

1993

Michael Gottesman

Influenced by the success and excitement of the Soviet Sputnik space program in the 1950s, Michael Gottesman experimented with rocketry as a child in Flushing, New York. He first became interested in biology while in high school after learning of John Enders' basic science contributions to the successful polio vaccine. Although he did not become a rocket scientist, Gottesman graduated Flushing High School as valedictorian and enrolled at Harvard in 1962.

During his sophomore year, he entered a tutorial program in biochemistry and studied Arthur Kornberg's series of articles about DNA replication under the direction of his tutor, William Beck. This tutorial had a profound impact on his intellectual and professional development, as he became convinced of the power of combining biochemistry and genetics to study cell biology, which has been the theme of his professional career.

Gottesman gained invaluable research skills doing summer research at the Albert Einstein College of Medicine and in Beck's laboratory at Harvard. While still an undergraduate, Gottesman married Susan Kemelhor. Susan Gottesman is a noted bacterial geneticist and active member of the American Society for Microbiology and the American Society for Biochemistry and Molecular Biology, who Gottesman credits with tilting him away from biochemistry and towards genetics. To broaden his education in human biology, he went to Harvard Medical School. While at medical school he continued his research activities in the protein chemistry laboratory of Bert Vallee. He graduated in 1970 and completed a medical internship and residency at the Peter Bent Brigham Hospital in Boston. Gottesman recalls his medical school and residency experience as very rewarding, both in terms of his education and the satisfaction of interaction with patients. However, Gottesman became discouraged by the limitations of clinical treatment and knew from his undergraduate days that he would want to return to do basic research.

Gottesman went to the NIH from 1971-1974 to do his postdoc in the laboratory of Martin Gellert. He moved back to Harvard Medical School as an Assistant Professor for one year before he and Susan joined the permanent staff of the National Cancer Institute in 1976. Gottesman became Chief of the Molecular Cell Genetics Section of the Laboratory of Molecular Biology in 1980, Chief of the Laboratory of Cell Biology in 1990, and was Acting Director of the National Center for Human Genome Research (NCHGR) until this spring.

At NCHGR, Gottesman felt there was a need to convince his fellow cell biologists of the utility of the human genome project and its cost effectiveness. He felt a strong sense of obligation to support both the intramural and extramural communities at NIH. His colleague Martin Gellert notes that Gottesman is widely praised within and outside the human genome project for stepping into a difficult situation and effectively and responsibly satisfying the concerns of the science community. Gottesman himself more modestly describes his greatest success at NCHGR as helping to recruit its new director, Francis Collins. Thankful that he is back in his lab, Gottesman can now build upon his

many innovative contributions to molecular genetics: he was the first to demonstrate that resistance to chloramphenicol was encoded by a transposable element in *E. coli*. Studies on recombination and DNA repair in *E. coli* resulted in the discovery of a novel recombination system in *E. coli* which could be partially reconstructed in bacteriophage known as λ reverse. His isolation of mutations affecting levels and activity of *E. coli* DNA ligase proved the essential function of this enzyme in DNA regulation and repair and became important tools for recombinant DNA technology.

Since 1975, Gottesman has concentrated on cancer cells. He isolated and cloned a major protein secreted by malignantly transformed cells and showed that it is an acid protease (cathepsin L) which interferes with antigen processing by cells of the immune system. His isolation and characterization of somatic cell mutants with altered α - and β -tubulins remains the only genetic proof in cultured mammalian cells of the role of microtubules in spindle formation. Similarly, his mutants affecting cAMP-dependent protein kinase demonstrate the critical role of this enzyme in mediating all effects of cAMP in animal cells.

Recently, Gottesman, together with Ira Pastan, has used molecular genetic tools to analyze the clinically important problem of multidrug resistance in human cancer. His laboratory developed human multidrug-resistant cell lines which he then used to isolate the gene and cDNA responsible for multidrug resistance (MDR1). The MDR1 gene encodes an energy-dependent multidrug efflux pump which has become a paradigm for the analysis of a growing family of ATP-dependent transport proteins. Gellert calls this discovery an example of how "basic science is the beginning of something that has real medical importance."

Gottesman's contributions to our understanding of the normal function of the multidrug transporter, its mechanism of action, its role in mediating drug resistance in human cancer, as well as the development of strategies to circumvent its activity and to use MDR1 retroviral vectors as gene therapy to protect bone marrow against the toxic effects of chemotherapy, are having a major impact on the treatment of cancer. Clinical trials have begun to test the efficacy of inhibitors of the multidrug transporter to reverse chemotherapy resistance in cancer, and trials are planned to use MDR1 vectors to protect bone marrow in cancer patients from the toxic effects of chemotherapy.

Gottesman has been an active member of the ASCB since he joined in the late 1970s. He currently serves on Council and is a member of the Public Policy Committee. Gottesman's interest in these activities stems from his strong belief that educating members of Congress about the critical importance of basic science should be a fundamental concern of the ASCB. He has served on the ASCB Nominating Committee and as ASCB representative to the FASEB Publications Committee and FASEB Summer Research Conference Committee. Gottesman has served on the Editorial Board of The Journal of Cell Biology and continues to serve on the Editorial Board of Molecular Biology of the Cell. He has also edited three books on molecular cell genetics.

His strong commitment to public policy is matched by his dedication to public education. Gottesman believes that the role of education in science is vital and has emphasized this in his own lab and through a number of education programs that he has designed to encourage greater understanding and appreciation for science. Over five years ago, Gottesman began to bring in a number of high school teachers to NIH labs during the summer. The program, initially supported by the Foundation for Advanced Education in the Sciences (FAES), has allowed science teachers to gain a greater appreciation for the excitement of laboratory-based science. The program pre-dates and served as a model to the ASCB's Summer Teacher Research Fellowship Program. Gottesman notes that many of the participating teachers have altered their teaching styles and are encouraging their local school administrations to change the biology curriculum to reflect new developments in cell and molecular biology. Other programs instituted by Gottesman at the NIH include summer grant programs for high school students supported by FAES and the Howard Hughes Medical Institute, where over 200 students have worked in NIH laboratories over the past five years.

Despite the many professional and community responsibilities that he and Susan assume, they manage to reserve some family time at their Greenport, Long Island summer beach house. He notes that Greenport is where Einstein used to sail and current famous summer visitors include singer Billy Joel. Gottesman enjoys soccer but hung up his cleats several years ago as a coach when his two children were in high school. Now Daniel, age 23, is a first-year graduate student in theoretical physics at California Institute of Technology, and Rebecca, 20, is a junior at Columbia College with an interest in psychology and the theater.