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FOREWORD

Dr. Michael Smith was an uncommon scientist who used synthetic organic chemistry to create an extraordinarily powerful tool that is now used by biologists worldwide. We often forget the remarkable influence that tools have on our ability to conduct research since so much more attention gets focused on the results of that research and the exciting findings that constantly seem to emerge from our studies of biology. Wisely, the Nobel Committees in Stockholm have frequently recognized the immense contributions of the tool developers. In 1993 they awarded the Nobel Prize in Chemistry to the developers of two tools, without which we could not now imagine doing modern molecular biology. Kary Mullis received it for inventing PCR (polymerase chain reaction) and shared it with Michael Smith, who pioneered the technique of site-specific mutagenesis.

Until Michael Smith came along, the methods available to geneticists for producing mutations were incredibly crude. The use of X-ray irradiation, for which Muller was awarded the Nobel Prize in 1946, was still common as were a variety of chemical mutagens. However, those methods suffered from the disadvantage that the mutations produced were random, and elaborate screens or selective procedures were required to find the mutations of interest. Enter Michael Smith, who had learned how to make short synthetic oligonucleotides in Gobind Khorana's laboratory as a post-doctoral fellow. He realized in the 1970s, during a stint in Fred Sanger's laboratory, that with the sequence available for the DNA of a small virus, there was a possibility of using synthetic oligonucleotides to introduce specific mutations. This was accomplished using an in vitro methodology with a mutagenic primer and a DNA polymerase to elongate it. Site-specific mutagenesis was born. Together with Clyde Hutchison, Mark Zoller and many others, Michael Smith went on to develop the technique so that it could be used by researchers everywhere. This was truly a ground-breaking methodology that is now so widely used we have almost forgotten who invented it!

To appreciate the significance of site-specific mutagenesis we need merely look at the evolutionary process. During evolution random changes in DNA lead to random changes in the proteins encoded by that DNA and those that are beneficial eventually become selected. But natural evolution is a terribly slow process. We might wait for hundreds or thousands or even millions of years for truly advantageous mutations to arise. Thanks to the methodology developed by Michael Smith we can now hasten that process dramatically in the laboratory. We can introduce specific mutations into specific proteins at positions that we judge will make those proteins work better. In this way we can overcome the inherent limitations of slow natural processes to produce beneficial changes with great rapidity. Michael Smith was truly a pioneer whose insight, skill, and humanity make him a real hero of molecular biology.

Richard J. Roberts
1993 Nobel Laureate in Physiology or Medicine
New England Biolabs, Beverly, MA
March 2004

PREFACE

by Eric Damer

One Saturday evening in 1994 I attended The Vancouver Institute, a free and longstanding public lecture series held on the University of British Columbia campus. The speaker was Professor Michael Smith, and his topic was his trip to Stockholm to receive the 1993 Nobel Prize for chemistry, awarded for his development of an important technique to manipulate DNA. I was curious to see a Nobel laureate for myself, especially since he was the first person from "my" university ever to have won the prestigious honour. I was immediately struck by his popularity — I sat in one of two overflow rooms since the main lecture hall of five hundred had filled early. Professor Smith proved to be a charismatic speaker with an easygoing and unpretentious manner. His pleasant and witty commentary was richly illustrated with elegant slides of the regal event in Stockholm. He closed his presentation by thanking his research associates and the university that had supported his work, and by offering a sincere thank you to the people of British Columbia for supporting the university and thus his career.

The audience in the main hall jumped to its feet and burst into applause. When Smith toured the overflow lecture halls, others stood and applauded enthusiastically. I marvelled at the response — the audience behaved like fans welcoming home a sports hero. Smith was no hockey player, yet all who had come that night to hear him responded overwhelmingly to the man and his achievements. To many people of the University of British Columbia and Vancouver, perhaps even the province and country, Professor Smith was indeed a hero.

When I was approached to help write a biography of Michael Smith I had a number of concerns. As is so often the case in historical research, information about Michael Smith's life was unevenly distributed with an abundance of archival records on his later years and very few on his early ones. No one had kept family records in the event that he would become famous, or so it seemed. Fortunately, there were several people whose memories could help fill those gaps. Because the biography would include recent history, I had to expect that I might stumble into current politics or recently settled or dormant controversies. My biggest concern, however, was that I did not simply want to write a hagiography. I knew many people admired Michael Smith as a scientist and as a person, but I wanted to peer beneath the rapidly developing myth to form my own view. I am grateful to have had the freedom to do so.

As I reviewed archival material and talked with his family, his partner Elizabeth, friends, colleagues, and students, I decided that the myth contained much truth. As a scientist and member of the academic community, Michael Smith was extremely well-regarded and well-liked for many good reasons. He was intelligent, creative, and ambitious in his work, but also modest and never ruthless. He had a well-earned reputation both inside and outside the academy for congeniality and conviviality despite a brusque manner and sharp-tongued sense of humour. In fact, I came to admire much about him as a person although I realized that he had his shortcomings and his failures. Many people told me that his ascension from rural English beginnings to the Canadian scientific elite "couldn't have happened to a nicer guy."

This biography is largely an account of Michael Smith's professional life, although personal elements are included to illustrate aspects of his character. His career in science might never have begun had the English school system not been sufficiently reformed by the 1930s to allow children from poor families to obtain an academic education. After completing his university studies, he still faced an uncertain academic future because of the nature of English society. In Vancouver, British Columbia, where he arrived almost by chance, Smith found a new home and began his academic life in earnest. For thirty years his laboratory at the University of British Columbia conducted scientific research of the highest quality.

Smith's ambition to excel as a scientist invariably led him into political issues, first in his own laboratory, then in his home institution, and later in Canadian science policy. He was, for example, part of the movement to "democratize" the University of British Columbia in the 1970s but part of the movement to "commercialize" the university fifteen years later. During the 1990s he played crucial but somewhat controversial roles in building new scientific institutions in British Columbia and Canada.

This account would be incomplete without some explanation of Smith's remarkable scientific work. This has been ably provided by molecular biologist Caroline Astell, a former student and colleague of Smith's, whose collaboration in this biography has been most fruitful and who was, in several key respects, also part of the story. She initiated this project and her participation ensured the cooperation of others.

It has been a pleasure and a privilege to have examined the life of Michael Smith, and to have been entrusted to write a biography that was fair and balanced while respecting his memory and the privacy of his family and closest friends. Perhaps in later years, with greater historical perspective, additional material may come to light that will add further dimensions to the story of this extraordinary man. Although the book is intended for the general reader interested in science, scientists, universities, British Columbia, the Nobel Prize, or Michael Smith himself, I believe that historians and scientists will also find something of value here.

One final prefatory remark seems appropriate. I have generally referred to the subject of this biography as "Mike" despite, I have been told, his preference for "Michael." I assume such familiarity because virtually everyone referred to him as Mike, particularly before his Nobel Prize. As the reader will soon learn, he had a very down-to-earth and informal personality that led to familiar appellations. But as a friend and colleague of his reminded me, he was no ordinary Mike.

> — Eric Damer March 2004

PREFACE

by Caroline Astell

I knew Michael Smith from 1964 until his untimely death in the fall of 2000. During that time our careers often intertwined and sometimes in very significant ways. Our first encounter took place at UBC while I was a graduate student. Mike sat on my magistral committee and later, as my doctoral supervisor, he provided a supportive environment in which to learn state-of-the-art biochemistry. Early on he instilled in his students and post-doctoral fellows self-motivation and a drive to succeed by granting them considerable freedom to pursue their particular research topic. Many students were not ready for such self-reliance and subsequently went their different ways — sometimes before completing their degrees — although to my knowledge all achieved considerable success in their chosen fields. Those of us who persevered with a career in scientific research surely would agree with Mike's dictum that the ultimate motivation is the thrill of discovery, whether in a simple project to improve the efficiency of linking oligonucleotides with cellulose paper or to sequence the genome of a newly emerged pathogen.

Throughout my career I have met many students who say they would rather interact with people than work in a lab. They believe that scientists toil for long hours alone in a smelly laboratory wearing a white lab coat — the stereotypical mad scientist. I learned in Mike's lab and others that this is not the case. I did wear a white lab coat, but I was surrounded by fellow lab workers who became a sort of second family, offering suggestions on my work, showing enthusiasm when experiments succeeded, and providing support when projects failed. Mike also initiated me into the often intense work schedule of the laboratory. Scientists spend many long hours in the lab but for those who really enjoy what they are doing, it is little different from pursuing a passion for mountain bike riding, gardening, or world travel.

Part of the excitement of being in Mike's laboratory was meeting high profile visiting scientists who talked with students and research fellows. In my case this included Gobind Khorana, Rich Roberts, Ben Hall, Edward Reich, Clyde Hutchison III, Chuck Dekker, Fritz Rottman, Peter Gilham, Roy Vagelos, and Fred Sanger, to name a few. Many of these scientists had won or would win the Nobel Prize for their achievements. Mike had an extensive network of first-rate scientific colleagues.

I left UBC for postdoctoral training at Rockefeller University in New York City. When I arrived I was in awe of the stature of many of the researchers. However, like Mike, many of the senior scientists at "Rocky U" were friendly and took a genuine interest in trainees. One of them, who recognized I was new, asked me where I was from, who my supervisor was, and what research I would do. Only later did I learn I had been talking with Christian deDuve, famous for his studies on fractionation of cellular organelles. My work in Mike's lab proved to be good preparation for my post-doctoral training.

In 1977 I returned to UBC where I again worked for several years in Mike's laboratory, partly to develop a new technique called sitedirected mutagenesis but mostly to establish DNA sequencing and begin my own project: sequencing the genome of a small mammalian virus. I subsequently joined the Department of Biochemistry as a faculty colleague of Mike's where I continued my virus research until 2001. I am deeply grateful for four years of support by the British Columbia Health Care Research Fund and the continuous support of the Medical Research Council of Canada (now the Canadian Institutes of Health Research) for my research program.

In January 2002 I retired from UBC but soon found myself associated with the legacy of Michael Smith. When I returned from a holiday to New Zealand, I joined the Genome Sciences Centre at the British Columbia Cancer Agency as Projects Leader. This was the genomics centre that Mike co-founded with Victor Ling in late 1999 to implement genomics as a tool for cancer research. The GSC is currently Canada's largest genomics centre with a staff of over 140. Mike would have been proud to know that during the Sudden Acute Respiratory Syndrome (SARS) crisis in March/April 2003 "his" centre was the first to report the complete DNA sequence of the SARS coronavirus, allowing scientists around the world to begin devising diagnostic tests, methods to control the virus, and even a vaccine.

I first considered a biography of Mike in the summer of 2000 and contacted him with my idea. Our busy schedules prevented an immediate meeting, but we finally agreed to discuss the matter over lunch in October. Regrettably, his health failed rapidly towards the end of September and he passed away October 4. Although we never did discuss what a biography might include, I am confident he would have approved of *No Ordinary Mike* although, in his usual self-deprecating way, he would likely have said that he really had not accomplished that much.

I began writing my own account of Mike's life in November of 2000 but had little time because of commitments at UBC. When my appointment to the Cancer Agency ended my early retirement (almost before it started) I realized the book would not happen without assistance. I am indebted to historian Jean Barman for suggesting that I take on a co-author and for referring me to Eric Damer. Without Eric's hard work and more than considerable talent this book would never have been published. The result is an opportunity for the wider public to know about the career of a remarkable scientist and person.

> — Caroline Astell March 2004