Cancer causes and cancer research on many levels of complexity

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America has poured about 200 billion dollars into cancer research since President Nixon declared war on cancer in 1971. How is the war going after three decades? Why do assessments vary as widely as "beating cancer" and "loosing the war on cancer?"

"Today the boundaries between medical and biological disciplines have vanished. . . . In an anatomy department, biologists, chemists, and physicists can present the human body to medical students as an uninterrupted ascent from atoms to man: from the tens of atoms that make a small molecule, to the thousands of molecules that make a polymer (such as a protein or a nucleic acid), to the millions of such polymers that make a cell, to the billions of cells that make a tissue, and the trillions of specialized cells that create a body. In a wider, panoramic view, the human body and its behavior becomes a tiny decoration in the tapestry of life interwoven with the incredible variety of plasmids, viruses, bacteria, plants, and animals in a 4-billion-year evolutionary development." Thus observed physician and biochemist Arthur Kornberg.[1]

Medical students are not alone in confronting myriad levels of complexity and scales of spatial and temporal organization. Freshman biology textbooks present a similar panorama from chemical bonds between atoms to the evolution of ecological systems. A first lesson for physics students is the vast range of scales from subatomic particles to medium-size things we handle everyday to galaxies and the universe itself. The expansive education is invaluable. When students later specialize in a particular area of research, they are likely to focus on one or a few levels that are more relevant than the others. The concentration comes with the risk of digging oneself into a hole and studying the sky from the bottom a well, as is expressed by ideologies asserting that all is nothing but genes or nothing but ecology. To avoid such traps is a constant struggle in scientific research.

Analysis and synthesis in cancer research

Consider a medical phenomenon, cancer. Which of the following do you think true?

A. Cancer is essentially a genetic disease.[2]
B. Cancer is a disorder of unregulated proliferation of abnormal cells.[3]
C. Smoking accounts for roughly 30 percent of all cancer deaths in the United States, overweight and obesity account for 15-20 percent.[4]

D. Inherited genetic dispositions contribute significantly to 5-10 percent of breast cancer and 5-13 percent of colon cancer incidences.[5]
E. In the industrialized nations, roughly 7 percent of cancer deaths are attributable to viral infections; 4 percent to occupational hazards; 2 percent to sunlight; 2 percent to pollutions of air, water, and soil; and less than 1 percent to food additives and industrial products.[6]
F. All of the above.

It is F, according to available scientific data, although some people reject any answer that does not conform to their pet ideology. Statements A to E describe cancer from the perspectives of different organizational levels: molecular, cellular, personal, familial, and environmental. A major achievement in cancer research is the introduction of a framework that accommodates phenomena in these levels and roughly explains their interrelationships. Its center of gravity lies on the molecular and cellular levels. Nevertheless, its explanations of how certain viruses, chemicals, and radiations contribute to cancer suggest links to environmental and social researches on people's exposure to these carcinogens.

Cancer research underscores the systematic approach that makes natural science and modern engineering so powerful. Faced with a complex phenomenon, scientists analyze or reduce it to components and simpler factors that can be investigated thoroughly, for instance analyzing cancer development into cellular dynamics and gene mutations. The fruitfulness of the reductive approach is apparent when one compares the abundant solid knowledge it yields to the empty rhetoric of mystical holism that insists all is a seamless web impervious to analysis.

To analyze, however, is not to analyze away. Reducing cancer to genes is not subscribing to a dogmatic reductionism that regards a patient as nothing but a bag of genes. Despite the success and glamour of genetics and molecular biology in disease research, few if any researcher would disagree with the editors of a recent segment on complex diseases in *Science*: "It's not just the genes."[7]

Holism that reviles analysis and reductionism that reviles synthesis are both detrimental to science, in which analysis and synthesis are complementary. For scientific research, reduction of a phenomenon into elements is incomplete if not followed by integration of relevant elements for the goal of explaining the original phenomenon. Socrates recommended the methods of division and collection. Galileo's methods were described as resolution and composition. Newton explained the effects of analysis and synthesis in scientific investigations. Descartes followed a similar vein and went further to combine analysis and synthesis as two steps of a single method.

Perhaps the most comprehensive articulation comes from engineers. In designing complex systems such airplanes, engineers must ensure the functions of the airplane as an integral whole and specify minute details of its ten thousand parts that must work together. To rationalize design processes, they have developed systems engineering, in which analysis and synthesis are graphically depicted as the letter "V." The downward stroke of the V represents the decomposition of a system into smaller and smaller parts and the upward stroke the assemblage of the parts into the system as a whole.[8]

The systems-engineering V model can be extrapolated to science. Twentieth century biology mainly follows the downward stroke as it anatomizes organisms into organs and cells and molecules. Now that molecular biology has completely cataloged the genes for human and many other species, biology is turning the corner of the V. Centers of systems biology, which begin to appear in Harvard and other places, turn to study how molecular dynamics contributes to life phenomena on higher levels. Let us look at how the V model fares in explaining cancer.

Is something wrong with the war on cancer?

"Beating cancer: the new frontier of molecular medicine," enthuses a cover story of *The Economist.* An opposite mood pervades a cover story of *Fortune,* "Why we're loosing the war on cancer."[9] Both articles appeared in 2004, thirty-three years after President Richard Nixon signed the National Cancer Act that declared "war on cancer." The difference between them would not be the last in a long line of controversies on cancer research that stretched back to the beginning of the war if not earlier. Undoubtedly all sides are united in their hope of beating cancer. They disagree, sometimes bitterly, on the manner in which the war is waged and the achievements so far. The debates involve many issues, including science under siege.[10] Here we will concentrate on problems regarding the levels of complexity, more specifically, how much scientific knowledge on the level of cancer genes contribute to needs on the level of health care.

Americans have poured roughly $200 billion, in inflation-adjusted dollars, into cancer research and cancer drug development between 1971 and 2004. Almost one-half of the bills went to several government agencies, the balance to philanthropies and pharmaceutical companies.[11] In comparison, the government put up about $ 3 billion, matched by a similar contribution from the private sector, for the thirteen-year-long human genome project. That research money bought duplicate catalogs of human genes. What has the much larger fund for cancer research bought?

In 1986, the director of National Cancer Institute predicted the eradication of cancer by 2000.[12] Reality was not anywhere close. In 2004, a new director envisioned "the elimination of the suffering and death due to cancer by 2015."[13] Critics deem such unbridled optimism irresponsible; unending rosy promises raise false hopes that turn into cruel disappointments for patients and their families. Sure, generous research funding has bought enormous knowledge about the biology of cancer. However, critics complain that this knowledge about mechanisms on the molecular and cellular levels has little practical impact. Few new cancer drugs have resulted, and drying pipelines hang like a stubborn black cloud over the pharmaceutical industry. On the level of human suffering and death, the 1.5 million papers on molecular cancer biology seem to contribute less than the campaign to dissuade people from smoking.

Cancer death rate in America, after climbing unrelentingly for a century, peaked in 1990. Since then it has dropped by 12 percent back to its level in 1960. It was a welcomed relief, but hardly a victory. The largest decline occurred in lung cancer, which was attributable less to breakthrough research than to decreasing prevalence of smoking among men. Furthermore, cancer still claimed 564 thousand American lives in 2004, which constituted 24 percent of deaths from all causes.[14]

The picture is a little different in the developing countries, where cancer death rate is lower but rising. Worldwide in 2000, cancer caused 6.7 million deaths or 12 percent of total. The World Health Organization estimated that if unchecked, annual global cancer deaths could rise to 15 million by 2020.[15]

Although cancer is an ancient disease that afflicts humans and other animals, its prominence in the Western world rose from the nineteenth century to become "a disease of civilization." There are several explanations of this. Cancer is primarily a disease of elders; its risk increases roughly as the fourth power of age. Thus it was less threatening when infectious diseases and grinding poverty killed before it could strike. Its turn came when gradual alleviation of harsh conditions lengthened life expectancy, first of the aristocracy then of the general population. A subtle and complex disease, it was difficult to diagnose. Identification of cases increased with development of microscopy and scientific knowledge. Case load itself also increased, less because of environmental pollutions than because of changes in diet and life style. An affluent diet rich in meat and refined carbohydrates is enjoyable but not always healthy, so is a comfortable life spared of physical exertion. Widespread tobacco usage is the worse scourge. These demographic and life-style trends are being repeated in the developing world. The "disease of civilization" is spreading.

Not all is grim, however. Much could be done to stem the trend, although it would not be easy. The World Health Organization stated: "World Cancer Report provides clear evidence that action on smoking, diet and infections can prevent one third of cancers, another third can be cured." Is this cautious optimism warranted?

Causes of cancer at the personal level

Cancer is a group of diseases characterized by unregulated division and spread of cells. The cancerous cells may occur in liquids, as in leukemia. Most, however, occur in solid tumors that originally appear in various tissues in various parts of the body. By their original locations they are classified into various types of cancer, such as lung, colon, breast, or prostate cancer. Localized tumors can be removed by surgery or irradiation with high survival rates. As cancer progresses, however, it metastasizes – invading the surrounding tissues, entering the blood stream, spreading and establishing colonies in distant parts of the body. Only a third of patients with metastasized cancer survive more than five years. Invasive distensions spreading crab-like from a tumor in the breast were described by Hippocrates. From the crab, *karkinos* in Greek and *cancer* in Latin, came the name of the disease and the name of its inducing agents, carcinogens.[16]

What cause cancer? A complex event usually involves many causal factors, which in turn are causally linked to other factors. In talking about cause and effect, we customarily designate as its cause one or a few salient factors most directly connected to its salient effects, noting a few other factors as indirect causes, relegating many factors as background conditions, and ignoring factors too vague to determine. For example, when arson investigators decide that a fire was caused by sparks from an exposed electric wire, they treat as background conditions the presence of oxygen and flammable materials nearby. What made the wire exposed they regard as indirect causes, which may interest criminal investigators. Saliency and relevancy are context dependent.

In cancer research, two scientific approaches operate in two general kinds of context. Epidemiology focuses on causal factors on the levels of people and population, with results that are more useful for disease prevention. Molecular cell biology focuses on causal mechanisms on the levels of genes and cells, with results that are more useful to treatment and cure. To biologists, factors identified by epidemiology are indirect causes in the mechanism of cancer development. For most people, however, these factors are the only cancer causes that they care about; they can do something about them.[17]

Back in 1775, a London physician, noticing that boys who worked as chimney sweeps were more prone than average to develop cancer later in life, surmised that the disease was provoked by soot particles. Astute clinical observations such as this provide clues to cancer-inducing conditions. However, case reports alone are seldom sufficient in establishing causation; they cannot tease apart tangling factors to pinpoint causes.

For stronger evidence of causal associations, epidemiologists design careful studies to eliminate biases and zero in on crucial factors. Such projects often take a long time and involve many subjects. A famous study that started in 1951 questioned some 40,000 British physicians about their ages and smoking histories. Then it followed them for more than two decades, recorded their changing smoking habits and health conditions, and calculated statistical correlations between the number of cigarettes smoked and lung cancer incidences. This and other epidemiological studies succeeded to defeat the tobacco industry and establish a strong causal association between smoking and lung cancer.[18]

To evaluate the causal consequences of a particular factor, epidemiologists often compare groups whose members are as similar in everything else as possible. For instance, patterns of cancer incidences vary greatly across countries. Natives of Japan had high rates of stomach but low rates of colon cancer. Natives of Hawaii had high rates of colon but low rates of stomach cancer. Was the difference caused mainly by genetic or cultural factors? The second generation of Japanese immigrants in Hawaii exhibited the cancer pattern not of their ancestors but of native Hawaiians. Such studies of immigrants reveal that most variations in cancer patterns are not inherited.

Only about one percent of cancers are unmistakably inherited. They occur in childhood.[19] Strong genetic dispositions contribute to a small portion of adult cancers, (see statement D earlier in the chapter). Hormone production during reproductive cycles and other internal factors can also contribute. However, the vast majority of cancers are attributable to what people eat and inhale, how they behave, their working conditions, viruses and bacteria, and natural and artificial radiation and chemicals, (see statements C and E).[20] These are usually called “environmental” risk factors for cancer.

This usage of “environment,” which includes diet, life style, and personal behavior, is unfortunate. It deviates from common meaning of the word and is easily abused, leading to much confusion. A government report, after carefully explaining the broad meaning of “environment,” goes on: “Unfortunately, the statements [that 60 to 90 percent of cancer is associated with the environment and therefore is theoretically preventable] were sometimes

repeated with 'environment' used to mean only air, water, and soil pollution."[21] Confusion and abuse of scientific results persist.[22]

Epidemiology identifies risk factors and establishes causal associations but cannot pin down the mechanisms by which risk factors induce the appearance of tumors. Discovering mechanisms is the font of laboratory science, which delves into more microscopic levels. Nevertheless, epidemiological results do expose salient peculiarities that must be explained by whatever mechanism. Unlike poisons that act quickly, carcinogens take effect very slowly. Hiroshima survivors developed cancer ten years after their brief exposure to intense radiation of the atomic bomb. Lung cancer incidences rose more than two decades after the widespread of smoking. The long latent periods accede to cancer being a disease of elders; it takes so long to develop. But what mechanisms proceed so leisurely? And why do they act so unevenly? Why does cancer develop only in a small portion of smokers?

Heritable cancer genes

Cellular biologists had identified cancer with abnormal cell growth in the mid nineteenth century. They observed in 1914 that cancer cells contain irregular number of chromosomes, which indicates genetic aberrancy. With biochemistry and molecular biology, they analyzed the cell into its constituent pathways and chromosomes into genes to isolate the sources of abnormality. The mystery of cancer began to unravel in 1976, when investigators of tumor-inducing virus stumbled on oncogenes (from Greek *ogkos*, lump), genes that play major roles in cancer development. Genetic engineering, which came on line around that time, gave cancer research a big boost. Many more oncogenes were discovered and their functions illuminated in the last quarter of the twentieth century. A picture emerged depicting cancer as essentially a genetic disease – genetic mainly on the level of cells rather than organisms.[23]

Human beings and other animals have two kinds of cells: germ cells and somatic cells. A germ cell, an egg or a sperm, contains only one copy of each chromosome. Specialized to sexual reproduction, germ cells are responsible for genetics on the level of organisms, in which parents transmit their genes to their offspring. Two germ cells combine to form a fertilized egg, from which spring some ten trillion cells of an adult human. Each of these somatic cells contains the same genes as the fertilized egg, including any defective genes.

Inherited genetic defects account for some rare childhood cancers. They also predispose carriers to some common adult cancers so that the disease develops much earlier in life. Strengths of predisposition vary from gene to gene. Mutations of the genes *BRCA1* and *BRCA2*, for example, are strongly predisposing. Women who inherited them have about 80 percent life-time risk of developing breast cancer, an eightfold increase over breast cancer risk in the general population. Such strong genes are rare. More numerous are weak genes, inherited mutations each having a small effect but combined wield significant predisposition. Strong and weak, inherited mutations together accounted for 5-10 percent of breast cancers.[24]

Variations in genetic predisposition partly explain why some people are more susceptible than others are to a particular environmental carcinogen. Many genes involved are not cancer genes;

they do not themselves induce cancer. Rather, they code for enzymes with vital normal functions, mainly to metabolize chemicals, breaking them down for excretion. These normal processes detoxify many chemicals to protect the body. In metabolizing some chemicals, however, they produce other chemicals that may damage DNA and induce cancer. Some of these genes assume different forms in different people, resulting in different rates of metabolizing various chemicals. A raised metabolic rate may decrease or increase the caner risk of a chemical to which one is exposed, depending on whether the chemical itself or its metabolic product is carcinogenic. The study of how genetic and environmental factors interact in cancer risks is becoming a fast growing science, molecular epidemiology.[25]

The selfish cell and its genes

Cancers that are not inherited are called "sporadic." This means not that they have no genetic component but that their genetics occurs not in germ cells but in somatic cells, which constitute the bulk of our body. Some somatic cells, such as muscle cells or neurons in the brain, stop dividing upon maturity. They can grow bigger in size or establish more connections, but their numbers do not multiply. Cancer seldom if ever appears in such non-dividing cells. It appears in tissues where cells die and are replenished by new cell divisions.[26]

Cell division is a genetic process in which a cell passes its genes onto two daughter cells, each of which is a clone or exact of itself, unless accidents occur. Accidents are rare but not impossible. The genes in a cell may have suffered a mutation, or some mistakes may occur in DNA replication and recombination during cell division. Most mutations or mishaps are deleterious and are promptly eliminated with demise of the cell. One rare occasion, however, a genetic mutation confers a survival advantage to a somatic cell. Then the cell prospers and proliferates, happily passing the beneficial gene to its progenies. If luck has it that a second beneficial mutation renders one of the progenies even more competitive, then it would multiply and amplify the mutated gene. Cycles of random mutations followed by survival of the fittest are the essence of Darwinian evolution. In evolution on the cellular level cancer originates. The mutated genes that enable cells to proliferate abnormally are called oncogenes, cancer genes.[27]

For somatic cells, cancerous growth represents the consummate Darwinian ideal of passing one's genes to as many progenies as possible. Sure, cancer kills the organism, but possibilities for somatic cells are bound by an organism's lifespan anyway. Cancerous cells are making the best of their possibilities.

On the level of organisms, however, the cancerous ideal is selfish and subversive. Equipped with germ cells to produce younger generations, organisms have much more opportunity and longer time to evolve countermeasures. Our bodies are equipped with many mechanisms that regulate cell division and suppress insurgency. To overcome these hurdles, somatic cells require four to seven genetic events to become fully malignant.

The multi-stage process of cancer progression explains its long latent period. Exposure to strong radiation may initiate the process by inducing mutations to create an oncogene. One oncogene alone is unable to turn a cell cancerous. It needs cooperation of other oncogenes. Additional

mutations to create more oncogenes take years and much luck to accumulate. Multi-stage cancer progression also explains why an inherited oncogene is a contribution rather than the cause of cancer. Having an oncogene at birth gives cancer progression a head start, resulting in early disease onset. However, cancer still requires extra genetic mutations.

Cancer researchers have succeeded in identifying many cancer genes and explaining how the proteins they encode malfunction in various biochemical pathways that regulate cell division. New challenges lie in using this knowledge for medial purposes: to develop effective preventive regimes, to devise means for detecting tumors in their early stages of progression, and to design drugs that target specific malfunctions to retard if not cure cancer.

Oncogenes and the cell's revolt against the body

Exceptions accentuate the rule. The aberrant growth of cancerous cells accentuates the meticulous restrictions for normal growth. Growth here refers mainly to *clonal growth*; the crux is not that a cell grows larger but that the number of its clones produced by cell divisions grows. A normal cell has many genes for regulating cell division. Among them are growth stimulators for approving division only under appropriate conditions, tumor suppressors for triggering suicide for abnormal cells, and caretakers for quality control in genetic duplication. The functions of all three classes of genes are susceptible to disruption, by mutation or epigenetic means. These disruptions are beneficial to their host somatic cell, which gains an evolutionary edge to proliferate, but detrimental to their host organism, which takes a step towards cancer.

Cells live in a community that is an organism's body, where they signal each other on the necessity to grow. Normally, a cell divides only in response to appropriate signals from the body. To receive these signals and process them in several regulatory pathways are jobs of proteins coded by growth stimulating genes. Cancer researchers, who like automotive metaphors, compare growth-stimulating genes to the accelerator pedal of a car that is the somatic cell. They enable the body to control the cell's division, just as the accelerator enables a driver to control the car's speed. Growth stimulating genes evolved very early in natural history, because their functions are vital to growth and survival of organisms.

Unfortunately, for organisms, some mutations can turn them into oncogenes. Oncogenes are heroes in their host somatic cell; they emancipate it from communal restriction and make it self sufficient to divide without any external growth signal. Oncogenes are like an accelerator stuck to the floor, enabling the car to speed ahead freely but endangering the car's environment.

Knowledge about their functions suggests a way to rescue the organism: to unstuck the accelerator; to inhibit specific growth proteins rendered overactive by oncogenes. This is the targeted-drug philosophy behind Gleevec for treating a form of leukemia and Iressa for lung cancer.

Mutant growth stimulating genes are the original oncogenes. They were first to be discovered. During the following decade, scientists realized that these genes are not sufficient for cancer. Like a car equipped with brakes, our body is equipped with tumor suppressor genes, the first of

which was discovered in 1986. Proteins coded by tumor suppressor genes perform several crucial functions. They inhibit growth by switching cells into a quiescent state. They survey conditions inside a cell and out, and upon detecting abnormalities, they trigger the ultimate safety measure hardwired into each cell: the sequence to self destruct. Tumor suppressor genes are like gatekeepers staffing checkpoints on the road to cancer. As long as they work properly, no cell can pass.

To the triumph of somatic cells and defeat of organisms, tumor suppressors are vulnerable to debilitating mutations and epigenetic suppression. When their functions fail, a cell gains full freedom to multiply. The tumor suppressor gene *p53*, which some scientists call "the hub of cancer pathways," is mutated or deactivated in most human tumors.

Fortunately for organisms, the failure of tumor suppressors is not irremediable. The body has evolved many redundant pathways. To discover alternative pathways and activate them by drugs or other means are active topics in cancer research. The cancer drug Taxol, for instance, activates an alternative pathway that bypasses the debilitated *p53* to trigger suicide for the cancer cell.

Whenever a cell divides, its DNA duplicates. Every second in an adult human body, about 100,000 cells divide to compensate for roughly 100,000 cell deaths. During an average human lifetime, more than 10^{15} cell divisions occur. Despite the large number of DNA duplications, mutations are uncommon. This may be surprising because DNA duplication is a complex process occurring not in a clean room but in a chemical factory that is the body. Many chemicals can interact with DNA and damage it. Most carcinogens are generated inside the body, for instance oxidants, byproducts of normal metabolism of food. To help organisms survive such molecular vulnerability, elaborate DNA repair mechanisms have evolved. We have many "caretaker" genes. Some of their proteins repair DNA damages and others correct mistakes that occur in normal cell division, thus minimizing genetic changes.

When caretaker proteins are unavailable or unable to perform their maintenance jobs properly, other mutations are more likely to occur. The resulting genetic instability is conducive to cancer development. *BRCA1* and *BRCA2* are caretakers. Their mutations greatly increase the risks of their carriers in developing breast and ovarian cancers. Genetic instability explains chromosome anomalies and the large number of mutations observed in cancerous cells. It also poses a great obstacle to drug therapy. When a drug successfully kills certain mutant cells, varied and rapid mutations can produce new variants that are resistant to it. This happens to Gleevec, the first and most famous of rationally designed cancer drugs; acute cancer patients develop resistance to it after several months.[28]

Genetics and epigenetics

In inducing cancer, growth-stimulating genes gain extra functions, while tumor suppressing and caretaking genes lose normal functions. To lose functions, a gene need not be mutated. Only its expression need be suppressed, so that it does not make the proteins necessary for healthy cell functions. In fact, a significant portion of tumor suppressor and caretaker genes malfunction in

cancer cells because they are silenced in epigenesis, in which patterns of gene expression are passed onto descendent cells without mutation in genes. It is as if the selfish cell acquires heritable ability to gag dissident genes unfavorable to its proliferation.[29]

The importance of epigenesis in cancer shows that contrary to popular portrayal, genes do not control everything. Genes are crucial to biochemical pathways in two ways. They provide the templates for proteins that work in the pathways, and they specify the regulatory sites for switching on the templates. However, just as Detroit turns out cars but does not control the dynamic of traffic, genes do not control the dynamics of biochemical pathways vital to life. Dynamic of gene expression – when a gene is switched on to make proteins – is regulated by cellular and extracellular conditions. In short, controls run both ways, from genes up and from body physiology down.[30]

Preponderant attention to genetics is the characteristic of cancer research in the past three decades. Researchers have identified almost three hundred cancer genes, 90 percent of which are products of somatic mutations. Cancer genes already exceed one percent of the human genome. More are expected to be discovered in the rapid advancement of genomics.[31] With the catalog of cancer genes, researchers have analyzed cancer to its basic level. They know, however, that it is far from sufficient to understanding cancer, not to mention finding cures for it. Cancer is essentially, but not merely, a genetic disease.

From cells to tissues and organs

Douglas Hanahan and Robert Weinberg remarked that hitherto, cancer research has been guided by a reductionist focus on individual cell and its genetic and biochemical components. It had been a gold mine, but the veins are being exhausted. Among the six hallmarks of cancer that they identified, at least two require researchers to proceed beyond the reductionist focus and encompass higher-level organizations and phenomena. "Looking forward in time, we believe that important new inroads will come from regarding tumors as complex tissues in which mutant cancer cells have conscripted and subverted normal cells to serve as active collaborators in their neoplastic agenda."[32] From cancer genes to selfish cells to tumor tissues, cancer research is turning from downward analysis to upward synthesis.

A car with its accelerator floored and brakes disabled zooms ahead, but it would not go far if it cannot find a gas station. Just as cars need gasoline, cells need oxygen and other nutrients. To obtain them, a cell has to be located within 200 micrometer of a capillary blood vessel, beyond which oxygen cannot reach by diffusion. At first, multiplying tumor cells can rely on the blood vessels already in place. If a tumor is to grow beyond a few cubic millimeters, however, its increasing demand on nutrients require fresh supply from a new network of blood vessels. Growth of new blood vessels – angiogenesis – is a strictly controlled process regulated by the balance of inhibitory and stimulatory factors in a tissue. A tumor must develop the capability to subvert the regulation and recruit blood vessels to grow in its midst. Tumors that have acquired capability grow fast; those that do not stagnate in their tiny sizes. The importance of angiogenesis for cancer progression was articulated in the early 1970s, but interest in it grew

slowly. Not until 2004 was the first anti-angiogenesis drug, Avastin, approved for treating colorectal cancer.[33]

Like a car in a parking garage, normal cells are confined to their locality by intercellular matrices, neighboring tissues, and basement membranes. The most deadly ability of cancer cells is to break free from local confinement and spread to distant tissues and different organs, to metastasize. To escape from the primary tumor, cancer cells secret enzymes that dissolve surrounding matrices and obstructing membranes, until they make their way into the blood stream.

Like seeds dropped into a river, vagrant cells in the blood stream disperse. The majority conform to blood flow patterns that sweep them to arresting sites, where they dig out of the blood vessel and find themselves in tissues of foreign organs. About a third, however, buck the flow patterns and home in on specific soils favorable for their growth, as breast and colon cancer cells spread to bones. How these cells find their destinations is mostly a mystery. However, scientists agree that cancer cells do not make it alone but are aided by their surroundings. The conspiracy includes signals from distant organs that beckon cancer cells.[34]

Despite the turbulence of blood flow, the voyage to outposts is the easy part of metastasis. Over eighty percent of blood-born cells make it. Then hard trails begin. Even in ideal destinations that issue welcoming signals, they are still aliens. Only a few percent of the landed cells succeed to divide and form microscopic colonies. And only one in a hundred of these succeeds to recruit new blood vassals and grows into a metastatic tumor. The processes may take years and even decades. Metastasis sometime break out decades after the primary tumor was successfully removed.

Metastasis is responsible for about 90 percent of cancer deaths. However, its mechanisms remain largely unknown, partly because most researchers ignored them. Less than one in two hundred grants from the National Cancer Institute over the past three decades focused on metastasis.[35] It did not fit into the dominant research paradigm. Metastasis, which involves organs in various part of the body, necessarily lies beyond the reductionist focus on cells and their genes. Integrative processes break fresh ground and are much more difficult to study than mopping up details of cancer genetics. But they are also much more important.

As scientists begin to realize the limits of reductionism, research trends show signs of turning, albeit slowly. Metastasis and other cancer biological processes above the level of genetics are beginning to attract more attention. Hanahan and Weinberg call for a more synthetic approach for future cancer research. Bert Vogelstein and Kenneth Kinzler, predicting information overload and confusion brought by surefire advancements in molecular genetics, remark that "cancer biology has not kept up with cancer molecular genetics and new biological systems are needed to separate wheat and chaff."[36]

Molecular genetics and cancer biology, Vogelstein and Kinzler add, are only the first two challenges for cancer researchers. "The third challenge, involving practical benefits to patients, will be much more difficult to meet." The patient, a whole organism, exists on a higher level of complexity than tissues and organs.

The ultimate level: cancer patients

Cancer scientists often emphasize that theirs is basic research aiming to understand the biology of cancer. Basic science is important, but it usually does not consume large resources. The 2004 research budget for the entire U.S. National Science Foundation was $ 4.2 billion, which supported researches in mathematics, physics, chemistry, biology, engineering and computer sciences, and more. That same year the National Institute of Health spent $ 4.7 billion on cancer research alone.[37] This disproportionate extravagance can hardly be justified by cancer knowledge for knowledge's sake. More than thirty years after the National Cancer Act started pouring money into cancer research, taxpayers are justifiably impatient for practical results. Scientific knowledge has undoubtedly improved prevention, diagnosis, and treatment. However, the benefits fall short of expectations. Some disappointed scientists and physicians wonder if cancer research, spoiled by generous support, has fall into groupthink and become an academic game detached from medical reality.[38]

Each of more than a hundred types of cancer is a tremendously complex disease, if only because it involves so many genetic anomalies at once. In their fight against it, scientists are hamstrung by methodologies. Some restrictions can be circumvented by abolishing innovation-stifling ideologies. Other restrictions, however, are necessary; scientists cannot experiment on humans for good reasons. In compliance with ethical restrictions, cancer experiments usually adopt two approaches, both proved invaluable in acquiring basic knowledge but defective when applied to drug discovery.

The first approach uses human cell lines cultured in petri dishes. Scientists expose cells with known characteristics to various carcinogens or potential drugs, observe their responses, and analyze their genetic and biochemical changes. This method, which enforces the reductionist focus on cells and their components, discourages study of higher-level phenomena such as angiogenesis. Furthermore, it does not yield consistent results in drug screening; cells in a dish do not behave the same as cells in a body.[39]

A powerful approach employs laboratory animals as models for human diseases. The mouse is a favorite; it is easy to manipulate and its genetic and physiological systems are similar to that of humans. Researchers play all kinds of trick on the mouse by sophisticated genetic engineering. They suppress its immune system so that it accepts transplants of human tumor, on which effectiveness of candidate drugs can be tested. They switch a specific cancer gene on or off, for instance knocking in a growth stimulating gene or knocking out a tumor suppressing gene. When is a tumor is thus induced, they analyze it or test drugs designed to target certain defective steps in the regulatory pathway controlled by the mutant gene.

Mouse models have yielded many secrets of cancer biology and many cancer cures – cures for mice. The transplanted tumor may be human and an engineered mouse gene may be identical to the human gene, but the mouse as a whole is very different from a human being. Consequently results obtained on mice are notoriously unreliable when applied to people. Few new cancer drugs flowed from this pipeline, and they are only marginally better than existing ones. Scientists are striving to improve mouse models by "humanizing" the mouse genome. It remains

to be seen how much the mouse can be engineered to provide a good representation of human diseases.[40]

Cancer prevention and detection

More than cures, scientists are cautiously optimistic about the possibility of improving early detection and prevention of cancer. Cancer takes several steps and a long time to develop. Its long latent period gives many opportunities to catch cells in their early stages of mutation and intervene to stop cancer progression. For instance, the pap smear followed by surgical removal of detected lesions have reduced death rate of cervical cancer by almost 80 percent.

To extend the success in cervical cancer to cancer in general, scientists strive to identify biological markers that can finger incipient cancerous cells and predict whether they will evolve to significant cancer. They hope to develop noninvasive and inexpensive ways to screen for these markers in cells or body fluids that a person discharges. Novel imaging techniques will locate the cancerous lesions in the body, so that they will be removed before metastasis. Or drugs targeted at specific regulatory defects will be developed that, if not curing cancer, would push its onset to beyond person's natural life span. These are tall order, but properly synthesized, knowledge on the molecular and cellular level can contribute to preventing a person from becoming a patient.[41]

A fashionable vision in the genomic era is drugs customized to specific groups of people with certain genetic dispositions. It is especially pertinent to cancer, where genetic dispositions play heavy roles and a drug is frequently effective only in a subset of patients. Instead of treating a common cancer such as breast cancer as a single disease, why not divide it into twenty diseases according to their different genetic defects, design drugs for each, and prescribe them to target patients identified by genetic tests? It sounds great, until one considers the costs of drug development. Pharmaceutical firms are counting on large markets to recover the exorbitantly high costs of drug discovery. Already, orphan diseases with few patients and third-world diseases such as malaria for which patients are too poor to pay must depend on public or philanthropic support for drug research. Will the fine subdivision of a common cancer turn it into a bunch of orphan diseases? Who is willing to fund drug research for them? Will the resultant drugs, if they appear, be so expensive that only the richest can afford? We land on problems of a higher socioeconomic level.

From environmental conditions that can induce cancer, scientists have successfully analyzed the disease into its molecular components. More difficultly, they are synthesizing knowledge to alleviate patient suffering and address environmental problems. From the top to the bottom and back, with numerous detours and backtracks, the complex journey belies simplistic ideologies such as holism and reductionism.

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