzing the structure of DNA rapidly, in small amounts, and with great precision allowed some of the power of genetics, so well demonstrated in other organisms, to be applied to the study of human disease and normal human physiology. The real roots of the genome project were in yeast genetics, nematode genetics, and bacterial genetics. A few pioneers had long used molecular methods to dissect human diseases, and with some success. But the emergence of new technologies, demonstrably useful for studying other organisms, made the direct analysis of DNA much more tractable in humans. The genome project grew from thinking boldly about how to apply emerging technologies of DNA analysis to the study of human biology and, ultimately, to the task of tackling the entire human genome.

This book is an account of the origins of the Human Genome Project. The scientific ideas took hold only after they were publicly aired, provoked a vigorous debate, and were then repackaged to make them politically palatable. The main story line is the creation of a bureaucratic structure to carry those ideas to fruition. The ideas derived from science and technology; the genome project as a sociological phenomenon, however, came from the actions of many people, often working without knowledge of others treading on convergent paths.

The book describes two kinds of history: the technological advances that predated the project and the events that followed, once the idea of a genome project came to the surface. After an introductory chapter, the technical developments that led to discussions of a concerted genome project are described in Chapters 2 through 4. Those who want to go straight to the politics, or who are put off by the technical arcana, can skip these and go directly from Chapter 1 to Chapter 5. Chapters 5 through 20 and the Epilogue describe the political and historical events built on the technical foundation.

Throughout its early history, I was positioned as a close observer of the genome project, and was at times a minor participant. From 1986 through 1988, I was part of a team that prepared a report on the genome project for Congress. I then directed a small congressional bioethics commission, which died in the crossfire of abortion politics. Upon its death, I briefly joined the National Center for Human Genome Research at the National Institutes of Health as an outside consultant, beginning my association two months after it

was created. Along the way, it became clear that the policy story needed to be told. The Alfred P. Sloan Foundation, and subsequently the National Science Foundation, provided generous support to gather information and to begin writing the book. I conducted interviews with the main characters in this story beginning in 1986, and continued for six years. This is their story, the genesis of the Human Genome Project—a case study in the politics of modern science.