EDITOR

M.R. EL-GEWELY

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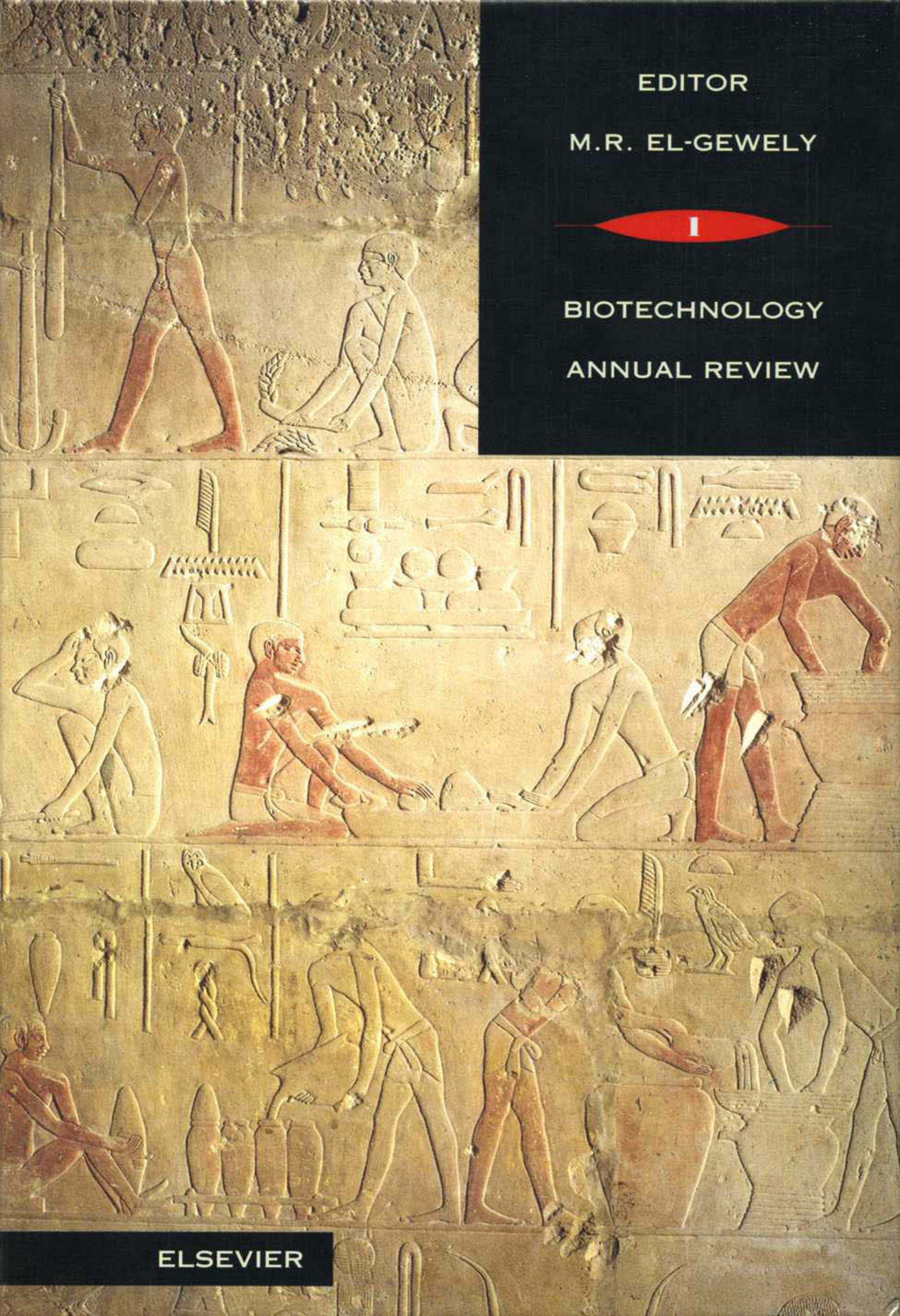
BIOTECHNOLOGY ANNUAL REVIEW



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Biotechnology Annual Review

Volume 1

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Biotechnology Annual Review

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Editor:

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Scope

The *Biotechnology Annual Review* aims to cover the various developments in biotechnology in the form of comprehensive, illustrated and well referenced reviews. Chapters are written by experts in the particular fields of biotechnology. With the expansion in the field of biotechnology, coupled with the vast increase in the number of new journals reporting new results in the field, the need for a publication that is continuously providing reviews is urgent. Such a publication will help students as well as teachers, researchers as well as administrators, to stay knowledgeable with all the relevant issues in biotechnology. Naturally, all aspects of biotechnology cannot be reviewed extensively in each issue every year, but each volume will have a number of reviews covering different aspects of biotechnology. Reviewed topics will include biotechnology applications in medicine, agriculture, marine biology, industry, bioremedation and the environment. Fundamental problems dealing with enhancing the technical knowledge encountering biotechnology utilization regardless of the field of application will be particularly emphasized. Examples of such vital topics are promoters, vectors, media, induction, genetic stabilization during heterologous gene expression and relevant new techniques. Essential information dealing with the utilization of data banks such as protein and nucleic acid data banks will be reviewed. Homology studies as related to biotechnology, as well as issues dealing with the characterization of motifs and motif data bases will be also dealt with. New developments in protein engineering, optimization of protein function and protein design will be addressed. These problems dealing with protein functionality are important not only for the production of active recombinant proteins and enzymes, but also for the purpose of drug development and design based on screening using such proteins, whether by employing in vivo or in vitro assays. Drug screening and discovery using proteins of cloned and expressed genes of interest, is one of the major biotechnology activities in recent years. Newly discovered open reading frames or proteins identified by 2-D gel electrophoresis will be updated whenever the opportunity arises. Additional problems dealing with policy and regulation of biotechnology as well as the problems of development in the developing countries as related to biotechnology will be included in the various issues.

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Volume 1

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Introduction

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Biotechnology and the utilization of biologically based technologies has a long rooted history in human activities. Ancient cultures as documented 4,000 years ago by ancient Egyptians for example, knew some secrets of fermentation and leaven bread-making, but without identifying the exact microorganisms involved. Today, a lot is known about *Saccharomyces* and its utilization not only in fermentation, but also as a host for heterologous gene expression and as a model organism for eukaryotic molecular biology. The first sequence of a complete nuclear chromosome of any eukaryote was that of *Saccharomyces cerevisiae* [1–4]. Nevertheless, most of the yeast genes are not identified, in spite of massive efforts to sequence all of the individual chromosomes or segments (European Yeast Sequencing Program, for example). The issue of what proteins the discovered open reading frames (ORFs)/genes are coding for or how are they regulated will remain a mystery, at least for a while. Naturally all of this information on yeast as well as on other organisms will increase our understanding of biological systems in addition to being assets for further progress in biotechnology.

Currently, at least 25% of all copper produced worldwide is bioprocessed, but the Romans presumably were the first to use bacterial action for biomining in Rio Tinto Copper mine in Spain 2,000 years ago [5]. Other minerals as precious as gold or as cheap as phosphate are being bioprocessed. There is a lot to be learned in this field of application which promises to increase efficiency without the use of toxic and dangerous chemicals. Hopefully, biomining could deliver the required minerals with environmentally sound procedures at a feasible cost that permits its use even with lower grade ores.

Our knowledge about human genes as a result of the human genome project [6,7] or by rapid cDNA sequencing, expressed sequence tags (EST) [8–10], will eventually increase, thus providing a wealth of information about our genetic makeup and open the potential for providing better diagnostic tools, therapy and a powerful basis for drug discovery.

The potential for improving plants, animals, marine organisms using modern biotechnology might be the only hope to improve food resources globally.

In the field of biotechnology, in spite of its current momentum and expansion and deeply rooted history, modern applications are still young relative to the potential and expectations.

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In the first issue of this series the following topics are covered:

1. Biotechnology domain (M.R. El-Gewely)
2. Application of 2-D protein gels in biotechnology (R. VanBoglen and E. Olson)
3. Prokaryotic promoters in biotechnology (M.A. Goldstein and R.H. Doi)
4. Comparative methods for identifying functional domains in protein sequences (S. Henikoff)
5. Peptide and protein display on the surface of filamentous bacteriophage (F. Felici, A. Luzzago, P. Monaci, A. Nicosia, M. Sollazzo, C. Traboni
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12. Ultrasensitive enzyme immunoassay (S. Hashida, K. Hashinaka and E. Ishikawa)
13. The politics of patent legislation in biotechnology: an international view (G.K. Rosendal)

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Biotechnology Annual Review
M.R. El-Gewely, editor

Biotechnology domain

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Abstract. Biotechnology and the use of biologically based agents for the betterment of mankind is an active field which is founded on the interaction between many basic sciences. This is achieved in coordination with engineering and technology for scaling up purposes. The application of modern recombinant DNA technology gave momentum and new horizons to the field of biotechnology both in the academic setting and in industry. The applications of biotechnology are being used in many fields including agriculture, medicine, industry, marine science and the environment. The final products of biotechnological applications are diverse. In the medical applications of biotechnology, for example, the field has been evolving in such a way that the final product could be a small molecule (e.g. drug/antibiotic) that can be developed based on genetic information by drug design or drug screening using a cloned and expressed target protein.

What is biotechnology?

There are several definitions for biotechnology in the literature. This mainly reflects that the field is changing too dynamically for a definition to stay conclusive. Webster's dictionary for example defines biotechnology as "the use of data and techniques of engineering and technology for the study and solution of problems concerning living organisms". The US Congress, Office of Technology Assessment (OTA) defines biotechnology as "Any technique that uses organisms or parts of organisms to make or modify products to improve plants or animals, or to develop microorganisms for specific use" [1], while the Organization for Economic Cooperation and Development (OECD) specifies that "biotechnology is the application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services" [2]. These definitions give a global description of the field without really revealing too much about its nature.

The word "biotechnology" itself was coined in German, biotechnologie, by Kar Ereky, the Hungarian engineer, in 1917, to describe all work by which products are produced from raw materials with the help of living organisms [3]. This description comes at a time of activities to use microorganisms and aseptic fermentation for much needed products such as glycerol, butanol and acetone [3].

However, the use of microorganisms to produce or to modify a product did not start at the beginning of this century. The ancient Egyptians, for example, were documenting

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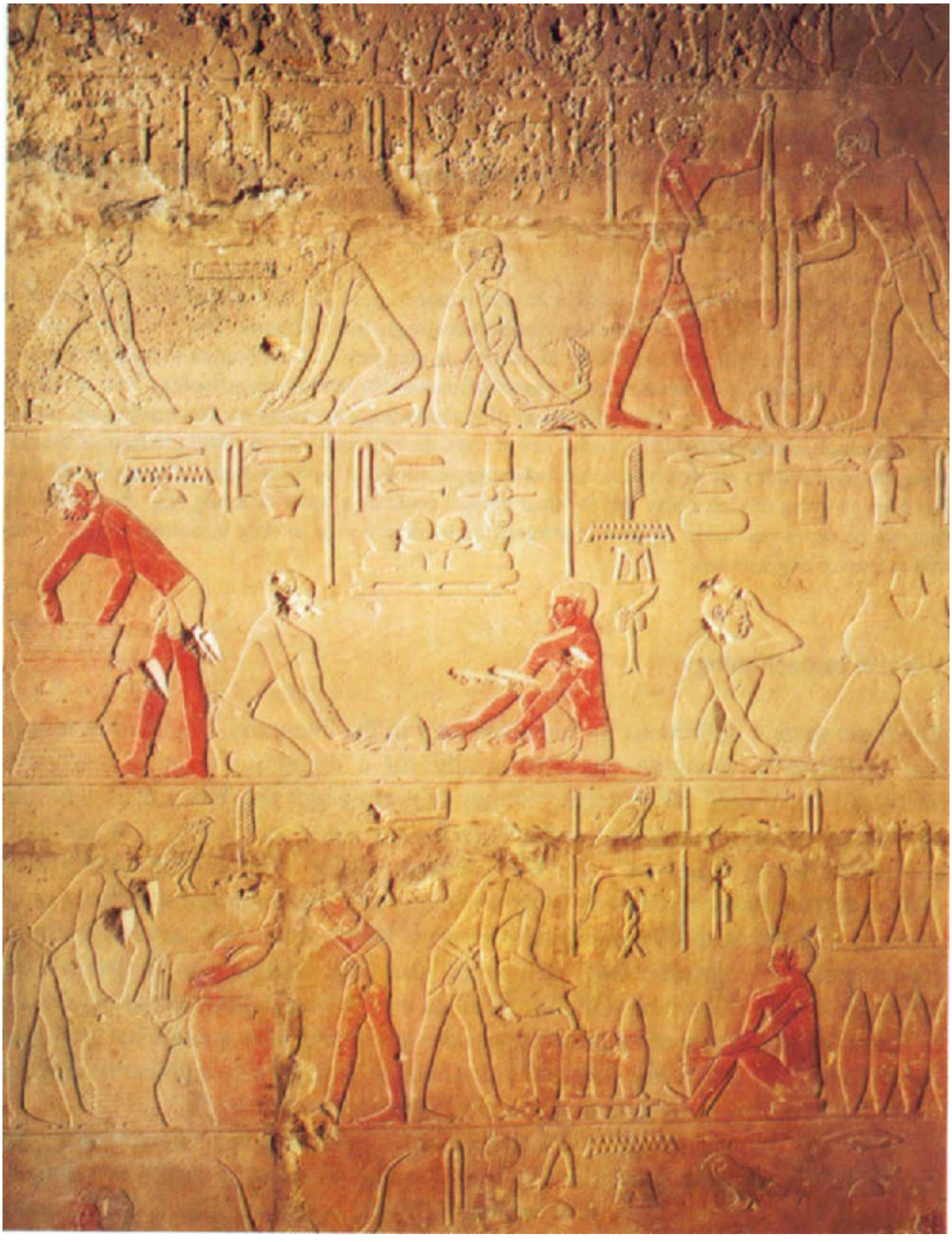

Fig. 1. This unique beer making scene shows the various phases of the ancient Egyptian beer making process as depicted on the entrance of the Mastaba chapel of Hetepherachet, a great official of the Egyptian Old Kingdom. Beer was made from baked bread. The bread was soaked in water and mixed with sweeteners like honey. The fermented mass was filtered and stored in large red pottery jars. Hetepherachet, the owner of the tomb lived under several pharaohs of the 5th dynasty (ca. 2400 BC). Hetepherachet was a judge and a priest of the goddess of Truth, Maat. The tomb from which this chapel scene derives stood at Saqqara, where the cities of the dead of Egypt's ancient capital Memphis are situated. The chapel is at the National Museum of Antiquities at Leiden, The Netherlands, since 1904.

the process of making bread, and the stages of the brewing process over 4,000 years ago (Fig. 1). They did not identify the exact microorganisms involved, or have all the conditions of these processes controlled, but it cannot be disputed that such "final" products could not be obtained without the use of living organisms. Robert Bud [3], in his elegant work, "The Uses of Life, A History of Biotechnology" emphasizes the last hundred years of development in the field, but argues that it would be wrong to grant equal antiquity to the concept of biotechnology. However, biotechnology, similar to many aspects of human activities, including the sciences, also has historical roots. A few decades ago, prior to the utilization of recombinant DNA in biotechnology, the field of biotechnology was quite different from the current expectations of biotechnology. We cannot by analogy, deny the status of a "biotechnology" company to all those companies that did not employ modern genetic engineering tools in their production methods. Human activities are always subject to continuous development, but we should try not to forget the roots, history, or the key mechanisms underlying progress.

Biotechnology, in its broad sense, has been utilized for centuries through its application in brewing, wine-making, bread-making, food preservation and waste treatment. Agricultural practices themselves, even before the rediscovery of Mendel's Laws of Genetics in 1900, reflect human activities in using the magic of harnessing solar energy through biological catalysis to produce valuable products directly from plants such as carbohydrates, oils, proteins, fibers and thousands of chemicals that included medicinal chemicals (Fig. 2).

The surface of the earth receives an immense amount of solar energy every day. The amount of solar energy received in 1 week equals all the estimated proven reserves of oils, natural gas, coal, and uranium (8×10^{11} tons coal equivalent) [4]. Recent estimates of the total annual amount of biomass (plant matter produced by photosynthesis) indicate about 2×10^{11} tons of organic matter, reflecting an average coefficient of utilization of the incident photosynthetically active radiation by the entire flora of the earth of only 0.27% [5]. Although the energy utilized by photosynthesis relative to the potential of utilizing the photosynthetically active radiation, plants are considered to be the biggest factory for the above compounds. The utilization of this energy by plants, algae or photosynthetic bacteria of higher efficiency theoretically could allow them to act as solar energy collectors at least in some geographical areas where water could

$$CO_2 + H_2O + \text{Nitrogen/minerals} \xrightarrow[\text{Plants/algae}]{\text{Solar Energy}} \begin{array}{l}\text{Biomass}\\ \text{(carbohydrates,}\\ \text{proteins, oils,}\\ \text{wood, fibers,}\\ \text{vitamins and}\\ \text{thousands of}\\ \text{other chemicals}\\ \text{including}\\ \text{medicinal}\\ \text{chemicals)}\end{array} + O_2$$

Fig. 2. The primary biological reaction in plants and algae.

also be available. Thus, harnessing solar energy by biological means could be a key to solar energy utilization, and it could be an area where developed and developing countries could cooperate for their mutual benefit.

It is of importance to understand that ancient civilizations did not just utilize "life forms"/microorganisms and plants, but they used also other biological materials that they considered to be of help. Such a use again was without fully understanding the exact mechanism of what they are doing or the exact product or benefit. Here I have to state the example of "Hirudin" which is now cloned and expressed in yeast cells, currently on the scale of several kilograms a year. Its market introduction as a recombinant therapeutic protein is planned for 1996 [6]. This protein was found to be a potent anticoagulant without any detectable side effects and allergic reactions [7]. Research indicated that recombinant hirudin appears to be effective as an antithrombotic [8,9] and following balloon angioplasty [10]. However, its natural use was from the ugliest and creepy organisms, *Hirudo medicinalis,* known as the leech (Fig. 3). The earliest documented record of leeches being used for medicinal/remedial purposes appears in a painting in an Egyptian tomb of around 1500 BC [11]. Leeching is also documented in medical encyclopedia from India compiled between 500 BC and AD 200 [12]. The history of the leech and leeching is exquisitely reviewed [7,11]. It is interesting to note that the company "Biopharm" was established to raise leeches for the production of chemicals and reagents from their saliva for pharmaceutical use [13]. Even microsurgery has found a use for leeching or leech products in preventing blood clotting around tissues/parts to be reattached [3]. Eglin C also produced by the leech, is a potent protease inhibitor (Fig. 4). It has been cloned and produced heterologously by *Escherichia coli* as a therapeutic protein against emphysema, septic shock, Crohn's disease, arthritis and arthrosis [14].

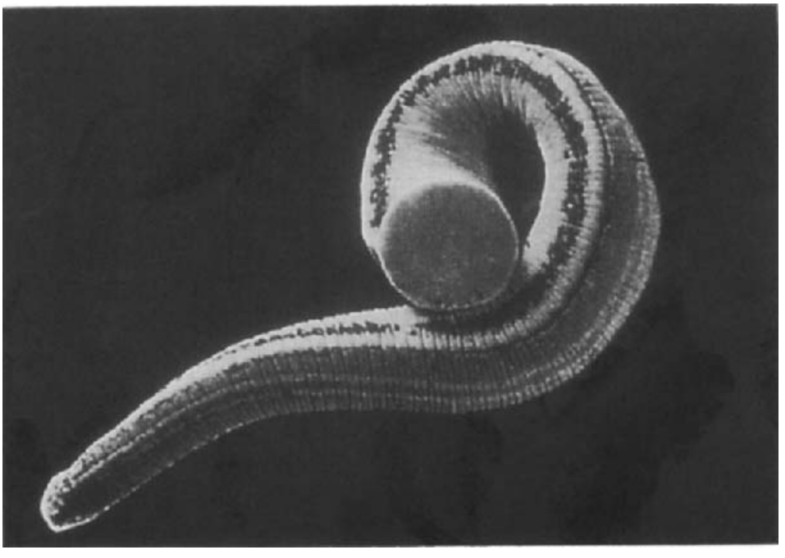

Fig. 3. The leech, *Hirudo medicinalis.* © Ciba-Geigy.

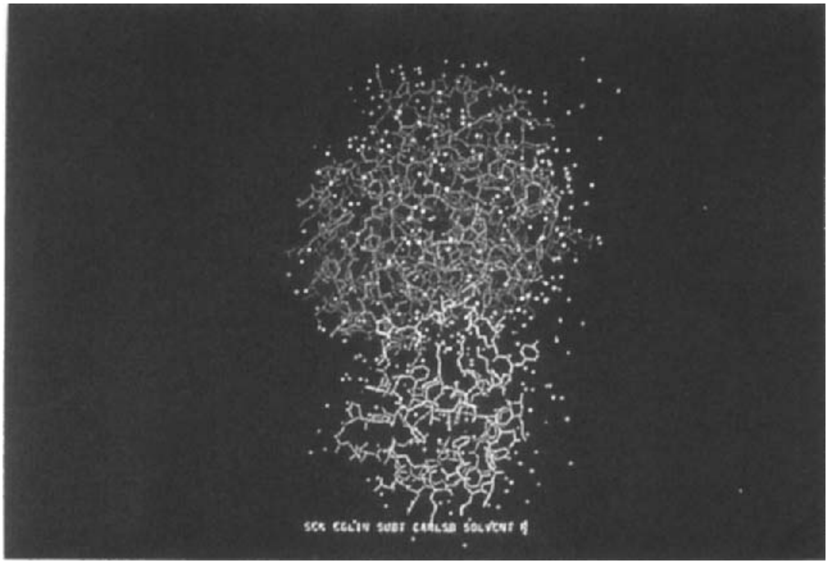

Fig. 4. Structural model of the enzyme eglin C, the lower and smaller molecule, in a complex form. © Ciba-Geigy.

This aspect of the utilization of biological life forms to produce products is still in harmony with the above definitions of biotechnology and does not really clash with the concept of biotechnology. As engineering techniques developed the whole process became much more efficient.

Early civilizations, in contrast, utilized some form of biotechnology based on unmodified organisms. This is conceptually similar to the current production of important products from unmodified organisms.

It is not the purpose of this chapter however to review the history of biotechnology. The history of biotechnology, particularly of the last 100 years, has been recently and elegantly reviewed [3,15].

If biotechnology in its utilization of microorganisms and aseptic fermentation as a form of viable and economical industry has existed for nearly a century, the word biotechnology itself became a common word only in the last two decades. This is mainly due to the use of genetic engineering in biotechnology in the mid-1970s. Modern genetic engineering and molecular biology techniques revolutionized the whole field of biotechnology. It is equally important to indicate that these techniques also revolutionized all aspects of academic research in biologically related fields, enabling scientists to do and verify what could not have been done before, at least not with the same speed. These techniques made it possible to research how genes and cellular mechanisms work by physically isolating genes, resolving their nucleotide sequence, finding regulatory elements, and verifying the protein or RNA product, in addition to providing a wealth of information about the molecular similarities or differences between genes of the same organism or between different species. These similarities not only helped in

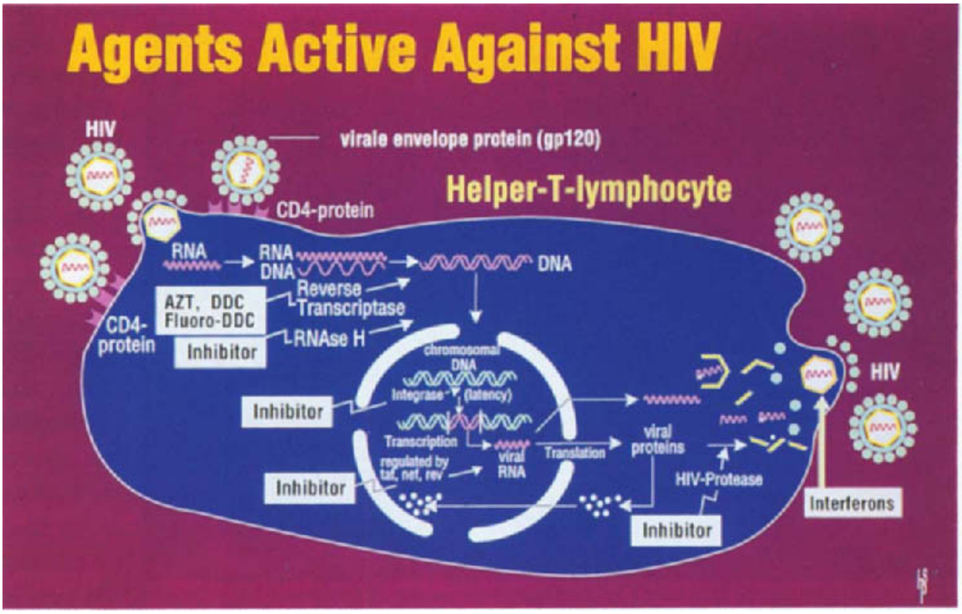

Fig. 5. Anti-HIV agents and sites of action. © F. Hoffman-La Roche Inc., Basel [15].

establishing the evolutionary lineage between related or unrelated species on a molecular basis, but, more importantly, could provide additional insight into how proteins work and how the primary sequence of a protein is correlated to its function, since the active sites of proteins are usually least subject to change.

Similarly, the application of genetic engineering techniques in the field of biotechnology made it possible to study and use important proteins that are naturally produced in normal cells but are not, for example, produced in amounts permitting investigations to elaborate on the understanding of their precise role in the cell. Several of the proteins in the pharmaceutical market now are therapeutic proteins that are produced through the application of genetic engineering. Other therapeutic proteins that are produced by biotechnology now include proteins that were utilized prior to the utilization of genetic engineering and that were produced for example from animal sources (e.g. insulin) or from the human cadaver (e.g. human growth hormone).

Recently, with further developments in the field of biotechnology, proteins that are produced by genetic engineering by themselves are not the final product, but rather are the tool in drug design and screening. As an example of this new strategy, recombinant transcription factors are the basis for the development of new pharmaceuticals [16]. Several of the antiviral strategies to develop drugs for the treatment of the HIV virus are based on the screening of inhibitors of the function of key viral specific proteins [17] (Fig. 5).

Therefore, gene technology and genetic engineering should be at the core of modern biotechnology. These technologies are continuously opening new potentials and applications. At the same time new advancements in basic research have a direct impact on the field of biotechnology. No single biological system so far has been fully characterized in terms of our total knowledge of its genetic information or even its expressed proteins under normal or different physiological conditions. The impact of this knowledge to further enhance the potential of biotechnology cannot be underestimated. The application of 2-D gels to identify proteins of *E. coli* and other organisms is discussed in this volume [18].

Modern definition of biotechnology

Biotechnology is an interdisciplinary science dealing with optimization and utilization of biological catalysis and genetic information for the development of useful products or systems.

The economic impact of biotechnology cannot be ignored as a vital progressing industry. In the USA alone, in 1991, sales of biotechnology products approached $4 billion and are expected to reach $50 billion in about 10 years [19].

The interdisciplinary nature of biotechnology

Clearly, many basic fields such as genetics, molecular biology, biochemistry, cell biology, microbiology, immunology, chemistry, pharmacy, pharmacology and chemical engineering are providing basic information and depth to the field of biotechnology. Several types of products/output of biotechnology could result from such a positive interaction (Fig. 6).

Why gene technology?

Genes control biological processes in all living organisms in coordination with environmental or external stimuli. Therefore, it is only logical that the genetic approach is the most direct approach to harness and optimize bio-catalysis, or to design a product based on the function/structure of a biomolecule that can be produced by genetic engineering.

Several companies were formed that were entirely dedicated biotechnology companies (DBC) in addition to the established companies that started to use biotechnology and genetic engineering methods.

Although the applications of biotechnology are expanding rather rapidly to cover a great deal of human activities, some aspects of catalysis could be accomplished chemically rather than biologically. The use of biological catalysts of course could be carried out at much lower temperatures and under less extreme conditions with virtually no pollution and other health hazardous compounds that are dangerous both to workers and society. Biotec hnology itself is used to solve the problems of industrial waste or chemical pollution. Chemistry remains a very important aspect of modern biotechnology; however, several aspects of modern biotechnology could not be achieved by chemistry alone.

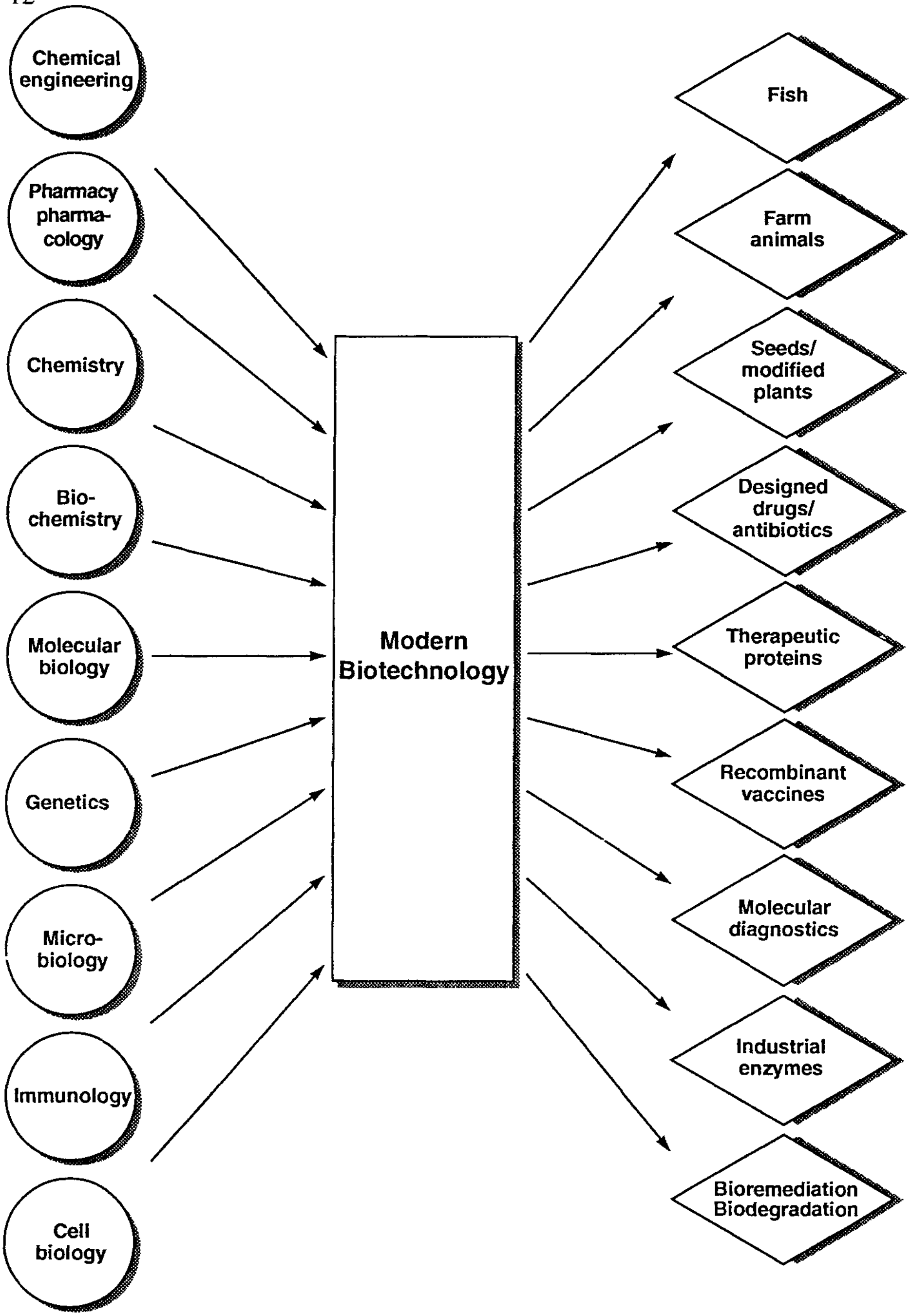

Fig. 6. Input–output of biotechnology.

Advantages of genetic engineering and modern biotechnology in comparison to classical methods of biotechnology

1. *Amplification of rare, but useful proteins.* Gene technology can help in produc-