What Causes Cancer

MICHAEL BISHOP, M.D. ’62, is a self-described inveterate baseball fan and inadvertent microbiologist. His sports aspirations have been thwarted of late (he is a San Francisco Giants loyalist), but not so his professional life. He and colleague Harold E. Varmus, A.M. ’62, S.D. ’96, were awarded the 1989 Nobel Prize in Physiology or Medicine for discovering within normal cells certain growth-controlling genes which, when mutated, play a role in initiating growth of cancerous tissues. (The announcement describing their work, with each scientist’s autobiography and Nobel Lecture, can be found at www.nobel.se/medicine/laureates/1989/index.html.)

Bishop, who has worked since 1968 at the University of California, San Francisco—a renowned health-science center—became chancellor there in 1998. He was a member of Harvard’s Board of Overseers from 1996 until last June. His memoir, How to Win the Nobel Prize: An Unexpected Life in Science, will be published in May by Harvard University Press. The title and subtitle seem a fitting measure of the man: a bold proclamation (poking just a bit of fun at other scientific memoirs), modified by a very personal appreciation of the serendipity and human elements crucially involved in research and discovery.

Along with engaging autobiography and acute comment on the interaction between science and society, the book is an intriguing history of microbiology and associated discoveries in medicine: the slowly gathering understanding of plague and puerperal fever, researchers’ sometimes appalling self-administered experiments with cholera and gonorrhea, the ad-

Genetic sloppiness, the cellular “social contract,” and malignancy

by J. MICHAEL BISHOP
vent of cell theory and vaccination and antibiotics, the elaboration of genetics. Bishop populates his telling with vivid portraits of the theorists and tinkerers who did the pivotal science.

Many readers will find the story’s culmination in “Opening the Black Box of Cancer,” the chapter progressing toward and beyond the work of the Bishop-Varmus laboratory, from which issued fundamental contributions that have changed perceptions and research paradigms. “Where once we viewed cancer as a bewildering variety of diseases with causes too numerous to count,” Bishop writes, “now we are on the track of a single unifying explanation for how most or all cancers might arise. The track is paved with cells.”

The excerpts that follow come from near the beginning and the end of that chapter, necessarily omitting the textured account of the researchers and science on which Bishop and his colleagues built. The underlying knowledge (a mystery in 1950, now rudimentary material in high-school biology courses) begins with the cell, its nucleus, and the chromosomes therein—bearers of the instructions for cellular structure and function.

Those instructions are carried by the DNA molecule, Bishop explains, and written in the chemical vocabulary called genes. The genes act through a universal process that first copies DNA into smaller molecules known as RNA, and then RNA into still smaller molecules—proteins. In this scheme, DNA encodes the master plan for the cell, RNA is a messenger that shuttles information in the plan from one part of the cell to another, and the protein molecules perform most of the jobs of the cell. By that process, genes direct the growth of the fertilized egg into myriad cells and the cells’ differentiation into distinct forms and tissues and organs ultimately recognizable as you and me.

Of critical importance, genes also control the proper regulation of that growth within the healthy organism. For it is a fact of life that the DNA and genetic “words” are changed, in random and unwanted ways, time and time again. Cells come equipped with systems to guard against these mutations’ potentially dysfunctional effects by repairing the damage, by halting the processes of cellular reproduction, or by inducing cellular suicide. Such checks keep the organism from veering off into unviable paths, and, in most instances, from constantly falling prey to uncontrolled proliferation of defective, undifferentiated cells—cancer.

Much of the current knowledge of cancer depends on a simple “retrovirus”—a virus that carries its genetic knowledge in RNA and copies it onto DNA through a “reverse transcriptase” enzyme. Working with the Rous Sarcoma Virus—which carried an “oncogene” capable of igniting cancer in chickens and rodents—Bishop, Varmus, and colleagues teased out the presence of “proto-oncogenes” in the cells of vertebrate species. These progenitor oncogenes, which normally regulate replication and other vital cellular functions, can be disturbed so that they signal for unlimited proliferation and other errant behavior. If that step is followed by others, a tumor is born.

Bishop’s story proceeds through five levels of scientific insight. First came the understanding that cancer is a cellular inheritance: it begins in a single cell and passes its malignant potential to subsequent generations of cells. Second, scientists learned that a carcinogenic event is usually set off by some
external factor: cancer begins with disruptive exposure to sunlight, x-rays, smoking, a dangerous chemical. Third, that event is mutagenic: the DNA is somehow deranged, because genes are mislocated among different chromosomes (as in the “Philadelphia chromosome” associated with chronic myelogenous leukemia), or changed at a precise point, or overgrown (a hyperprevalence called “amplification”). Fourth, as they use cells to effect their own replication, certain viruses can convert benign proto-oncogenes into cancer agents—a vital finding, because the simple genetic structure of viruses is much more readily susceptible to study than is that of cellular species. Finally, the rare, truly inherited cancers reveal the repair genes and “suppressor genes” whose loss or malfunction permits other mutations to proceed to the point of tumorigenesis.

In the excerpts, Bishop summarizes the genetic understanding of cancer, and considers its implications. ~The Editors

**Cells are the bricks with which all creatures are built, and 300 trillion of these bricks exist in each of our bodies. But these are not ordinary bricks: they have an elaborate internal structure that allows them to live and breathe; they move from one place to another with purpose; they have distinctive personalities and assignments; they converse by means of chemical and molecular languages; and they multiply—10,000 trillion times during the course of each human lifetime. The greatest wonder of cells, though, is that each knows what it is to do, and when and where. Cancer is a failure of the order that creates this wonder. The cancer cell violates its social contract with other cells, proliferating and spreading in an unfettered way.**

The manner in which the proliferation and spread of cancer cells occurs was first appreciated in accurate detail by [the German anatomist] Wilhelm Waldeyer. In 1867, Waldeyer published a microscopic description of how human breast cancer develops, beginning as a nidus of hyperproliferation in the glands of the breast, then proceeding to invade adjacent tissue, penetrate blood vessels, and spread to distant sites by transport of cancer cells through the lymphatic and blood vessels. Coming just a decade after the enunciation of the cell theory and produced with microscopes of dubious optics, Waldeyer’s description was an astonishing achievement that has stood the test of time and could be little improved on today. But again, the images were static and the conclusions were inspired inference. To achieve a dynamic image of cancer we must turn to the behavior of tumors in living organisms. The cells continue to grow even when crowded by their neighbors. They develop a very different appearance from their normal counterparts. In one batch of chicken cells alive and propagating for 32 years. We no longer consider that claim credible, but there can be no denying the influence of his work. Carrel’s personality never moderated. He spent his last years in France, espousing a toxic anti-Semitism.

Why has the cell culture pioneered by Carrel been so important to cancer research? The answer lies in simplification. Whole tumors are not easy objects for experimental study. So we resort to the assumption that the properties of individual cancer cells account for the behavior of tumors. We can define those properties by growing the cancer cells in glass or plastic vessels, using an artificial mixture of nutrients to feed the cells. Under these circumstances, cancer cells misbehave exactly as we might expect from the behavior of tumors in living organisms. The cells continue to grow even when crowded by their neighbors. They develop a very different appearance from their normal counterparts. And they behave like misfits, crawling over one another in a convincing caricature of the cells in an invasive cancer.

The early steps in the genesis of cancer probably occur in many of our cells during a lifetime, only to be aborted before matters get out of hand. But occasionally, the course of events continues to a lethal end, a homogeneous colony of cancer cells with the potential to expand unendingly. Biologists suspect that billions of cells may take the first step toward cancer in each of us during the course of our lives. Why then do any of us survive to tell the tale? The answer to that question has at least two parts.

First, one step is not enough. Several insults are required to produce a fully malignant cell, and the likelihood that these will combine in a single cell is very low. We will speak more of these combined insults later. Second, the immune system of our body can mount potent defenses against both foreign intruders (such as microbes and transplanted tissues) and errant natives (such as cancer cells). These factors combine to limit the frequency of cancer among humankind and to delay the emergence of most cancers until the later years of life.

What changes the cellular personality in a way that gives rise to cancer? Science has spent the last century trying to answer this question. Now, in a breathtaking sequence of discovery achieved over a brief period of time, an answer has emerged. All cancer can

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be attributed to a single underlying malady of the genetic program that directs the lives of our cells.

The Genetic Paradigm for Cancer

We have arrived at the confluence of our five disparate themes. The malign behavior of the cancer cell is heritable because it is rooted in the genes of the cell. Genetic targets for the mutagenicity of carcinogens and the mangling action of chromosomal damage have been identified—proto-oncogenes and tumor suppressor genes. The cancer genes of viruses and the inherited elements of congenital cancer have engendered a comprehensive view of tumorigenesis. We have come to understand the genesis of cancer as a protracted and stepwise process, a sequence of mishaps that we believe are largely genetic. We have developed a genetic paradigm that unites all of cancer under one roof.

Genetic portraits of human tumors exemplify the paradigm. Virtually every human tumor that has been properly examined contains a combination of lesions in proto-oncogenes and tumor suppressor genes. These combinations appear to embody the multiple steps required to produce a malignant tumor. Each individual lesion adds insult to injury, the eventual sum being a malignant tumor. The catalogs of genetic lesions in cancer cells now available to us are astonishing. Less than 20 years ago, we knew nothing of the lesions and had no means by which to find them.

Proto-oncogenes cause trouble only when they do something they should not, whereas tumor suppressor genes are problematic only when defective or lost. These are diametrically opposite maladies, yet they play cooperatively on the cell to produce a single outcome—cancer. How does this happen?

The behavior of cells is governed by an elaborate network of molecular interactions that resembles electrical circuitry. Some portions of this circuitry mobilize the cell to necessary actions, such as proliferation, migration, differentiation, and other behavior required to create and maintain the structure and function of individual tissues. Proto-oncogenes represent switches in this part of the circuitry. The damage to proto-oncogenes in cancer cells creates molecular short-circuits: the network now signals relentlessly, driving the cell to unwanted actions. (Another useful simile is that of a jammed accelerator.) Other portions of the circuitry bridle the actions of cells. In this part of the network, tumor suppressor genes are switches, and inactivation of these genes deprives the cell of bridles, unleashing the cell to unwanted actions. (Here, the alternative simile would be that of a defective brake.)

The reduction of cancer to its genetic essentials is a source of pride and gratification for biomedical scientists. But their achieve-
ment was anticipated by an artist. In 1934, Diego Rivera painted an expansive mural in the Palace of Fine Arts of Mexico City entitled *Man, Controller of the Universe.* He had painted the same mural previously in the newly constructed Rockefeller Center of New York City (albeit with a different title—*Man at the Crossroads*), but that version had been destroyed after Rivera refused to remove an image of Lenin. At the heart of the mural is a fanciful portrayal of the apparatus that facilitates chromosomal replication, and the apparatus is in turn gripped by a robust human hand. Rivera was unusual among artists in his strong belief that science and technology offer the greatest hope for the future welfare of humankind. The grip of that human hand exemplified his faith that we would someday understand the machinery of chromosomal replication and be able to turn that understanding to our advantage. That day now appears imminent.

**Malignancy**

*Norman Mailer* once captured the complexity of cancer: “None of these doctors has a feel for cancer… The way I see the matter, it’s a circuit of illness with two switches… Two terrible things have to happen before the crux can get its start. The first cocks the trigger. The other fires it. I’ve been walking around with the trigger cocked for forty-five years.” The speaker here was a smoker who died of lung cancer four pages later in Mailer’s novel *Tough Guys Don’t Dance.* Mailer’s conservative estimate of two “triggers” has since been revised upward for most cancers, but otherwise, the imagery is on target.

The multiple genetic events that contribute to tumorigenesis are thought to confer incremental properties that together create a malignant cell. For example, an emerging cancer cell might independently acquire capabilities for extended proliferation, for invasion into and migration through adjacent tissue, for penetration of lymph and blood vessels, and for spreading through the body. These are all properties that distinguish a malignant cancer from a benign tumor. We do not know the details of how this all happens. But we are reasonably certain that, some day soon, we should be able to assign distinct steps in tumorigenesis to individual genes.

It has been estimated that every gene in our DNA is damaged some 10 billion times in a lifetime. Yet the rate at which mutations arise is far lower, a tribute to the efficiency with which cells repair DNA. Given that efficiency, why do any of our cells ever accumulate the catastrophic combination of mutations required to generate a malignant cell? The answer to this long-vexing question is now in hand and represents an unexpected twist in the story. As cells reproduce, they monitor themselves for the completion of crucial events, such as the replication of DNA, repair of mutations, and construction of the apparatus required for cell division. If all is not well, a feedback device brings the reproductive process to a temporary halt, buying time for defects to be remedied. That failing, the cell can destroy itself by a form of suicide known as “apoptosis” in order to avoid becoming an outlaw.

Some of the genetic damage in cancer cells cripples either the failsafe device itself or the capacity for self-destruction, allowing the nature of what caused the damage and, thus, the cancer.

Second, genetic screening can be used to identify individuals who have inherited an increased susceptibility to cancer. But having such knowledge can be a mixed blessing. In some instances, such as hereditary melanoma of the skin, there is presently no means for intervention other than careful monitoring. Some established interventions are plagued with uncertainties—the use of anti-estrogens such as tamoxifen to deter breast cancer is a familiar example. And some interventions are draconian, yet only partially effective—prophylactic mastectomy to avoid inherited breast cancer leads this list.

The advent of genetic screening also confronts the practice of certain kinds of mutations can beget many more. The same sloppiness accounts in part for the ease with which cancer can become resistant to therapies.
oncology with new dilemmas. Will genetic screening for cancer improve detection sufficiently to justify its use and expense? How will it fit into the changing landscape of the medical marketplace? What implications might it have for insurance and employment? Alert to these concerns, an advisory council to the National Institutes of Health has warned against the general use of genetic screening for susceptibility to cancer until more is known about the efficacy of the screening and its societal effects. And states have begun to legislate prohibitions against the use of genetic profiles by employers and insurers.

Effective therapy of cancer is best assured by early detection of the disease. But we presently have screening techniques for only a modest number of human cancers, and several of these techniques remain beset with uncertainty. For example, there is continuing debate about whether the use of mammography has a beneficial effect on mortality from breast cancer, and disquiet over the unnecessary interventions occasioned by false positives in the test. Similarly, testing for prostate-specific antigen (PSA) may be detecting many tumors that are not life-threatening and would be better left alone, but we presently have no way to recognize that class of tumors.

Genetic screening may provide a helping hand with these uncertainties. For example, human excretions such as sputum, breast fluid, urine, and feces carry cells shed from the interior of the body. It is now possible to screen those cells for genetic damage that signifies the presence of cancer. This “genetic cytology” may be both more sensitive and more revealing than currently established techniques such as x-rays, scans, endoscopy, and microscopy. A retrospective look at the death of the American statesman Hubert Humphrey can illustrate these advantages.

Hubert Humphrey died of bladder cancer. Scientists have recently used genetic cytology to examine urine and tumor tissue taken from Humphrey and preserved after his death. They found that the bladder cancer could have been detected six years earlier than it was had genetic screening of cells in the urine been available; and that the analysis would have prompted immediate, aggressive therapy—in all likelihood, curing Humphrey of his cancer. Given the rigors of therapy, he might well have decided not to run for the presidency against Richard Nixon in 1968—the year that his cancer could first have been detected by molecular cytology.

Does the genetic paradigm promise new therapies for cancer? It is unlikely that we will be able to repair or replace the damaged genes of cancer cells in the foreseeable future: we have not yet learned how to operate on the DNA of living human cells with the necessary precision and efficiency. There are other genetic strategies that aim to switch off oncogenes in a direct and specific manner. But these too are far from realization.

If we focus on the protein handmaidens of genes, however, we can see more cause for hope. Given sufficient information about how these proteins act, we should be able to direct our therapies accordingly. In the case of proteins encoded by mutant proto-oncogenes, we seek ways to interdict the function of those proteins. The hope is to develop magic bullets of the sort first envisioned by German immunologist and hematologist Paul Ehrlich for bacteria, but directed instead at cancer cells. Targeting abnormal proteins in cancer may provide a way to avoid the toxicity for normal cells that engenders the noxious, sometimes life-threatening side effects of many current cancer therapies.

We can point to two promising examples, both involving abnormalities of proto-oncogenes. One is an agent known as Herceptin, which attacks a protein produced in abnormal abundance on the surface of approximately 30 percent of metastatic breast cancer cells. Herceptin has proven to be a valuable adjunct to the conventional therapy of breast cancer, but it is not curative. The other example is Gleevec, a drug aimed at the renegade chemical activity spawned by the Philadelphia chromosome in chronic myelogenous leukemia. Gleevec has demonstrated remarkable efficacy in the first phase of the leukemia, when the disease is relatively indolent; but it has been disappointing in the treatment of the later, highly aggressive phase of the disease, in part because the cancer cells quickly develop genetic resistance to the action of the drug.

In the case of proteins inactivated by mutations in tumor suppressor genes, we seek ways to revive the proteins or provide alternatives to their activities. The prospects here are probably less immediate than those for intervention against mutant proto-oncogenes.
We are also beginning to learn how genetic profiles of cancer cells can be used in the management of cancer. These profiles can be obtained in two different ways: by looking directly at DNA for abnormalities associated with cancer; and by surveying the expression of many genes for changes in tumor cells. It is already apparent that these tactics will be useful in categorizing tumors and predicting their outcome. In addition, there is hope that genetic profiles will eventually be used to choose the most effective therapy for individual cancers. Just as we presently base the choice of antibiotic therapy on the specific sensitivities of the infectious agent, the treatment of every cancer may someday be individualized and tailor-made, according to the inventory of genetic lesions in the cancer. The largest impediment to that advance may prove to be its cost; much will depend on how many different genetic fingerprints there might be for any given form of cancer, and thus how diversified the tailor-made therapies might have to be.

No single therapy for cancer, no matter how specific and elegant, is likely to become a panacea. We must deal with a large variety of damaged genes whose actions present great functional diversity. We shall also have to cope with the genetic sloppiness of cancer cells that can bring additional cancer genes into play as treatment proceeds, and that can create resistance to therapeutic agents during treatment. In 1983, a prominent figure in American cancer research told the New York Times that “scientists should learn how to manipulate oncogenes to protect or treat patients within the next five years.” The prediction has not been vindicated. The words ring hollow now, except as a cautionary tale.

Lessons

The genetic paradigm has provided a powerful view of cancer. The seemingly countless causes of cancer—tobacco, sunlight, asbestos, chemicals, viruses, and many others—may all work in a single way, by playing on a genetic keyboard, by damaging a few of the genes in our DNA. An enemy has been found, and we are beginning to understand its lines of attack.

The story of cancer research in our time embodies a great truth about scientific discovery. [American pathologist] Peyton Rous isolated his [cancer-inducing] virus from chickens, beasts not renowned for glamour. Yet the chicken virus isolated by Peyton Rous sired a remarkable lineage of discovery, replete with Nobel Prizes for five individuals.

The virus itself opened a new frontier in the search for causes of cancer, then served as the vehicle for additional discoveries of great consequence. These included reverse transcriptase, upender of genetic dogma; the viral oncogene SRC, the first explicit example of a cancer gene; proto-oncogenes, the first glimpse of a genetic keyboard for carcinogenesis; and the protein product of SRC, which provided the first example of a chemical reaction that can propel cancerous growth. All of this from a virus that, at the time of its discovery, was not deemed relevant to human cancer, all of this from the humble chicken.

Here is a familiar but oft-neglected lesson. The proper conduct of science lies in the pursuit of nature’s puzzles, wherever they may lead. We cannot pre-judge the utility of any scholarship; we can only ask that it be sound. We cannot always assault the great problems of biology at will. We must remain alert to nature’s clues and seize on them whenever and wherever they may appear. H. G. Wells understood this lesson well: “The motive that will conquer cancer will not be pity nor horror; it will be curiosity to know how and why…. Pity never made a good doctor, love never made a good poet. Desire for service never made a discovery.”

In 1978, Susan Sontag described cancer as “overlaid with mystification,…a triumphant mutation,…charged with the fantasy of inescapable fatality,…a scandalous subject for poetry.” Now the force of science has taken some of the sting from those words. The mystification is in retreat, the triumphant mutation has been exposed, we see new ways by which to confront that inescapable fatality, and there is even reason for poetry.

But the comfort is
In the covenant
We may get control
If not of the whole
Of at least some part
Where not too immense,
So by craft or art
We can give the part
Wholeness in a sense.