Into the 21st Century

Biotechnology and the pharmaceutical industry in the next ten years

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10 CELEBRATING A DECADE OF EXCELLENCE

Morphology and chemistry are the most successful of all the scientific approaches to interpreting disease and deriving consistent diagnostic and therapeutic methods from such interpretations. The morphological approach gave rise to a pathological anatomy and to morphological criteria that allowed the first systematic classification of human diseases. Clinical medicine was largely built on such foundations and, up to this very day, diagnostic methods in everyday practice aim at the assessment of morphological parameters.

The second paradigm was chemistry. The chemical interpretation of disease provided medicine with two particularly powerful conceptual tools: a novel approach to diagnosis (clinical chemistry, laboratory medicine), and drug therapy, which can be regarded as the most fundamental therapeutic approaches available to modern medicine. Drug therapy in itself provides effective and sometimes causal treatment for many pathological conditions, such as bacterial infections. Equally important, however, is its role as an essential prerequisite for many other therapeutic approaches: anesthesia in surgery, immunosuppression in organ transplantation, psychopharmaceuticals for certain forms of psychotherapy. The chemical approach to describing, diagnosing, and, in particular, treating diseases has also given rise to a whole industry that specializes in studying mechanisms of diseases and in finding and developing new drugs for their treatment.

Two events—one 1944, the other in 1953—opened new eras in biology, providing medicine with yet another idiom for describing, diagnosing, and treating disease. First, Oswald Avery, Colin MacLeod, and MacLyn McCarty's discovered that DNA is the molecule of inheritance;[1] next, James Watson and Francis Crick elucidated the double-helical structure of DNA.[2]

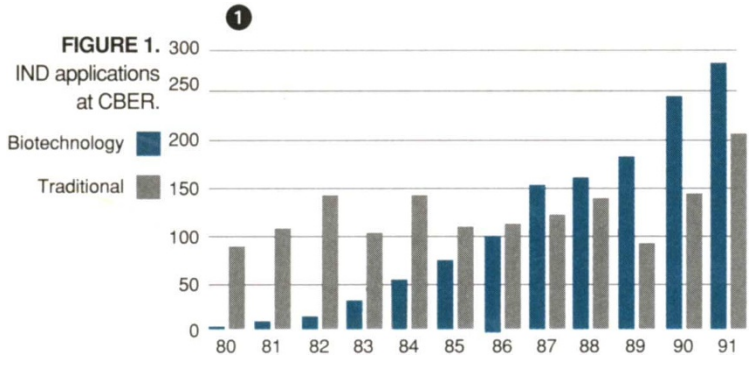

FIGURE 1. IND applications at CBER.

The new science emanating from these discoveries also brought to medicine an informational and cybernetic paradigm which will eventually complement the more traditional medical thinking.[3]

rDNA creates a new industry

Herbert Boyer and Stanley Cohen[4] carried out the first DNA recombination experiments, integrating a mammalian gene into a bacterial vector and eventually expressing the gene in bacterial cells. This marked the final proof, and reduction to practice, of this new thinking. Genes specifying the synthesis of human proteins—proteins once hardly accessible because of their scarcity or instability—could now be cloned, amplified, and expressed in microorganisms (and later also in mammalian, plant, or insect cells). The first proteins made available to medicine were human insulin and human growth hormone, peptides whose physiological and medical roles had already been well described. Soon thereafter, however, the new industry was able to provide proteins that had previously been difficult or almost impossible to obtain by isolation procedures: alpha-interferon, IL-2, IL-3, colony-stimulating factors, tissue plasminogen activator, to name but a few.[5]

At first, the pharmaceutical industry was slow to react to the new challenge. Many companies regarded molecular biotechnology as an esoteric science with little promise for substantial economic returns. The industry's culture was still largely chemical, and it needed time to understand the utility of recombinant DNA. This initial promise has since been convincingly redeemed. About 20 new proteins, interferons, colony-stimulating factors, thrombolytic enzymes, and peptide hormones are registered as drugs today, and some of them have gained outstanding therapeutic prominence.

The next decade

Despite this undisputed success, only one first-generation biotech company survives as a completely independent entity today. A few others—among them Genentech (S. San Francisco, CA), the first and arguably the scientifically most successful biotech company—chose to enter stable, long-term alliances with established pharmaceutical companies. Some biotech companies merged with one another. Some simply disappeared. Overall, the biotechnology boom was an economic and scientific success, providing one of modern history's best examples of technology transfer from universities to industry.

Today's biotech product-development portfolios bode well for the future. More than 40 monoclonal antibodies and about 150 new recombinant proteins

(including 11 engineered MAbs) have reached some stage of clinical development. Six of the recombinant monoclonal antibodies were also "humanized"—their murine or rat sequences, except those mediating antigen specificity, have been replaced by sequences from human antibodies (Table 1).[6] Most of these interact with receptors and have anti-inflammatory or immunosuppressive properties. Some of them, like the anti-HER antibody, bind to growth-hormone receptors and antagonize the interaction of these receptors with their physiological ligands; they will largely be used to stop or slow the growth of malignant tissues. Other proteins are cytokines that will be used to stimulate immune responses against tumors or infections. Recombinant vaccines—killed and live—are among the best hopes for preventing or treating certain viral infections, such as AIDS. This is especially true for recombinant HI-viruses which have been deprived of small portions of their genome and which have lost their pathogenicity but are still capable of replication, though at a lower rate than wild-type virus.[7]

Some of the proteins under development have no precedent in nature: they are combinations of certain domains from several proteins. One molecule, for instance, represents the greater part of an interleukin-2 molecule fused to those parts of diphtheria toxin that are necessary for the translocation of the toxin through endocytotic vesicles and for the adenosyl ribosylation of elongation factor-2 (inhibition of protein synthesis). This protein will bind to the interleukin-2 receptor on activated T-cells and will selectively destroy cells that have expressed the interleukin-2 receptor. Other artificial constructs comprise soluble receptors for cytokines such as TNF, IL-1, or IL-5 fused to a heavy chain from human IgG.[8] These constructs are expected to bind cytokines produced in large amounts during some disease processes. They might thus mitigate the resulting pathology.

While there are some redundancies among the 150 or so novel proteins in development, about 100 represent truly novel substances that have no precedent in medical therapy. Not all of these proteins will reach the market, but it is fair to assume that their attrition rate will be lower than that for small chemical entities because they should cause few unmanageable toxicological problems. A conservative estimate would expect 30-40 of the recombinant proteins now under development to become successfully marketed products over the next 5-6 years. This means that an average of 5-8 novel proteins should become available each year. Since the recombinant proteins now in clinical development correspond to an even greater number that are still under experimental investigation, one would project that this development would continue well into the next millennium. At first sight, this may not seem impressive, but these figures must be judged against the background of only 40-45 new chemical entities introduced annually by the international pharmaceutical industry.[9] Assuming that the novel recombinant proteins would rank fairly high in innovativeness among newly introduced compounds, we can expect these drugs to have considerable therapeutic impact. This value will be reflected in a commensurate generation of economic value. During the next five years, at least 10-15 percent of revenues and profits derived from new drugs will stem from recombinant proteins. It is fair to expect this figure will show a tendency to increase during and—even more so beyond--the imminent 5-year period. If we assume an average sales volume for the forthcoming recombinant proteins equal to the average revenues generated by today's recombinant drugs, the portfolio of recombinant proteins now in clinical trials should amount to $10-20 billion in today's currency. In 2003, ten years from now, the total pharmaceutical market is expected to reach $250 billion. So recombinant proteins should account for at least 10 percent of this market. Looking at the relationship between biotech and non-biotech IND applications, one might expect an even higher proportion of recombinant proteins among future drugs (Figure 1).[10]

These figures do not, however, reflect the total impact of molecular biology on the pharmaceutical industry, not even on pharmaceutical sales over the next 10 years. At this time, molecular biology has invaded all areas of biology and pharmacology: There is hardly any drug research project that is not somehow benefiting from recombinant DNA work. Recombinant enzymes or recombinant receptors are prominently figuring as drug targets. The genes specifying the synthesis of these molecules can now be obtained from gene banks with relative ease, impacting drug research in a major way. Thus, the advances

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Protein	Number	Selected Indications
Growth Factors (e.g., TNF, CSF, EPO, FGF, PDGF)	27	Cancer, anemia, wound-healing, viral and bacterial infections, bone marrow transplantation
Hormones (e.g., insulin, IGF, hGH, GRF, relaxin)	13	Diabetes, growth disorders, osteoporosis
Interferons	11	Cancer, viral infections
Interleukins	19	Cancer
Fibrinolytics (e.g., tPA)	14	Cardiovascular diseases
Vaccines	28	Hepatitis-B, AIDS, malaria, pertussis, typhus, influenza
Recombinant. proteins	22	
Recombinant live vaccine	6	
Recombinant monoclonal antibodies	11	Cancer, infections, inflammation
Soluble receptors (e.g., CD-4, IL-1-receptor)	2	Inflammation, HIV-infection
Others (e.g., Factor VIII, DNase)	18	Enzyme deficiencies
Total	**143**	

Source: Pharmaprojects Data Base, February, 1993.

TABLE 1. Recombinant products in clinical development.

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in small-chemical-entity drug therapy will also be contingent on recombinant DNA work and on biotechnology. It is impossible to quantify this influence in monetary terms. One *can* say, however, that research-based drug companies that are not strong in molecular biology and biotechnology are suffering from a critical competitive disadvantage which—if not corrected—may eventually lead to their demise.

In drug development, 10 years—even 15 years—is not a particularly long time. As a matter of fact, this period quite well corresponds to the number of years that elapse between the conceptualization of a new method of treatment and its final materialization in the form of a drug. This means that whatever drugs—biotechnological or chemical—will reach the market over the next ten years should already be recognizable today. The reverse, of course, is not true: not every item that can be detected today will eventually become a marketable product.

Given these constraints, we can make the following predictions for the next 10 to 15 years: there will be an abundance of monoclonal antibodies, antibody-toxin conjugates, or constructs containing cytokines, cytokine receptors, and antibody heavy chains or other protein components with immunosuppressive and anti-inflammatory properties. These molecules should carry significant advances in the treatment of rejection episodes after organ transplantation, graft versus host disease, acute flare-ups in autoimmune diseases, and septic shock.

Sometime around 2003, we will witness the arrival of new cytokines and the combined use of cytokines, which will improve the prospects for treating certain tumors like renal cell cancer, melanomas, lymphoproliferative diseases, and leukemias. Besides the colony stimulating factors already available (G-CSF, GM-CSF, and erythropoietin), new factors that stimulate the formation of granulocytes, macrophages—and, more important, platelet and lymphocyte formation—will become available.

Obviously, some existing or novel cytokines will be used in combinations, with each other and with chemical entities. The concomitant use of alpha-interferon and retinoids in treating epithelial cancers represents a typical example of the former; the combination of IL-3 with G-CSF, the latter. The number of possible combinations, of course, becomes very high as the number of candidates increases; and it will take a long time to establish the clinical utility of such regimes.

New thrombolytic enzymes will be introduced into therapy, offering greater specificity, fewer side effects, and a longer duration of action. The greater safety margin of these modified enzymes will allow for early intervention after myocardial infarction, pulmonary embolism, and strokes. Other recombinant enzymes—like DNase, which has already demonstrated good clinical efficacy—are likely to make an important contribution to the treatment of cystic fibrosis and certain forms of chronic bronchitis.

Neural growth factors like NGF or BDNF will be used to treat the peripheral neuropathies that complicate type II diabetes, alcoholism, or heavy metal poisoning. Since peripheral neuropathies are also a complication of cancer chemotherapy and certain forms of antiviral chemotherapy (ddC, for example), neural growth factors may help to extend these traditional therapies. They may also offer therapeutic advantages in the treatment of traumatic spinal paralysis and myelodegenerative diseases. Modifications that allow large molecules to move across the blood-brain barrier might make them suitable for treating chronic degenerative diseases of the brain, like Alzheimer's and Parkinson's diseases.

Are any of the new recombinant proteins going to be blockbusters? Probably. But there seems little reason to assume that the proportion will be higher among the recombinant proteins than among small molecules. According to an analysis we have carried out over the last few years, the pharmaceutical industry has succeeded in producing an increasingly greater proportion of important drugs, or at least of drugs that offer substantial improvements over already existing therapy. The degree of drug redundancy has decreased steadily since 1986 (at least as compared to the preceding 10 years).[11] This trend is likely to continue and to embrace recombinant proteins as well as small molecules.

The principle of base complementarity of nucleic acids is reasonably close to being therapeutically exploited. Oligonucleotides complementary to well-chosen mRNA sequences can bind to it and block translation into a functional protein. In addition, ribonuclease-H can digest the mRNA of an antisense/mRNA fusion, releasing the antisense fragment to scavenge up mRNA of the same type. To attain the necessary specificity, an oligonucleotide must be some 12 base pairs long. It must also withstand nuclease attack and be able to enter cells. All of these criteria have at least been partially met. These agents have demonstrated, *in vitro* and *in vivo*, the ability to reduce or prevent production of target proteins, and the first molecules are now about to enter clinical trials. Antisense molecules that are stable, selective, and well-tolerated will first be used as antiviral agents. Once this technology has been established as a therapeutic modality in principle, it will find many applica-

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TABLE 2. Potential impact of gene therapy on the worldwide pharmaceutical market.

Diseases Amenable to Gene Therapy	Current Drug Therapy	1991 Worldwide Market ($Million)
Cancer	Cytostatics Cytokines (Immunomodulators)	4701
Hypercholesteremia	HGMCoA reductase inhibitors	2500
Parkinson's Disease	DOPA Benzaseride Parlodel™	1206
Alzheimer's Disease	Hydergine™ Nootropics and Neurotonics	1379
AIDS	RT inhibitors	320
Cystic Fibrosis	Mucolytic agents	1300
Growth Hormone Deficiency	Recombinant growth hormone	273
Hemophilia	Purified Factor VIII	179
Muscular Distrophy	N/A	
Hepatitis-B	Vaccines	175
Influenza (pandemic)	Vaccines	174
Total		**12,207**

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tions in the treatment of other diseases such as inflammatory conditions and cancer.

Our knowledge of such cellular structures as receptors, signal transducing proteins, and transcriptional regulators will increase greatly and offer a multitude of possibilities for intervention via new, low-molecular-weight drugs derived from both screening programs and rational design.

Recombinant vaccines against all major viral infections—hepatitis A, B, and C, and, most important, AIDS—will mitigate the impact of these diseases, but will not make them disappear.

Selective receptor agonists and antagonists will become available for treating migraine, epilepsy, depression, and schizophrenia. Growth-factor antagonists mitigating atherosclerosis and smooth-muscle-cell proliferation are likely to appear in the early years of the next decade. The search for low-molecular-weight antagonists to cytokine receptors, notably IL-1 and IL-2 receptors, is sufficiently advanced to augur the emergence of novel anti-inflammatory or immunosuppressive drugs shortly after the year 2000.

Beyond 2003

All of these advances, and others not mentioned, are the fruits of molecular biology. They can nevertheless fit comfortably into the conceptual framework of the traditional chemical paradigm on which the pharmaceutical industry is built. Beyond the 10-to-20-year horizon, though, we can dimly foresee more radical paradigmatic changes.

Predictions about new drugs and new types of therapy become very difficult as one extends the period of anticipation beyond the average development cycle. As Karl Popper has pointed out, we can extrapolate many developments, but the knowledge of tomorrow is impossible to predict; otherwise we would already have it today.[12] The following remarks are made, therefore, with this essential reservation in mind.

In contrast to chemistry, molecular biology allows us to interpret diseases as errors in genomic information storage and transmission. In this context, one could also define diseases as incompatibilities between specific genomic structures on the one hand and environmental factors on the other. This view obviously applies to classical genetic diseases in which dysfunction of one gene causes a particular pathological phenotype. But it also applies to diseases caused by several genes and to "predispositions"—that is, genetic configurations that entail an increased risk of acquiring a certain disease. The effort to understand the structure of the human genome will eventually make it possible to identify and locate disease-causing genes. Then, through gene diagnosis, we may provide each individual with an assessment of his or her personal disease risks. Many of such risks could then be reduced by preventive strategies—nutrition, pharmacological measures, and life-style changes among them. Medicine would become more diagnostic and more preventive, a tendency very much in line with current emphases on affordability.

Understanding the human genome (and, concomitantly, unraveling genes' physiological function and their roles in disease processes) will help identify many new proteins with therapeutic potential. It will also illuminate an even greater number of possible targets. Given the inherent kinetics of drug discovery and development, however, the practical consequences of these discoveries will not become manifest within the next ten years.

Gene therapy will eventually become a therapeutic modality that will complement and even replace drug therapy in many areas. It will first be used to manipulate immune cells to secrete more cytokines or to express surface proteins that would enhance their effectiveness or to make tumor cells more immunogenic by providing them with genes for cytokine formation. For gene therapy to become a more generally applied method of therapy, a number of fundamental problems will have to be solved. First, the vectors containing the desired genetic information will have to be delivered selectively to certain cells or tissues. Second, one would have to ensure that the information is integrated in a site-specific way, preferably at "generic" docking sites. Finally, it would be desirable to have the information expressed in a regulated and tissue- or organ-specific way. While solving these technical problems will require substantial effort, few scientists doubt that they will eventually yield.

In the more distant future, we would, therefore, expect gene therapy to become a major force in medicine. For that to happen, though, this therapy and the science surrounding it will have to be effectively institutionalized. Right now, it is difficult to decide whether gene therapy will become an industry of its own or eventually be incorporated in the traditional pharmaceutical industry. In any case, it will be the most rigorous expression of new thinking in medicine, an informational paradigm that will otherwise tend to emphasize diagnosis and prevention. Taking a radical view, one could assume that gene therapy will eventually make many forms of drug therapy obsolete. If we assume that gene therapy will become a successful treatment for just those diseases now identified as experimental targets, the impact on drug therapy would be substantial, replacing the equivalent of $12 billion in drug sales in today's currency.

Again, such a scenario takes us well beyond the 10-year time limit of this "preview." Whatever the future may bring to the pharmaceutical industry and to drug therapy, the question is no longer whether biotechnology and molecular biology are important sciences. Molecular biology has long become the mainstream of pharmaceutical and therapeutic research. Therefore, the question is no longer "How important is biotechnology for medicine or for the pharmaceutical industry?" but rather "Where is it going to take us?"

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