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HISTORY OF BIOTECHNOLOGY

Robert Bud

For almost a century, entrepreneurs, policymakers and scientists have used the word biotechnology to describe imminent revolutions based on the application of biology.[1] Yet although novel clusters of techniques, products, and promises were clearly momentous to visionaries, they repeatedly failed to achieve their foreseen potential.

The old frustration seemed to have been overcome in 1980 when the U.S. Supreme Court permitted the patenting of a transgenic bacterium that could consume oil spilled at sea. Many were enthused by the new development, and foreign governments felt that this was an American challenge they could not afford to duck. Although a few quaked before this new appropriation of science, the majority of commentators assumed that finally the subdivision and exploitation of the world of primitive living beings was about to begin.[2] The possibility of patenting new organisms made by means of modern biological techniques and, in particular, the methods of recombinant DNA that had first been developed in the early 1970s would, it seemed, open up hitherto undreamed of possibilities. Rather than relying on traditional breeding, which entailed combining genes of animals and plants within the same species, genes could now be combined from across the entire spectrum of living organisms. At this moment, when an oil crisis suggested that old energy-intensive industries had had their day, and the success of electronics had demonstrated the possibility of a new industrial revolution, every major country created its own biotechnology plan.[3]

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[1] The treatment here is based on Robert Bud, *Uses of Life: A History of Biotechnology* (Cambridge: Cambridge University Press, 1994). Where no other source is given, that may be the most useful starting point.

[2] Daniel J. Kevles, "*Diamond v. Chackrabarty* and Beyond: The Political Economy of Patenting Life," in *Private Science: Biotechnology and the Rise of the Biomolecular Sciences*, ed. Arnold Thackray (Philadelphia: University of Pennsylvania Press, 1998), pp. 65–79.

[3] Margaret Sharp, *The New Biotechnology: European Governments in Search of a Strategy*, Sussex European Papers no. 15 (Brighton: Science Policy Research Unit, 1985).

Even in recent years, the scientific and technological content and focus of biotechnology have changed significantly. When the techniques of recombinant DNA were first deployed, scientists and entrepreneurs anticipated that they could use genetically engineered organisms to make therapeutic proteins that would compensate for genetically induced deficiencies. More recently, attention has shifted to the human genome, modified genes, and genetically engineered crops, and now to cloning and the use of stem cells.

Biotechnology is characterized by an approach to biology and technology rather than by any particular methods. In 1981, the Organization for Economic Cooperation and Development (OECD) provided the following definition: "the application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services."[4] Uncertainty over whether biotechnology is more like a science or a technology has confused chroniclers, particularly because the conventions for the histories of sciences and those for technologies are rather different. Accounts of the first have tended to be about knowledge and understanding, whereas the tradition in the history of technology has been to focus on practice and economic consequences. The space between fundamental science and technology, occupied by subjects such as biotechnology, has been found confusing.

Biotechnology is often held to be an "applied science," but there has been an enduring uncertainty as to what this means. Some have held that applied science is the application of pure science, whereas others hold that applied science is an activity in itself.[5] The French founder of microbiology, Louis Pasteur, famously proclaimed in a much quoted quip, "There are no applied sciences . . . there are only . . . the applications of science." By contrast, his contemporaries developing thermodynamics framed their science, so Timothy Lenoir has argued, to make it useful toward applications such as Fritz Haber's synthesis of ammonia from the gases hydrogen and nitrogen in 1909. Through much of the twentieth century, the nature of applied science was explored – without resolution – through evaluations of the engineering curriculum. To what extent should engineering itself be taught, and to what extent was it seen as the application of fundamental principles?[6]

During the 1960s, the relationship between science and technology was widely debated as the growth of science funding slowed and previous optimism that the two were intimately interconnected seemed to be misplaced.

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[4] Allan T. Bull, Geoffrey Holt, and Malcolm D. Lilly, *Biotechnology: International Trends and Perspectives* (Paris: OECD, 1982).

[5] Robert Bud and Gerrylynn K. Roberts, *Science versus Practice: Chemistry in Victorian Britain* (Manchester: Manchester University Press, 1984). See also Thackray, *Private Science.*

[6] The epigram of Pasteur is cited in René Dubos, *Louis Pasteur: Freelance of Science* (New York: Scribner, 1976), pp. 67–8. For chemistry as an applied science, see Timothy Lenoir, *Instituting Science: The Cultural Production of Scientific Knowledge* (Stanford, Calif.: Stanford University Press, 1997).

Since then, meticulous studies of particular industrial research laboratories, relations between scientists and military sponsors, and industrial networks around universities such as Wisconsin and Stanford have enriched concepts of science–technology relations. Scholars studying the uses and development of instrumentation have been able to identify more complex interactions; devices such as cell counters and gene sequencers have brought the language of automation to biochemists as mass processing of enormous numbers of samples has become possible. Moreover, techniques have traveled between apparently industrial devices and scientific instruments, so, for example, the design of the inkjet printer has made possible the fluorescent activated cell sorter. The word "technoscience" has become a popular indicator of the reduced distance between pure science, applied science, and technology.[7]

Nonetheless, the partners who have made and remade biotechnology have remained self-conscious about their allegiance to science or technology. The recent sequencing of the human genome offers a case in point. Two teams have produced similar outputs but have held quite different models of their activity. One, based at a corporation, Celera, was funded privately for the purpose of privately selling knowledge like any other product. The other, publicly funded, was based on the model of publicly accessible scientific knowledge.[8]

In the early 1980s, biotechnology seemed distinctively based on the contemporary science of molecular biology. Accordingly, it was given the name "new biotechnology" to distinguish it from anything more familiar, which was dismissed as the "old biotechnology." This distinction was made in *Commercial Biotechnology*, an important 1984 report from the United States Office of Technology Assessment.[9] Biotechnology so defined as "new" could not have a past or even a history. Even when cursory reference was made to Gregor Mendel's founding of genetics, typically the founding event of biotechnology was cited as the 1953 discovery of the double helix by Francis Crick (1916–2004) and James D. Watson (b. 1928).[10] This was treated not as a historical event but as one of the key moments of the present – part of an ongoing and essentially contemporary discussion between scientists and entrepreneurs; most practitioners were trained within one or two academic generations of the founding act.

Subsequent key dates in the cognitive development of molecular biology with significance for biotechnology included the 1961 breaking of the genetic code by Marshall Nirenberg and Heinrich Matthei, who showed how RNA (ribonucleic acid) codes for proteins, the synthesis of short stretches of DNA (deoxyribonucleic acid) by Arthur Kornberg in 1967, the 1971 development by Paul Berg of enzymes that could precisely cut DNA, and the work of Stanley Cohen and Herbert Boyer published two years later that enabled the transfer of a section of DNA from one organism to another. During the late 1970s, genes for producing human growth hormone and insulin were transferred to the bacterium *Escherichia coli*, and subsequently other proteins such as the proposed anticancer drug interferon and a blood anticlotting factor were also made in a similar way. In 1988, Harvard University obtained a patent on a whole genetically engineered mammal. Harvard professor Philip Leder had transferred a gene not just from one cell of *E. coli* to another but from a virus to a mouse to produce a novel organism.[11] The science of cloning was also linked to mammalian models when the genetically engineered sheep Dolly was produced from the cells of adult sheep in 1997.[12] The implications of the draft sequence of the human genome announced in the millennium year 2000 are still emerging. Meanwhile, the genomes of bacteria and other disease organisms are being explored.

There were also political and regulatory links between the science of molecular biology and the practice of biotechnology. The anxieties in the early 1970s about the release of dangerous organisms within or even outside laboratories were so great that they led first to a moratorium and then to controls that affected academic scientists and industry alike (even if by custom rather than regulation).[13] The moratorium was called for by the leaders of the research themselves, anxious not to repeat the heedless progressivism of their physicist forebears, who, without proper controls on the use of their work, had plunged into the development of the atomic bomb and incurred public opprobrium. Those concerned with not overly controlling the practice of

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[7] David Noble, *America by Design: Science, Technology, and the Rise of Corporate Capitalism* (New York: Knopf, 1977). On industrial networks with research universities, see John P. Swann, *Academic Scientists and the Pharmaceutical Industry: Cooperative Research in Twentieth-Century America* (Baltimore: Johns Hopkins University Press, 1988); Stuart W. Leslie, *The Cold War and American Science: The Military-Industrial-Academic Complex at MIT and Stanford* (New York: Columbia University Press, 1993). On technoscience, see J. V. Pickstone, *Ways of Knowing: A New History of Science, Technology and Medicine* (Manchester: Manchester University Press, 2000). On debates over whether there has been a fundamental change, see Terry Shinn, "Change or Mutation? Reflection on the Foundations of Contemporary Science," *Social Science Information*, 38 (1999), 149–76; Terry Shinn and Bernard Joerges, "The Transverse Science and Technology Culture: Dynamics and Roles of Research-Technology," *Social Science Information*, 41 (2002), 207–51; Michael Gibbons, Camille Limoges, Helga Nowotny, Simon Schwartzman, Peter Scott, and Martin Trow, *The New Production of Knowledge: The Dynamics of Science and Research in Contemporary Societies* (London: Sage, 1994); Peter Weingart, "From Finalization to 'Mode 2'; Old Wine in New Bottles," *Social Science Information*, 36 (1997), 591–613.

[8] John Sulston and Georgina Ferry, *The Common Thread, A Story of Science, Politics, Ethics and the Human Genome* (London: Bantam, 2002).

[9] U.S. Congress, Office of Technology Assessment, *Commercial Biotechnology, An International Analysis*, OTA-BA-218 (Washington, D.C.: U.S. Government Printing Office, 1984).

[10] Soraya de Chadaravian, *Designs for Life: Molecular Biology after World War II* (Cambridge: Cambridge University Press, 2001).

[11] Donna Haraway, *Modest_Witness@Second_Millennium.FemaleMan_Meets_OncoMouse: Feminism and Technoscience* (New York: Routledge, 1997).

[12] On Dolly and cloning, see Ian Wilmut, Keith Campbell, and Colin Tudge, *The Second Creation: The Art of Biological Control by the Scientists Who Cloned Dolly* (London: Headline, 2000); Gina Kolata, *Clone: The Road to Dolly and the Path Ahead* (London: Allen Lane, 1997).

[13] Sheldon Krimsky, *Biotechnics and Society: The Rise of Industrial Genetics* (New York: Praeger, 1991); Susan Wright, *Molecular Politics: Developing American and British Regulatory Policy for Genetic Engineering, 1972–82* (Chicago: University of Chicago Press, 1994).

molecular biology ensured that debates about the future of the science would engage with the anticipated benefits of the industry as well as its threats.[14]

An emphasis on the means of modifying cells downplayed the engineering and chemical skills needed for their cultivation and for the extraction of their delicate products. And there are linguistic as well as philosophical reasons for the balance that has been struck in various accounts. Molecular biology and biotechnology are linked particularly in English-language sources, whereas the historical literature on the technologies of the bacterium and the yeast cell are less accessible to anglophones. Whereas molecular biology research has been reported almost entirely in English, the study of fermentation and its history were dominated in the nineteenth century and much of the twentieth century by writers of German. Even today, the most substantial account of brewing technology is in German.[15]

THE EARLY HISTORY

Traditionally the crafts of fermentation evolved slowly, and although many have had a stake in their practice, few have had an interest in change. Nonetheless, there have been pivotal places and times in which scientific interpretation and technical skills have been reintegrated to produce quite novel techniques and approaches. At the very end of the seventeenth century, the era of the scientific revolution, new skills of thermometry and hydrometry, as well as chemical theories of fermentation, were introduced into the old craft. The Prussian court physician Georg Ernst Stahl (1659–1734), pioneered the concept of a specific fermentation technology, which he called "zymotechnology" in his book *Zymotechnia Fundamentalis* (Fundamental Zymotechnology) published in 1697.[16] This influential text can be seen as the founding document of biotechnology.

Stahl's fermentation theories, based on a rigorous separation of what he saw as the living and the inert worlds, withered early in the nineteenth century after the spectacular murder of his phlogiston theory of combustion. The familiar story of *Frankenstein*, by Mary Shelley, in which a beast that is increasingly "alive" is created from dead material, is both a product of the immediate post-Stahlian age and an enduring legacy to biotechnology.[17]

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[14] Robert Bud, "Biotechnological Dancers to Different Tunes: Enthusiasts, Sceptics and Regulators," in *Resistance to New Technology*, ed. Martin Bauer (Cambridge: Cambridge University Press, 1995), pp. 293–310.

[15] Mikulas Teich, *Bier, Wissenschaft und Wirtschaft in Deutschland: 1800–1914; ein Beitrag zur deutschen Industrialisierungsgeschichte* (Vienna: Böhlau, 2000).

[16] Kristoff Glamann, "The Scientific Brewer: Founders and Successors during the Rise of the Modern Brewing Industry," in *Enterprise and History: Essays in Honour of Charles Wilson*, ed. D. C. Coleman and Peter Mathias (Cambridge: Cambridge University Press, 1984), pp. 186–98. See, for instance, M. Delbrück and A. Schrohe, eds., *Hefe, Gärung und Fäulnis* (Berlin: Paul Parey, 1904); A. Schrohe, *Aus der Vergangenheit der Gärungstechnik und verwandter Gebiete* (Berlin: Paul Parey, 1917).

[17] Jon Turney, *Frankenstein's Footsteps: Science, Genetics and Popular Culture* (New Haven, Conn.: Yale University Press, 1998).

Nonetheless, Stahl's word zymotechnology lived on in texts and institutions. In mid-nineteenth-century Prague, Carl Balling, a full professor for thirty-three years, certainly saw himself employing chemical principles but also serving the entire brewing industry. He looked to the history of his subject for inspiration, and Stahl offered him an ancestry, identity, and historic location. Balling espoused the term "Zymotechnik," entitling the fourth volume of his classic text on brewing *Bericht über die Fortschritte der zymotechnische Wissenschaften und Gewerbe (Account of the Progress of the Zymotechnic Sciences and Arts).*

The work of Louis Pasteur reinforced the distinction between living creatures and merely chemical entities, and by the end of the nineteenth century one sees attempts to develop a newly scientific study of fermentation. The centers of brewing research were not the blasted sites of the industrial revolution such as the Ruhr or industrial Lancashire; instead they were metropolises of agroindustry such as Paris, Berlin, Copenhagen, and Chicago. The last was the center of the world's greatest agricultural market; the nearby prairies supplied the world with wheat, while Chicago's production-line meat processing was the model for Henry Ford's car assembly lines. At the same time, Denmark was the world leader in creating value-added agricultural produce, pioneering industrialized methods of pig fattening and bacon, butter, and beer production. It was here that the systems of biological science and technique were integrated and reintegrated, conceptualized and reconceptualized.

The classic text of zymotechnology in the late nineteenth century was *Microorganisms and Fermentation* by Alfred Jørgensen of Copenhagen, which first appeared in Danish in 1889 and would be translated, reedited, and reissued for over sixty years. Jørgensen was a Copenhagen consultant closely associated with the Tuborg brewery. He also ran a school that attracted students from around Europe; he claimed eight hundred by 1903. So influential was Jørgensen that his "institute of fermentology" was imitated in name and function in Chicago by a Danish expatriate, Max Henius.[18] Jørgensen's magazine *Zymotkniske Tidende* was copied by Henius's Chicago competitor, the German expatriate John Ewald Siebel, who founded the *Zymotechnic Magazine. Zeitschrift für Gährungsgewerbe* and *Food and Beverage Critic*, and later the Zymotechnic Institute. In 1906, the Chicago brewing consultants created a professional club, the Zymotechnica Association.[19]

The central matter of concern was still beer, and even at the end of the century, beer sales in Germany were as valuable as those of the steel industry.

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[18] We are fortunate that while Jørgensen awaits his biographer, there are biographical treatments of both Henius and Siebel. See Max Henius Memoir Committee, *Max Henius: A Biography* (Chicago: privately printed, 1936); John P. Arnold and Frank Penman, *History of the Brewing Industry and Brewing Science in America, Prepared as a Memorial to the Pioneers of American Brewing Science Dr. John E. Siebel and Anton Schwartz* (Chicago: privately printed, 1933).

[19] Still the best introduction to early twentieth-century Chicago is Upton Sinclair, *The Jungle* (New York: Jungle Publishing, 1906). Although a novel, its impact is widely credited for the 1906 Food and Drug Act.

In the wake of France's humiliation in the Franco-Prussian War, Pasteur had published on brewing to assert his country's superiority in an industry traditionally associated with Germany. However, it was the Dane Emil Christian Hansen who discovered that infection from wild yeasts was responsible for numerous failed brews, and the application of pure yeast brewing was developed in Berlin by Max Delbrück. Although the scientists involved were closely connected across national borders, the conceptions of what was being done were different. Whereas in Paris the new study was seen as the application of microbiology, scientists in Copenhagen and Berlin saw prospects for a newly reinvigorated zymotechnology.

The science and technology of fermentation went beyond brewing. The making of cheese and yogurt, wine and vinegar, tea and tobacco, even the removal of hair from hides in the making of leather, required the control of fermentation. At the end of the century, the first chemicals began to be made: lactic acid, citric acid, and the enzyme takaminase. A conception of "zymotechnology" associated principally with the brewing of beer began to look too limited to its principal exponents, particularly those in Denmark.[20]

FROM ZYMOTECHNICS TO BIOTECHNICS

The broadening scope of zymotechnics was recognized in 1913 in Copenhagen, when the professorship of agricultural chemistry and fermentation physiology held by Orla Jensen, a former pupil of Jørgensen, was retitled as the chair of biotechnic chemistry. Jensen's course linked treatments of proteins, enzymes, and cells with the analysis of particular foods such as milk and margarine and with chocolate manufacture. A new discipline was emerging. Jensen would explain his approach some years later in a book that addressed the nature of applied science. For him, it was not the mere application of pure science but instead a fundamental form of knowledge growing out of practical experience. Thus, Jensen argued, botany had grown out of the search for medicinal plants or chemistry from the study of minerals. Orla Jensen may not feature in the annals of the great biochemists, but by the time he returned to Denmark from Switzerland, he had optimized the conditions for producing the holes in Emmenthal cheese.

Science and technology were also brought together under the pressure of World War I. In Berlin, yeast for animal feed was grown on an enormous scale on substrates nutrified by Fritz Haber's new synthetic ammonia. In Britain, the Byelorussian Jew and future president of Israel Chaim Weizmann, having worked with Auguste Fernbach at the Pasteur Institute, developed his own way of using bacteria to make the solvent acetone from starch. Weizmann first wanted to find a use for Palestine's low-value agricultural produce, and later he wanted to help the Allies produce smokeless gunpowder, which depended on acetone. There is, however, no truth to the story that the British Balfour Declaration, offering Palestine as a national home for the Jews, was made out of gratitude to Weizmann.[21]

After the war, Weizmann's work was the basis for the manufacture of what had hitherto been a by-product, the alcohol butanol, now the solvent for the new cellulose paints found suitable for the newly numerous automobiles.[22] The Weizmann process also provided the inspiration for other applications of what came to be called economic microbiology.[23]

It was another wartime development that inspired the coining of the word "biotechnology." Hungary was the agricultural base of the Austro-Hungarian empire and aspired to Danish levels of efficiency. The economist Karl Ereky planned to go further and build the largest pig processing factory. Into a site fattening 50,000 swine at a time would come railroad wagons of sugar beets, and out would come fat, hides, and meat. In this forerunner of the Soviet collective farm, peasants (in any case now falling prey to the temptations of urban society) would be completely superseded by the industrialization of the biological process. Ereky went further in his ruminations over the meaning of his innovation; it presaged an industrial revolution that would follow the transformation of chemical technology. In his book *Biotechnologie*, he linked specific technical injunctions to wide-ranging philosophy. After the war, Ereky would become Hungary's minister of food.

Nonetheless, it was not through Ereky's direct action that his word seems to have been picked up. Rather, his book was reviewed by the influential Paul Lindner, head of botany at the Institut für Gärungsgewerbe in Berlin, who suggested that microorganisms could also be seen as making up a biotechnological machine as in the production of yeast and the work of Weizmann, which was widely publicized at that very time. It was with this meaning that the word "*Biotechnologie*" entered German dictionaries in the 1920s. Its links to zymotechnology were particularly clear in Chicago, where a Prohibition era consultancy in nonalcoholic fermented drinks was established under the title Bureau of Bio-technology. Shortly after, in England, a fermentation consultant set up a "bureau of bio-technology." The ongoing commercial importance of such fermentation-based activities was considerable.

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[20] The only English-language text on the development of Danish agriculture is Eimar Jensen, *Danish Agriculture: Its Economic Development, a Description and Economic Analysis Centering on the Free Trade Epoch, 1870–1930* (Copenhagen: Schultz, 1937).

[21] Jehuda Reinharz, *Chaim Weizmann, the Making of a Zionist Leader* (Oxford: Oxford University Press, 1985).

[22] H. Benninga, *A History of Lactic Acid Making: A Chapter in the History of Biotechnology* (Dordrecht: Kluwer, 1990).

[23] Keith Vernon, "Pus, Sewage, Beer and Milk: Microbiology in Britain, 1870–1940," *History of Science*, 28 (1990), 289–325.

If biotechnology had represented merely the updating of zymotechnology, then it would have been interesting but hardly the legitimate forerunner of modern enthusiasms. Since the middle of the nineteenth century, however, there had been another interpretation of the engineering of life – eugenics, associated with the "improvement" of people, collectively if not individually. It was this tradition that, as early as 1911, would first identify the twentieth century as the biological century. These two interpretations, the eugenic and the zymotechnic, would engender modern conceptions.

Today, eugenics has a bad reputation as the ideology underpinning the murder of the weak and undesired, and of the Holocaust.[24] In the early twentieth century, however, many of its proponents believed that the weak could be made strong. Unlike those who believed that the only means of improvement was by weeding out unwanted genes, some believed that humanity could be genetically improved. After all, it was widely reasoned, man through the use of technology had already progressed beyond his biological limits.

As early as 1828, a French pupil of Jean-Baptiste Lamarck, Jean-Jacques Virey, had coined the term "*biotechnie*" to describe man's ability to make technology do the work of biology.[25] Charles Darwin's contemporary and co-father of evolution theory, Alfred Russel Wallace, saw tool building as the human route to further evolution. Several biological thinkers thought that further human improvement would stem from the proper integration of the biological and the technological. Having seen poverty, poor nutrition, ill health, and failed pregnancies, they believed that the condition of mankind could be upgraded biologically. Even those who would dismiss such claims must recognize that, indeed, in many countries through the twentieth century, such "biological" characteristics as height, disease resistance, and life expectancy have been significantly increased.

An important French intellectual tradition most frequently associated with Henri Bergson and a German tradition of social biology both saw mankind transcending its traditional limitations through technology.[26] The Austrian sociologist Rudolf Goldscheid published a volume in 1911, *Höherentwicklung und Menschenökonomie*, whose title in English means "Further development and the human economy," and his proposal that the twentieth century would be the era of biotechnics was echoed by many contemporaries.[27] The proponents of biotechnics from the period before and immediately after the

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[24] The history of eugenics in Britain and the United States has been carefully described by Daniel Kevles, *In the Name of Eugenics: Genetics and the Uses of Human Heredity* (New York: Knopf, 1985).

[25] Alex Berman, "Romantic Hygeia: J. J. Virey, 1775–1846. Pharmacist and Philosopher of Nature," *Bulletin of the History of Medicine*, 39 (1965), 134–42.

[26] The tradition in France has benefited from William H. Schneider, *Quality and Quantity: The Quest for Biological Regeneration in Twentieth-Century France* (Cambridge: Cambridge University Press, 1990).

[27] Appreciations of German debates of the early twentieth century have been colored by knowledge of their tragic results, however. See Paul Weindling, *Health, Race and German Politics between National Unification and Nazism, 1870–1945* (Cambridge: Cambridge University Press, 1989).

First World War, such as Raoul Francé and Rudolf Goldscheid, are mostly forgotten, but in England such ideas were taken up in the interwar years by Julian Huxley and his close friend Lancelot Hogben, whose works were long famous. During the interwar years, both Julian Huxley (who coauthored a popular book, *The Science of Life*, with H. G. Wells) and Hogben (author of a middle-class primer for the "Age of Plenty," *Science for the Citizen*) saw biological engineering as the next generation of engineering. Indeed, Julian Huxley's dreams of biological and social engineering called forth a reaction from his brother Aldous, author of *Brave New World*.[28] The response was made through fiction, but the biotechnological ideals themselves had not been carefully worked out in detailed discussions between scientists; rather, they were expressed in lectures and books addressed to the general public. It has indeed been a continuing feature of biotechnology that the millennial visions of scientific thinkers have been expressed in their public writings.

BIOCHEMICAL ENGINEERING

From World War II, microbially produced antibiotics such as penicillin seemed to promise the conquest of infectious disease, biologically produced power alcohol would bring wealth to the world's rural poor, and microbially produced foods could solve the problem of world hunger. Exaggerated as these hopes proved to be, it could reasonably be argued at the end of the twentieth century that penicillin was the greatest individual product of biotechnology. Not only has it saved millions of lives, but by its example other antibiotics were discovered. Together, for a generation, they removed the fear of infectious disease from Western countries.

Penicillin was discovered in the juice produced by a naturally occurring mold. Although discovered by accident and then developed further for purely scientific reasons, the scarce and unstable chemical was transformed within three years during World War II into a powerful and widely used drug. Large networks of academic and government laboratories and pharmaceutical manufacturers in Britain and the United States were coordinated by agencies of the two governments. An unanticipated combination of genetics, biochemistry, chemistry, and chemical engineering skills had been required. When the natural mold was bombarded with high-frequency radiation, far more productive mutants were produced and subsequently all the medicine was made using the products of these man-made cells. Penicillin became cheap to produce and globally available by the 1950s, and this effort had an impact beyond the development and production of a single drug.[29] The

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[28] Gary Werskey has described some of the biological visions of this circle. See Gary Werskey, *The Visible College* (London: Allen Lane, 1978). See also Turney, *Frankenstein's Footsteps*.

[29] For a survey, see Robert Bud, *Penicillin: Triumph and Tragedy* (Oxford: Oxford University Press, 2007)

air-breathing mold was cultured in enormous continuously stirred fermenters, typically holding 50,000 liters. The skills developed in building and operating these fermenters proved useful for the industrial-scale production of many other microbiological products – including a host of new antibiotics as well as the steroids needed in the new contraceptive pill.

The new technology of cultivating and processing large quantities of microorganisms led to calls for a new scientific discipline. Biochemical engineering was one term and applied microbiology another. The Swedish biologist Carl-Goran Hedén, possibly influenced by German precedents, favored the term "*Biotechnologie*" and persuaded his friend Elmer Gaden to relabel his new journal *Biotechnology and Biochemical Engineering*. Beginning in 1962, major international conferences were held under the banner of the "Global Impact of Applied Microbiology."

The products of the new biochemical engineering could profoundly affect the lives of individuals as life-saving and health-maintaining drugs, as contraceptives, or as steroids that could eliminate pains hitherto considered inevitable. During the 1960s, the same technology was used to produce staples of modern life: fuel to provide energy and protein for food. Moreover, there was the prospect of doing this most efficiently in those tropical countries rich in biomass that were also the world's poorest. Alcohol could be manufactured by fermenting starch or sugar-rich crops such as sugar cane and corn. Brazil introduced a national program of replacing oil-based petroleum by alcohol.[30] In the United States, it seemed that oil from surplus maize would solve the problem of low farm prices aggravated by the country's boycott of the USSR in 1979. The alcohol fuels program targeted a six hundred percent increase in biofuel production and made more than a billion dollars available. The name "gasohol" came into currency.

Another new word for an old concept was "single-cell protein," which had been coined in 1966. During the First World War, the Germans had fed animals on yeast; now, by growing protein-rich bacteria and fungi on oil to produce a protein-rich food, it seemed the oil industry might eliminate problems of world hunger. In the Soviet Union, a major program of single-cell protein production was put in place.[31] In 1973, the German government, seeking a new, "greener" industrial policy, commissioned a report entitled *Biotechnologie* identifying ways in which biological processing was key to modern developments in technology.[32] Even though the report was published at the time when recombinant DNA was becoming possible, it did not refer

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[30] Harry Rothman, Rod Greenshields, and Francisco Rosillo Callé, *The Alcohol Economy: Fuel Ethanol and the Brazilian Experience* (London: Pinter, 1983).

[31] David H. Sharp, *Bio-Protein Manufacture: A Critical Assessment* (Chichester: Ellis Horwood, 1989); Anthony Rimmington, with Rod Greenshields, *Technology and Transition: A Survey of Biotechnology in Russia, Ukraine and the Baltic States* (London: Pinter, 1992).

[32] Klaus Buchholz, "Die Gezielte Förderung und Entwicklung der Biotechnologie," in *Geplante Forschung*, ed. Wolfgang van den Daele, Wolfgang Krohn, and Peter Weingart (Frankfurt: Suhrkamp, 1979), pp. 64–116.

to this new technique and instead focused on the use and combination of existing technologies to make novel products.

By the late 1970s, therefore, the renewed, self-consciously technological, zymotechnic endeavor had momentum. Major companies were investing in single-cell protein. Nations saw possibilities in new industries, and bioprocessing was becoming increasingly efficient. Single-cell protein, however, met consumer resistance, and indeed the problems of hunger in developing countries were more complex than absolute shortages of protein. The gasohol programs also proved uneconomical when oil prices dropped in the early 1980s. And the energy, enthusiasm, and vision that had been so characteristic of microbiology and biochemical engineering-based biotechnology were transferred to a new generation of companies applying new academic research in molecular biology. The eugenic and the zymotechnic would be wedded through genetics in the 1980s and 1990s – an integration already anticipated in the 1960s.

MOLECULAR BIOLOGY

By the 1970s, molecular biology, a hitherto esoteric science, was making considerable progress, but its practice was, in general, rather distant from the world of industrial production. The phrase "genetic engineering" entered common parlance in the 1960s as a description of human genetic modification.[33] Medicine, however, was now putting a premium on the use of proteins hard to extract from people: insulin for diabetics and interferon for cancer sufferers. A few prophets, such as Joshua Lederberg and Walter Gilbert, argued that the new biological techniques of recombinant DNA might be ideal for making these expensive proteins through their expression in bacterial cells. Small companies, such as Cetus and Genentech in California and Biogen in Cambridge, Massachusetts, were established to develop the techniques. Larger companies kept a wary eye on the potential of these and other new competitors.[34]

The mechanism for the transfer of enthusiasm from engineering fermenters to engineering genes was Wall Street. At the end of the 1970s, new tax laws encouraged already adventurous U.S. investors to put money into small companies whose stock values might grow faster than their profits. New technology, particularly a technology based on American science, seemed to

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[33] Gordon Wolstenholme, ed., *Man and His Future: A CIBA Volume* (London: Churchill, 1963); T. M. Sonneborn, ed., *The Control of Human Heredity and Evolution* (New York: Macmillan, 1965). At these two conferences Lederberg and Tatum launched the terms "euphenics" and "genetic engineering," respectively.

[34] Hall has described the competition between Biogen and Genentech to make the first recombinant-DNA–based insulin. See Stephen Hall, *Invisible Frontiers: The Race to Synthesise a Human Gene* (London: Sidgwick and Jackson, 1987).

hold particular potential at a time when the Japanese were doing particularly well in such established products as steel and automobiles. The stockbroker E. F. Hutton saw the potential of the new molecular biology companies such as Biogen and Cetus; in searching around for a word that would describe their business, the well-established term "biotechnology" was chosen.[35] The use of the term attracted five hundred participants to a symposium held in September 1979 that focused on the production of interferon. In December of that year, a trademark was taken out on the use of this word in the title of a mass-produced magazine. The following year, the U.S. Supreme Court ruled for the first time that a bacterium could be patented.

The discoveries in molecular biology engendered anxiety as well as excitement. In the early 1970s, scientists, concerned about public opposition to science that could be used unethically, sought to regulate recombinant DNA research while it was still an infant and controllable technology. In 1976, the National Institutes of Health instituted regulations for government-funded experiments that enabled research to restart, at first in the United States and then elsewhere. From the late 1970s, legally binding controls on experimentation ensured that concerns within the scientific community would decline. But among the public in the United States and Europe, anxieties about the potential of biotechnology persisted. It is remarkable that whereas in the 1970s biotechnology was proposed as a green alternative to established smokestack industries, thereafter it came to be seen as particularly "unnatural." How did this happen when such care was taken in the 1970s to establish protective legislation before experimentation was carried out? Sheila Jasanoff has argued that we need to look at the separate conceptions of risk and resistance in countries such as the United States, Germany, and Britain. In each, the idea of risk itself was intimately intertwined with national traditions of assessment, expertise, and debate. Moreover, questions of biotechnology became locked into concerns about the trustworthiness of experts in general. In Germany during the 1980s, biotechnology was linked to both the memory of state-sponsored eugenics and the contemporary concerns over another suspect technology, nuclear power. In Britain, biotechnology came to be linked to numerous food scares that experts had failed to prevent. In the United States, the exploitation of stem cells has been linked to debates over abortion.

The anxieties brought forth enthusiasms. In the United States, the fear of excessive regulatory controls encouraged business and scientific leaders to express the most optimistic projections about the potential of biotechnology.

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[35] For a first-class treatment of the enthusiasm of Wall Street, see Robert Teitelman, *Gene Dreams: Wall Street, Academia, and the Rise of Biotechnology* (New York: Basic Books, 1989). For the academic connections with business at the time, see Martin Kenney, *Biotechnology: The University-Industrial Complex* (New Haven, Conn.: Yale University Press, 1986). For a European view, see Luigi Orsenigo, *The Emergence of Biotechnology: Institutions and Markets in Industrial Innovation* (London: Pinter, 1989).

Those projections then fed back into the Wall Street enthusiasm that sustained the new industry. In business, the subsequent twenty years have seen two phenomena. On the one hand, there has been an explosion of small companies, mostly in the United States but also in Europe.[36] Between 1978 and 1981, the "cumulative equity investment in all types of biotechnology companies rose from fifty million [dollars] to over eight hundred million,"[37] and despite earlier predictions, the Japanese have not become the dominant force. However, the number of firms making profits has been small. Some of the early pioneers have been taken over: Cetus and Genentech now belong largely to other organizations. Small companies still have a key role in innovation, but production and marketing have continued to be led by such large companies as Monsanto, whose genetically modified soya beans were among the first widely used genetically modified products.

Large bioscience companies have indeed been remarkably successful. In 1939, Merck, the major research-oriented pharmaceutical company, was scarcely more than two percent of the size of the major chemical company Du Pont. Half a century later, its revenues and stock market worth exceeded those of Du Pont. Combining with other firms, the great German chemical company Hoechst evolved into the pharmaceutical company Sanofi-Aventis, while its once equally diverse British competitor ICI spun off its large and profitable pharmaceutical wing. Although a few large molecules produced by recombinant DNA techniques have been successful both for research and for medicines, small molecules made by chemists following research using recombinant DNA have been the more common ultimate products. Such superdrugs of the 1980s and 1990s as Prozac (the antidepressant), Losec (combating ulcers), and Viagra (promoting sexual function) have all been made through synthetic chemistry rather than by means of molecular biology.

Nonetheless, the industrial ascendancy of the pharmaceutical companies and the recurrent attraction of the smaller biotechnology companies do point to a profound change in industry and agriculture.[38] If information technology remains more important as a determinant of overall industrial character, biotechnology seems central to our "modernity."

The Human Genome Project to sequence and map the human genome, which was born in the 1980s as a great scientific underpinning for future

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[36] Sheila Jasanoff, "Product, Process or Programme: Three Cultures and the Regulation of Biotechnology," in *Resistance to New Technology*, ed. Martin Bauer (Cambridge: Cambridge University Press, 1995), pp. 311–34.

[37] Paul Rabinow, *Making PCR: A Story of Biotechnology* (Chicago: University of Chicago Press, 1996), p. 27. This book also presents a history of Cetus and an analysis of the PCR process it first developed.

[38] For the long-term history of agricultural biotechnology, see J. R. Kloppenberg, Jr., *First the Seed: The Political Economy of Plant Biotechnology, 1492–2000* (Cambridge: Cambridge University Press, 1988); Lawrence Busch et al., *Plants, Power, and Profit: Social, Economic, and Ethical Consequences of the New Biotechnologies* (Oxford: Blackwell, 1991); Daniel Charles, *Lords of the Harvest: Biotech, Big Money and the Future of Food* (Cambridge, Mass.: Perseus, 2001).

biotechnology, may of course further promote the significance of biotechnology.[39] Despite the frequent use of the singular, there have been several human genome projects, plus other parallel projects to decode the genomes of the nematode worm, yeast, and bacteria. They demonstrate the integration of diverse traditions of applied science: on the one hand, the belief that scientific knowledge of the human genome will lead to technological benefit; on the other, a complex technological revolution in the techniques of sequencing, with a shift to an industrial ideology of speed. The Human Genome Project manifests a technological tradition that Lily Kay has seen as generic to molecular biology,[40] and appropriately, the question of patenting has been central in its recent history.[41]

Our reconstructions of the history of biotechnology remain intimately connected with our conceptions of both science and technology. This applied science is not just an application of pure science, but nor are the two quite separate; for instance, the study, cultivation, and exploitation of the bacterial cell and lately of mammalian cells have been shared. Technologies of analysis and mass production have involved both engineering and biology. Metaphors of network and linkages, ambivalence, and multiple identities have replaced the simple model of scientific cause and technical effect. The history of biotechnology can be seen as a sequence of networks through which self-consciously scientific and technological groups shared their expectations of a shining biotechnological future – as well as their specific techniques and a common concern with "bugs."

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[39] Robert Cook-Deegan, *The Gene Wars: Science, Politics and the Human Genome* (New York: Norton, 1994).

[40] Lily E. Kay, *The Molecular Vision of Life: Caltech, the Rockefeller Foundation and the Rise of the New Biology* (Oxford: Oxford University Press, 1993).

[41] F. K. Beier, R. S. Crespi, and J. Strauss, *Biotechnology and Patent Protection: An International Review* (Paris: OECD, 1985).