Harnessing New Technologies for the 21st Century

Malcolm Gillis

The 20th century was a very good one for economic growth in the United States: Real GNP in 1999 was more than twenty times that of 1900. Replicating this performance—much less improving upon it—in the 21st century will not be easy. Science-based industry played a crucial part in 20th century economic expansion. This was most obviously so in the case of the chemical industry, the first major science-based industry to arise in the United States. Development of that industry helped accelerate growth in dozens of others, including oil and gas refining, pulp and paper, textiles, building materials, and, of course, pharmaceuticals.

If 21st century growth rates are to approach those of the past century, new science-based industries will have to play roles comparable with the chemical industry after 1900. Some of these are already appearing on the scene as infant industries. David Baltimore, Nobel laureate, now president of California Institute of Technology, correctly asserts that biotechnology is one of these infant industries.[1] The term *infant*, as applied to this industry, does not necessarily mean small; rather, it means that the young biotechnology industry today is not nearly as large or as pivotal as it is going to be within a few years.

Up until now, the principal application of the biotechnology industry has been in the development of drugs for the pharmaceutical industry. Credible estimates are that drugs and vaccines developed through biotechnology have already benefited more than 250 million people.[2]

Perhaps this is one reason why some tend to view the biotechnology industry as almost indistinguishable from the pharmaceutical industry, which itself accounted in 1997 for 1.2 percent of GDP.[3] Indeed, in an influential article as late as 1999, the biotechnology industry was defined essentially as a subsection of pharmaceuticals, specifically as "an industry that uses biotechnology to produce drugs or diagnostics previously unobtainable."[4] We will see that this definition no longer suffices.

Earlier presentations by Darby and Lichtenberg will have provided a comprehensive sketch of the macro importance of biotechnology. Here, I merely note that by the mid-'90s, the sales volume of the pharmaceutical industry was probably about fifteen times that of the biotech industry.[5] Sales of pharmaceuticals will doubtless grow apace, especially with the progressive graying of our population.[6] Sales of the now infant biotech industry, though, will surely grow even faster over the next two decades, as biotechnology applications extend further beyond pharmaceuticals, to the commonplace manipulation of DNA, proteins, and cells in fields ranging from agriculture, nutrition, and energy production to tissue engineering and, of course, gene therapy. Clearly, biotechnology will be an industry serving a very large market beyond that for drugs. For example, the near-term worldwide market for tissue engineering products has been estimated to be as high as $350 billion per year.[7] Moreover, the future flowering of biotechnology will not be limited only to advances in biosciences. Progress in biotechnology turns out to be no less dependent upon advances in information technology and nanotechnology. If I succeed today only in portraying the growing linkages between biotechnology, information technology, and nanotechnology, I will consider it a very good day's work. I have enlisted in my cause the testimony of several Nobel laureates, not only in medicine but also in economics.

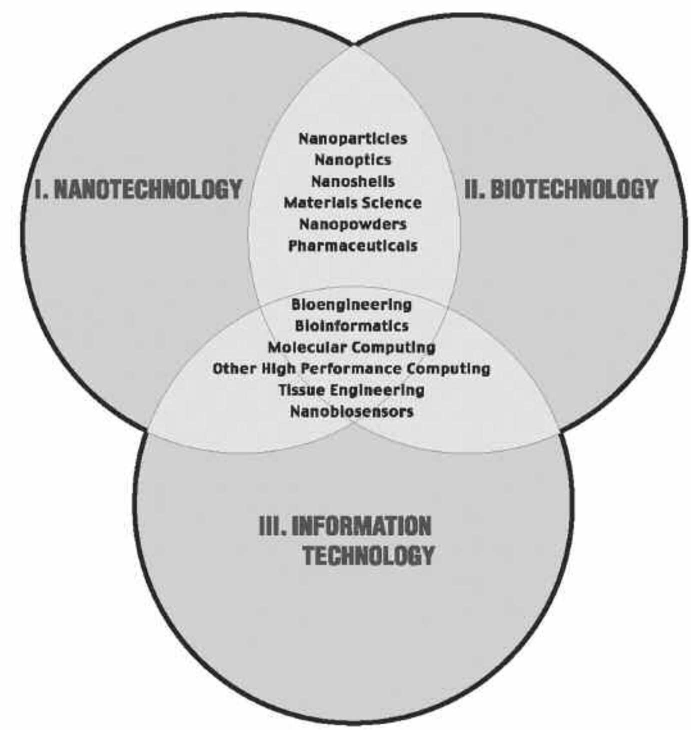
My remarks do not purport to cover all subfields of biotechnology but primarily the biotechnology I know best: that found today among Rice faculty and their research partners of the Texas Medical Center, just across the street. Necessarily, then, my comments are focused somewhat more on the longer-term societal payoffs from activity in research labs than upon near-term market prospects.

BIOTECHNOLOGY, INFORMATION TECHNOLOGY, AND NANOTECHNOLOGY

Pity those poor economists who will be specializing in national income accounting in the decades to come. In attributing economic activity to distinct sectors, how will they distinguish output in biotechnology from that in information technology and nanotechnology? To be sure, in 2050 we will still find individuals identifying themselves as biologists or information scientists or nanotechnologists. The economists could ask those people. But would those scientists be able to draw clear dividing lines for the economists? Probably not, because these rapidly evolving fields are becoming ever more closely linked. Not only that, but the nature of the linkages among the three is itself evolving rapidly. Figure 1 represents an attempt to depict intersections between them. The chart was probably obsolete by the time it was constructed in March.

The potential role of these technologies in reshaping our economy and society cannot be understood by examining each in isolation. We know quite

Figure 1
Linkages Between Key Technologies in Science and Engineering



well from the past two centuries of American economic history that technology-driven economic progress is almost never the result of a single invention or even a single set of technologies. Rather, rapid economic growth has generally been the outcome of the interplay between a collection of largely unanticipated discoveries, clumping and clustering in very different fields, not over months or years but usually decades. To illustrate: The economic progress often attributed to the steam engine unfolded over at least a century and a half after Watt. For example, in the United States even sixty-five years after Watt patented the steam engine—as you know, he did not discover it—almost all manufacturing was powered by water.[8] The steam engine began to yield truly revolutionary change only in the 19th century, when it was modified for use in transportation and in the textile industry's power looms. Watt's legacy was vastly magnified by the invention of the dynamo, pioneered by Faraday and Wheatstone and perfected by Edison in 1878. Even so, as late as 1940 electricity had not reached large swathes of the rural south in the United States. Herbert Simon, another Nobel laureate,[9] was clearly right on the mark in postulating that the ramifications of any one technological innovation depend greatly upon the stimulation it provides to and receives from other, often quite independent, innovations.

Biotechnology Generally

Yet another Nobel laureate, economist–historian Robert Fogel,[10] published a series of papers in the '80s and '90s showing vividly the remarkable extent to which investments in biomedical research made seventy-five and a hundred years ago are still paying off handsomely today, in affecting how well we live and how long we live. More recently, the distinguished economist William Nordhaus has suggested that the medical revolution qualifies, on economic grounds alone, as the "greatest benefit to mankind." He has estimated that the heretofore unmeasured value of "health income" (the value not captured in the national income accounts) attributable to increases in longevity in the last hundred years is nearly as large as the value of measured income attributable to nonhealth goods and services.[11] Others offer findings paralleling those of Nordhaus. Lichtenberg estimates that just between 1960 and 1997, life expectancy at birth increased by about 10 percent, to 76.5 years,[12] attributable primarily to both medical innovation and rising expenditures—especially public spending—in medical care. The conclusions of Fogel, Nordhaus, and Lichtenberg are reinforced by research from a growing body of economists (Mark McClellan, David Cutler, Elizabeth Richardson among others) working in new traditions of analysis of health economics.[13] As impressive as were the gains of the past, tomorrow's biotechnology holds out the promise of benefits that could make those of the last century appear pale in comparison.

Only thirteen years have passed since scientist W. French Anderson fired the biotech shot heard around the world by administering the first artificial gene to cure a hereditary illness. Since then we have learned more about the workings of human genes than in the entire half century following the 1953 discovery of the double helix by two modern counterparts of Prometheus, Watson and Crick. As a result, biology has been transformed from a discipline centering upon the passive study of life to one allowing the active alteration of life almost at will. Virtually all the molecular rungs on the chemical ladders of the human genome have been identified, providing us with an almost complete parts list for a human. As David Baltimore says, "Now we can discover all the secrets of nature."[14]

The theoretical understanding developed in genetics and clinical advances in gene therapy over the past fifty years bid fair to render commonplace medical applications that were once viewed as unthinkable. This new world of possibilities arises from the joining of the insights of the geneticist with advanced tools of information and computational science and the rapidly growing skills of biomedical engineers and nanotechnologists.

The promise of biotechnology is, however, not at all unalloyed: The possible blessings are very obvious, while the potential banes are not.[15] Moreover, there is the possibility that both our expectations and our worries over the biotech revolution have been overinflated. Knowing all the secrets of nature could bring utopia, but it could also usher in a nightmare world resembling that limned in Aldous Huxley's remarkably prescient book *Brave New World*, published seventy years ago. That world boasted some innovations already here and one we still lack: genetic engineering of humans *in vitro*, powerful mood-altering pharmaceuticals, and body implants to complement "feelies," the ultimate in participatory entertainment. All of these wonders were developed to assure human happiness. But Huxley's totally homogenized world could hardly be either brave or happy, for it allowed no scope at all for the exercise of human choice or respect for fundamental human values. Huxley's world has yet to encroach much on ours, but at the very least, it stands as an unsettling reminder that today's biotechnology involves ethical thickets and moral issues that society has only just begun to plumb, much less resolve.[16] When, for example, does gene therapy spill over into eugenics? To what extent will the accumulation of genetic information stigmatize affected people?

The Biotechnology–Information Technology Interface

Mathematical, statistical, and computer methods have become indispensable in the analysis of biological, biochemical, and biophysical data. Moreover, the interactions also work in reverse: A growing number of projects in computational science are being driven by biological problems. No less a scientist than David Baltimore flatly asserts: "Biology is today an information science."[17] He goes on to note that "the human genome, as it might be recorded in a web site, is a string of three billion units over four letters.... Only computers can store such data, only mathematicians can understand how to take sequenced DNA fragments and put them together in appropriate order."[18] Indeed, the human genome has been reconstituted perhaps as much by advanced computational technology as in wet labs.

The field of bioinformatics weaves together biology and information science. Although the early commercial promise of bioinformatics, like that of the Internet, has thus far proven to have been oversold, this should not obscure the fact that bioinformatics is beginning to usher in another technological revolution. Whereas classical medical research depended to a great extent upon trial and error, the discipline of bioinformatics allows research to be based upon information about networks of molecular interaction that control diseased, as well as normal, life.

The emergence of bioinformatics is merely the latest testament to the fruitfulness of university-based research in drawing together several disciplines to work on vital questions. Arguably, the most fundamental advances in biomedicine have come from advances in basic sciences in the academy. Virtually all the stunning advances in diagnostic and therapeutic tools of recent years were based on discoveries from the one place where one finds critical masses of questing physicists, biologists, chemists, mathematicians, engineers, and computer scientists, as well as clinicians: the research university.

Directly from physics came magnetic resonance imaging and laser surgery. From chemistry sprang fullerenes, first discovered at Rice University in 1985, as well as a host of pharmaceuticals. From mechanical engineering came robotics used in surgery. New insights from researchers in computer science and applied mathematics led to groundbreaking work in tomography, genomics, and now, proteomics.[19] The interrelationships between biomedicine and information sciences can be seen to be especially strong in the area of medical imaging. At Rice, at least a half dozen of our computational and mathematical scientists are involved in joint work in medical imaging with physicians from the Texas Medical Center.

Several subfields in bioinformatics are moving ahead at high speed. Computational physiology is one of these. The virtual heart is a very good example: A union of form and function on a computer screen, this heart is the result of the translation of thousands of mathematical equations and data points into a computer simulation. *The Economist* calls this a spectacular example of *in silico* biology that brings computing power to bear on a much wider range of biological problems from proteomic analysis to the re-creation of neural networks.[20]

Another new direction in the bio–info interface lies in computational cancer research. Clinicians at M.D. Anderson Cancer Center stress that cancer is not a hundred different diseases, but thousands of different diseases. At least five mutations may be required to create a cancer cell, each drawn from a repertoire of several hundred genes. Thus it is apparent that there is an overwhelming number of possible combinations and permutations of cancer-causing mutations.[21] This is exactly the type of problem that can be addressed only by biomathematicians, computational scientists, and biostaticians—that is to say, those in bioinformatics.

Finally, it is to be emphasized that new disciplines at the intersection of biotechnology and information technology have ample applicability to the mainstay of 20th century biotechnology: new pharmaceutical products. The difference is that for the 21st century, more and more pharmaceutical innovations will be IT-based.

The fusion of computational sciences with biochemistry and pharmacology has already given birth to the new discipline of pharmacogenomics, which promises to allow the personalization of much of medicine. This new field will augment and perhaps eventually replace traditional therapy based on the premise that "one drug fits all."

Pharmacogenomics, like its predecessor pharmacogenetics, deals with the genetic basis underlying variable drug response in different individuals. Pharmacogenetics also relies on the study of sequence variations in genes thought to affect drug response. But pharmacogenomics goes further: It looks at the entire genome, enabling not only the identification of variant genes governing different drug responses across patients but also identifying genes that affect susceptibility to disease. Thus, pharmacogenomics may allow new insights into disease prevention as well as individualized application of drug therapy.[22]

For this promise to be realized, scientists must understand fully not only the genome but the proteome as well. That requires the development of increasingly more sophisticated and powerful computational methods. The Gulf Coast Consortium for Bioinformatics, embracing Rice and six other institutional members in Houston and Galveston, is one of the venues where such computational approaches to drug design are beginning to blossom. There, researchers are developing powerful new tools for use in computer-aided design of drugs.[23] Interdisciplinary approaches at the consortium have been very fruitful. Robotic path planning, developed in engineering, has been applied to modeling biomolecular interactions to help solve problems in drug design.

The Biotechnology–Nanotechnology Interface

Nano is derived from the Greek word for dwarf. Nanotechnology is the application of findings of the highly interdisciplinary field of nanoscale science, which deals with objects as small as one billionth of a meter: a nanometer. Nanotechnology refers to activity involving the measurement, manipulation, and fabrication of objects from less than one to about 100 nanometers across. Nanotechnology is not to be confused with the more widely known, top-down approach called miniaturization. Nanotechnology devices are built from the bottom up, one molecule, or even one atom, at a time.

My thumb is about 30 million nanometers wide. The nanometer, the width of about ten hydrogen atoms, has come to be the preferred unit of measure among scientists and engineers working at or very near the atomic scale in biology, electronics, and materials science. Naturally, these individuals have come to be called nanoscientists and/or nanotechnologists, working in either “dry” or “wet” nanofields. The dry side is, naturally enough, waterless. The wet side centers on the study of biological systems that exist in a water environment. By 2002, the wet side of nanotechnology had become virtually indistinguishable from molecular biophysics, structural biology, and biotechnology. Chemistry Nobel laureate Rick Smalley goes so far as to assert that 21st century biotechnology could be considered a subset of wet nanotechnology.

The nanoworld is where much of nature’s weirdness resides—the borderland between the world of quantum mechanics and the more familiar macroworld of classical physics, where different laws apply. Navigation in this landscape is difficult indeed. Much of the most interesting work focuses on an intermediate domain between the two worlds, involving structures too large to be easily understood with ordinary quantum mechanics but not large enough to escape fully the weirdness of quantum effects.[24]

Until quite recently, nanoscale science was on the leading edge of research, while nanotechnology was on the “bleeding” edge of applications: lots of money going out and not much coming in. That is now beginning to change, as we will see, as investors and governments have begun to turn on the financial taps.

Government support of nanoresearch has risen sharply in recent years, growing faster than that from private sources. At the federal level, the total nanotech budget for FY 2003 is proposed to increase by 17 percent, with a striking 57 percent increase for the Department of Energy. A similar pattern may be found in other countries, where total funding for nanotechnology has jumped from $316 million four years ago to $835 million last year.[25] New nanotechnology centers have been recently established, both in Cambridge and Oxford, one focusing on wet nanotech, the other on dry nanotech.

While the dry side of nanotechnology, especially that involving new materials, is not irrelevant for biotechnology, the wet side is by far more significant. Biomedical applications of nanotechnology were given a large boost after it was established that the two nanoparticles discovered at Rice—carbon 60 (the Buckyball) and carbon 70—are nontoxic.[26,27] These particles, commonly called “fullerenes,” possess two other traits that make them especially suited for biomedical applications.

First, they are very, very small—about one nanometer wide. Second, their surfaces are particularly well suited for attaching therapeutic compounds. In the words of one of the discoverers, Rick Smalley, “They are molecular pincushions that can easily be decorated with other chemicals.” Exploitation of these properties of fullerenes is proceeding. One promising anti-AIDS application capitalizes on three features of the Buckyball: its size, its ability to carry chemicals enabling delivery of drugs to specifically targeted sites, and its unique shape that facilitates binding with HIV-infected cells.

At least as promising are the efforts under way at Rice and nearby M.D. Anderson Cancer Center involving nanoparticles other than fullerenes: gold nanoshells. These are biocompatible devices with a gold surface adhered to a silica core. At 100 nanometers in width, they easily pass through the circulatory system. The optical properties of nanoshells may prove extremely useful in both diagnosis and treatment. Once inserted into the body and delivered to sites of individual tumors by virtue of antibodies attached to them, they are hit by infrared light and heated up to 55 degrees centigrade, enough to destroy cancer cells while leaving intact healthy ones. This highly localized therapy can penetrate up to 15 cm. in tissues and thus reach all organs without the serious side effects of chemotherapy or radiation therapy.

The Grand Interface: Bio–Info–Nano

We have come to the juncture of all three of the new technologies: the design and utilization of nanomaterials for biomedical engineering. Especially notable is the rapidly growing field of tissue engineering, which focuses primarily upon the development of biological substitutes to restore, maintain, or improve tissue function. Put another way, tissue engineering will allow fabrication, on a large scale, of a range of spare human parts to replace diseased or spent ones, with or without the help of embryonic stem cells.

Twentieth century forms of biomedical engineering will doubtless persist for a time, until the field is largely eclipsed by tissue engineering. Traditional bioengineering has already brought us biomechanical body parts, including unduly bulky whole organs, various joints, heart valves, stents, and the like. It is notable that in 2001, thirty-three years after Christian Barnard's first transplant of a living heart, an artificial heart has allowed a handful of patients to remain alive for several weeks.

Veterinarians have contributed as well, drawing on their experience with large animals to fashion ingenious, highly compact devices that not only augment the activity of damaged human left ventricles but also in some cases even allow damaged natural heart tissue to heal and resume functioning. Also, innovative research is exploring how metal and ceramics can be used in the fabrication of artificial lungs.

Progress in providing other organs much more complex than the lungs or highly specialized heart tissue will be longer in coming but is no longer the stuff of science fiction. The overwhelming share of those advances will come from newer approaches to tissue engineering, some of which rely on stem cells taken from adults. Experiments are already under way using living cells to make bioartificial pancreases and livers. Virtually every other part of the body has attracted researchers seeking ways to find bioartificial replications of body parts.

Traditional biomedical engineering uses metals, polymers, and ceramics to construct temporary or permanent replacements of body parts that interact minimally with surrounding tissue. Tissue engineers take exactly the opposite approach: They design materials to interact extensively with adjacent tissues in order to facilitate the regeneration process.[28]

In bone regeneration, for example, tissue engineers use biodegradable polymers to create scaffolding shaped like the lost bone. A biopsy is taken from the patient himself, the bone-forming cells are isolated and expanded in the laboratory and seeded onto a scaffold. The cell/scaffold construct is grown in a bioreactor and then grafted back into the patient. As the cells integrate with the body's own tissue, the polymer scaffold gradually melts away, leaving only living tissue behind. With the right signals, this newly formed tissue regenerates the missing bone.

Scientists and engineers at Rice and other Texas locations are engaged in promising research for deploying tissue engineering to deal with a multitude of other medical problems: atherosclerosis, thrombosis, inflammations, osteoporosis, cartilage regeneration, and repair of tissue.

The objectives of tissue engineering are not limited to bone and organ replacement. Tissue engineers have already developed quite serviceable blood substitutes. Most recently, protein engineers at Rice together with industrial collaborators surmounted one of the most vexing problems in the development of blood substitutes. Recombinant technology was used to design new hemoglobin molecules that eliminate the hypertensive side effects of previously available blood substitutes, traceable to nitric oxide scavenging. This work is being carried out under the auspices of the Gulf Coast Consortia, plural because it is an umbrella organization for cooperative research and education in structural biology, computational biology, and molecular biophysics.

This type of research requires the most resourceful efforts not only of biologists but also information scientists and nanotechnologists. Wet nanotechnology is used to create tissue analogs to grow skin, muscle, and organs. The computational and structural skills of engineers are required to construct the scaffolds on which bioscientists build, after having used mathematical models to image their work.[29]

Nowhere is the interplay between bio-, nano-, and information technology more striking than in new forms of health maintenance, diagnosis, and treatment. Already nanometer-sized biosensors can be inserted into the bloodstream. More advanced nanosensors could eventually monitor all bodily functions.

CONCLUSION: OF PARTS LISTS AND SPARE PARTS

The potential for truly staggering applications of biotechnology in the marketplace is in little doubt. Whether much of this potential will be soon realized is, however, yet unclear. Financial constraints on biotechnological transfer may be shrinking, but legal constraints loom somewhat larger than in past technological revolutions.

On the bright side, biotechnology looks to be the principal arena for an ongoing, far-reaching synthesis in science and engineering. As the infant industry of biotechnology reaches its adolescence and later adulthood, it can be expected to provide a wide array of products and services to fuel sharp increases in living standards in the 21st century. Pharmaceuticals will doubtless remain prominent in this picture, but other types of new products and services should grow steadily in importance.

From genomics, biotechnology has already provided us with a complete parts list for both animals and plant life. As a result of advances in wet nanotechnology and information technology, tissue engineering promises to provide widely available, inexpensive, and reliable spare parts for humans. There is, however, a darker side: a still unresolved and complex welter of ethical—and perhaps moral—issues raised by our fast-expanding capacities in biotechnology. These are just beginning to be systematically addressed on many university campuses across the nation—including my own—and in boardrooms and the halls of Congress. Considerable wisdom will be required to ensure that the potential of the biotechnological revolution is realized without erosion in fundamental human values. With resolution of these issues, the economic and social impact could be as profound and as positive as that wrought by any previous revolution in human history.

NOTES

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[1] Baltimore (2001), 43–45.

[2] Feldbaum (2002).

[3] Landau (1999), xi.

[4] Scriabine (1999), 271.

[5] According to Landau, sales of the pharmaceutical industry in 1997 were $122 billion. Given ambiguities over the very meaning of biotech sales, few precise figures are available. Sales values for the biotech industry, according to leading biotech scientists, reached only $6 billion in 1993 and may have grown to $7.5 billion by 1997. See Landau (1999) and Rudolph and McIntire (1996).

[6] Nearly 30 percent of biotech products in Phase III of chemical trials are for cancer and another 11 percent for the nervous system, including Alzheimer's.

[7] As a measure of the potential present-day market for tissue-engineering products, consider that organ replacement therapies using standard organometallic devices constitute about one-twelfth of medical spending worldwide, or about $350 million. See McIntire (2002), chapter 1, 1.

[8] Rosenberg and Trajtenberg (2001).

[9] Simon (2001).

[10] Fogel (1994).

[11] Nordhaus (2002).

[12] Lichtenberg (2002).

[13] Cutler et al. (1998).

[14] Baltimore (2001), 49.

[15] This line of argument is developed skillfully at some length by Francis Fukuyama (2002) in his new book, *Our Posthuman Future: Consequences of the Biotechnology Revolution*. See also Wade (2002).

[16] See, for example, Rothstein (1996).

[17] Baltimore (2001), 44, 49.

[18] Baltimore (2001), 48.

[19] Proteomics is the study of the proteome, an organism's total protein set.

[20] *The Economist* (2001).

[21] M. D. Anderson Cancer Center, "The Ross and Margot Perot Center for Computational Cancer Research" (undated, but written in January 2002).

[22] See Mancinelli, Cronin, and Sadee (2000).

[23] See, for example, Finn and Kavraki (1999).

[24] Roukes (2001).

[25] Stix (2001).

[26] Wilson (1999).

[27] Researchers at Rice and the Texas Medical Center in 1996 found that carbon 60 (the Buckyball) does accumulate in the liver since it cannot be oxidized in mammals. However, no toxic effects were noted.

[28] Antonios Mikos, bioengineer at Rice.

[29] Jackson (2002).

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