EXPLOITING BIOTECHNOLOGY

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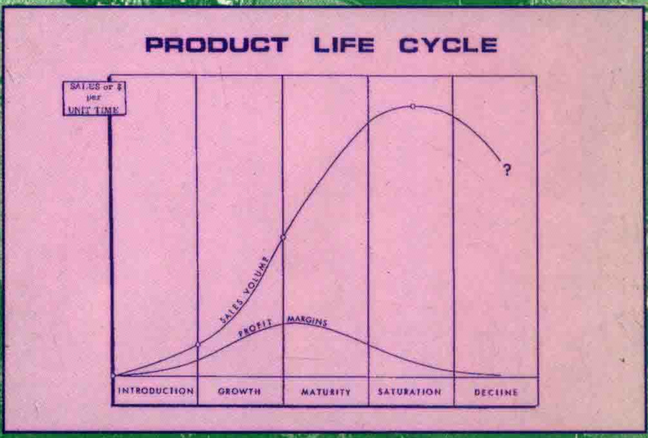

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Preface

Biotechnology is at once intensely technical and intensely commercial: looking at either aspect without the other might do for some applied sciences but would not make much sense for this important and growing industry.

The scientific basis of biotechnology powerfully excites the attention of biologists, chemists, engineers and indeed all manner of technically minded professional and lay people. Its commercial relevance inevitably attracts the curiosity not only of people who just wish to understand what is going on around them but also of those whose business it is to take stock of the world of industry, and to perceive patterns of development and the nature and sizes of present and future markets, in order to decide where investment should or should not be made. Understanding in any depth the impact that biotechnology will increasingly have on human affairs, or making commercial decisions about technical investments, must be more than a little difficult for anyone whose education and training does not include the science and engineering on which the technology is based.

It is for those readers, students of biotechnology as well as people without much direct experience of science, that the authors planned which topics to include, how to present them and the detail each one would merit. While mainly scientific and technical in its approach and in the material it covers, the book hopes to satisfy both scientific and business interests. It outlines the commercial and business contexts in which biotechnology contributes products and services to society; it also reviews the most relevant national and international regulatory and legal issues, and touches briefly upon some of the wider economic and ethical concerns. Primarily, however, the book seeks to explain to people with no special knowledge of chemistry, and with no more than a layman's appreciation of biology, both the promise and the limitations of using living organisms and their products in industry.

Mostly, but not entirely, taking that technical point of view, we look to future developments which might take place if the economic climate were right and the appropriate business opportunities perceived. Recognizing that people with scientific interests often have little understanding and limited experience of commercial activities, activities which are nevertheless critical for the success of biotechnology in the marketplace, we have tried to describe what commercialization in biotechnology is like, how it is managed, what has to be done and what avoided. But we do not attempt to predict, company by company or industry by industry, what is going to happen; commercial organizations are reticent about their future plans and the authors do not attempt to divine their intentions.

Rather than undertaking in-depth analyses of specific sectors — matters for the relevant industrial and commercial experts — the purpose of this book is to make accessible a general understanding of the technical base on which biotechnology rests. It also offers a broad view of the commercial and industrial applications which have already been made or are likely to be developed before too long. Having read it, those who do want to understand the significance of future biotechnological advances as they are reported, or who have to make decisions involving biotechnology, may do so with as great an understanding of the technology as a busy person can reasonably expect to acquire.

Inevitably, there are omissions. In no sense is this book a comprehensive catalogue of all that is going on. To satisfy that objective would have required a volume many times longer and demanded of its readers an extensive knowledge of the underlying sciences. Moreover, the subject is moving so fast that, however hard the authors might have tried to include every last bit of news, publication delays would inevitably have led to the omission of many interesting items. We have tried instead to offer a balanced presentation of current activity and where it might lead in the short- and medium-term. Long-term guessing is necessarily very risky and only rarely have we dared to do it. Those guesses should be taken in the spirit in which they were written: to provoke but by no means to predict.

Contents

1 What biotechnology is all about

THE WORD "BIOTECHNOLOGY"

Two or three decades ago the word would have meant little to biological scientists – something about biology, obviously, but what exactly? Had it been uttered at all it would have conveyed a sense of doing things, presumably in a useful way, perhaps involving machinery. But what connection had biology with machines? By the mid-1970s, however, *biotechnology* as the name for a new industry was clearly gaining popularity and in many people's minds was associated with some of the spectacular advances in what was then the new subject of *molecular genetics.*

Genetics is the study of inheritance. It has been used empirically throughout human history for breeding better strains of domesticated animals and crop plants. People knew how to achieve beneficial results but why their efforts were successful did not begin to become clear until the late 19th century and real understanding in terms of chemistry had to wait a further hundred years. About two decades ago geneticists discovered a series of biochemical activities, universal and normal in living systems, which showed them how to manipulate genetics to produce totally new effects; these permitted industrially convenient microorganisms to be used as living factories to make products until then available only from animals or people. That was the birth of what became known as *genetic engineering.*

Those discoveries had startling effects both on the scientific world and on sections of the industrial, commercial and financial communities. Excitement mounted as speculation grew about the possible impact of the new genetics. There were clearly going to be ethical considerations and effects on public policy. Parallels were drawn with the growth of computing, another area of novel development profoundly affecting human activity. And thus appeared that new word which at times, and for some people, became virtually synonymous with genetic engineering.

WHAT BIOTECHNOLOGY IS REALLY ABOUT

Biotechnology is not just genetics. It is a technology, a set of techniques for doing practical things, all of them with implications for the commercial and/or the public sectors: making products and providing services which can be sold for a price in the marketplace, or paid for from the public purse. In that way it differs fundamentally from the underlying sciences which are neutral with respect to industry and commerce. The biological sciences are dedicated to the exploration and comprehension of natural phenomena; biotechnology is about using those sciences as a basis for industry and commerce. Although some definitions are rather elaborate and perhaps a bit woolly,* biotechnology is fundamentally about making money with biology.

Logically it must include all the commercial ways of using biology, the old and traditional as well as the new, agriculture and brewing as well as manipulating genes to produce new drugs or designing biological procedures for mining minerals from the earth. While some people do take that broad view, for others biotechnology retains a strong genetic engineering connotation. It really does not much matter: what is important is an appreciation of the commercial opportunities which have developed and are developing in the current invigorating climate of biological innovation.

Recognizing its promise for the existing activities in agriculture, pharmaceutics, sewage treatment and fermentation, the broad view takes modern biology into areas where it has never had more than a tenuous presence: waste management, electronics, new materials, and the recovery and processing of minerals are among the more prominent. Even civil engineering is beginning to throw up opportunities for a biotech. dimension. Biotechnology, to the extent that it has something valuable to offer these activities, is becoming an integral part of modern practice and it might be more realistic in some of those contexts to use the term *biological engineering* rather than biotechnology – some people are beginning to do just that.

BIOTECHNOLOGY AND SCIENCE

One of the more remarkable things about biotechnology is that fundamental scientific advances proceed hand-in-hand with industrial development and commercial exploitation. Change has been and continues to be very rapid. The immediate scientific discoveries which led to genetic engineering were made in the late 1960s and early 1970s; the article which first brought the new possibilities clearly into public focus was published in 1975 and frontier research continues to be an essential part of technological advance.

By the end of the 1970s a number of commercial companies were already working directly to generate saleable products based on the new knowledge. Genentech and Cetus, among the first of them, became public corporations in 1980 and 1981 with major and highly successful public stock offerings. The laboratories of these and similar new companies were almost indistinguishable from the best in the universities except perhaps for the greater lavishness of their capitalization. And the scientists, too, were indistinguishable, hardly surprising as most had joined directly from university laboratories and many who remained professors accepted part-time consultancies with the companies.

Now, 20 years on, biotechnology has acquired maturity without losing zest and excitement. The earlier dedicated companies have long since recognized that they cannot do everything and have identified the areas in which they will concentrate their main efforts. While some of the original companies have merged with or been taken over by others, much of the pharmaceutical

* This one, for example, is from a document published by the UK Department of Trade and Industry: *Biotechnology, defined as the application of advancing understanding of living organisms and their components to create new and improved industrial products and processes.....*

and some of the chemical industry, once a little slow in perceiving what the advent of the new mood in the biological sciences might mean in industrial terms, made up for lost time and established their own biotechnological activities. Gradually, but gathering strength with each successive year, came the more obviously engineering-related developments: in mining, enhanced oil recovery, electronics and elsewhere. The incubation period to the market place has generally proved to be longer and the capital investment greater than many expected. But new products and services are now being sold profitably and many who keep a close watch on developments predict a rapidly rising revenue curve for the decades to come.

Prospects, Short- and Longer-term

A number of near-and longer-term biotechnological products and services can tentatively be identified with different degrees of clarity in the various industries. Science and technology permeate these categories, each of which primarily represents a set of marketing opportunities. Most of them will be discussed in greater detail in succeeding chapters and are listed here as a convenient summary.

Healthcare

Diagnostics and therapeutics are convenient to group together although their markets are rather different:

- Vaccines, including ones effective against AIDS and malaria;
- Anti-cancer drugs;
- Antibiotics;
- Gene therapy to treat inherited disorders;
- New diagnostic methods for improved recognition of specific disease;
- Genetic fingerprinting for medical and other purposes.

Industrial Products

Including new materials, they number:

- Polymers;
- Surfactants;
- Steroids;
- Intermediates in the production of chemicals;
- Bioplastics;

- Alcohol from sugar;
- Bone and tissue replacement materials.

Agriculture and Food

In an enormous area of activity with profound economic, social and political implications, important developments are likely to include:

- Genetically engineered plants via tissue culture and clonal propagation;
- Better resistance of crop plants to herbicides, insecticides and disease;
- On the other hand: better, especially "natural", pesticides;
- New plant strains for better quality, storage properties and processing;
- Reducing and avoiding the need for fertilizers;
- Animal healthcare;
- Use of hormones to give higher product yields;
- Genetically improved animals;
- "Biopharming" – using plants and animals to make foreign proteins;
- Novel foods and food ingredients, including single-cell protein;
- Modification and upgrading of existing raw materials;
- High-intensity sweeteners;
- New and improved flavours and fragrances.

Waste Management and Pollution Control

A cleaner environment is now everybody's dream. Biotechnology can help with:

- Oil spill clean-up;
- Removal of toxic metals, noxious organic materials and radioactive elements from discharge effluents;
- Landfill management and methane emission control;
- Bioremediation – the cleanup of contaminated sites;
- Improvement of natural waters.

Mineral Resource Recovery and Processing

As the best mineral ores and oil reservoirs become progressively exhausted, new methods will be needed to work both the remaining residues and the poorer deposits which will gradually become the main sources. Biotechnology is already involved with:

- Microbial mining: the leaching of metal from *in situ* ore bodies;
- Metal leaching from low grade ore dumps;
- Desulphurization of coal;
- Crude oil production: microbial methods for the enhancement of oil recovery.

Electronics

Interactions between biotechnology and electronics are already established. Some products are now on the market and others must be expected to follow in due course:

- Biosensors for detecting and measuring specific chemicals in medical diagnostics and manufacturing processes;
- "Biochips" — a new concept of biotechnology-based computers.

These are the real and prospective end products based on the discoveries of the basic sciences coupled to the practices of business, management and finance. Together they make up the present reality of biotechnology. The future is naturally more difficult to define but in a final chapter we will try our best to look ahead to see if it is possible to discern the shape of things to come.

Supplies for Biotechnology

The wide range of resources, many of them commercially available, needed for research, development, manufacture and the marketing of biotechnological services represents another major category well worth a mention. Because of their technical complexity and diversity, they are difficult in this general book to discuss in detail and are therefore presented in outline only. Biotechnological supplies include:

- Equipment for laboratory investigations, product testing and manufacturing;
- Chemicals, biochemicals, radioactive compounds and other consumable materials for the same purposes;
- Analyses, custom-syntheses and other specialist services;
- National and international collections of microorganisms. Payment of a small administrative fee will usually make a microbial culture available for academic research; their

use for industrial (profit-making) purposes is likely to involve a more extensive payment, perhaps via an up-front or royalty fee, or both;

- Information sources. Scientific and technical information is available in national, university and professional society libraries. Access may be entirely open, free to members of the relevant society or permitted for a small fee. Photocopies of individual articles can be obtained from central sources, again for modest fees. Many on-line data bases may be accessed on a commercial basis; searching can be expensive if a wide trawl is undertaken.

The supplies sector is currently the most mature in biotechnology and certainly the most profitable: more than half the companies involved report profits. In therapeutics, by contrast, no more than a quarter of the existing companies have sufficient resources to survive for three years while, with their present level of business activity and profitability, 40% will not be able to last more than a year without additional capital.

2 The science...

Biotechnology is essentially about commercializing biology; every aspect of this very broad subject may sooner or later provide opportunities for business development and as biotechnology grows so does the range of its biological involvement. The word "biology", however, conveys a sense of uniformity and cohesion that active biologists proclaim philosophically but do not necessarily practise. Biology is just too big. Individual practitioners usually affiliate to one or another of the biological sciences, of which there are many: a botanist, a biochemist or a zoologist are all biologists but all specialists.

The branches of biological science most intimately related to biotechnology at the present time are:

- *biochemistry*, which addresses the chemical structure and behaviour of all types of living beings; hence it is directly concerned with employing biological processes to provide useful products and services;
- *genetics*, the study of inheritance and the relationships between individuals and populations; in recent times it has become increasingly concerned both practically and theoretically with the biochemical mechanisms of inheritance and development, and the ways they can be used to do and make new things in biotechnology;
- *microbiology*, a field closely integrated with both biochemistry and genetics, which explores and manipulates microbes of all sorts, the main category of living organisms used industrially.

Each of them warrants some discussion here.

BIOCHEMISTRY

In a sense, biology is a special sort of chemistry and, as biotechnology is a way of using biology, it too is based on chemistry and things that change or are changed in a chemical way. Biotechnology uses biological mechanisms to generate products and services for sale. The products are chemical ones and the services chemical services. For the non-specialist, a short general introduction to chemistry might at this point be useful because people who have never studied it will have little familiarity with what chemistry is about or why it is so helpful for understanding biotechnology.

The Importance of Chemistry

All materials and substances constitute the province of chemistry, a subject concerned with the way that *atoms* are joined together to form *molecules*. A material made up entirely of one kind of atom is called an *element.* There are 105 of them and some, like iron, aluminium, chromium, nickel, platinum, carbon, chlorine, iodine, copper, lead, gold, silver, mercury, tin, zinc and tungsten are often encountered in a fairly pure form in everyday life. Others, including sodium, potassium, calcium, oxygen, nitrogen and neon, sound familiar enough but are rarely or never encountered in the pure elemental state outside the laboratory or factory. That leaves dozens more: phosphorus, silicon, uranium and plutonium are well-known words although the pure elements are beyond common experience, while obscure and exotic elements such as praseodymium, ytterbium and gadolinium abound.

Certain elements can be mixed together in any proportion: metallic alloys are mixtures like that. Brass, made of various proportions of copper and zinc, is a widely used material and its actual composition can readily be varied in order to fine-tune the properties of the alloy. *Compounds,* by contrast, are not mixtures whose composition can be altered at will but are collections of molecules: precisely defined groupings of certain atoms in specific proportions, joined together in a unique and invariant manner. Many common materials like wood, cloth, foods, air, petrol and most rocks are actually mixtures of chemical compounds which can more or less readily be separated from one another. Water, common salt, refined sugar, washing soda, chalk, glycerine, acetone and alcohol virtually exhaust the range of pure, or almost pure, compounds familiar to most people. Many elements which are rarely found in the pure state as elements are nevertheless major constituents of commonplace compounds. Salt is an example; it is composed of the two elements sodium and chlorine, neither of which occurs in nature as the free element although chlorine manufactured industrially is used to purify water and many people will recognize its odour.

The number and variety of atoms in each molecule of a compound, and the way they are joined together, are all critically important in determining the properties of that compound. For example, water and salt are made of entirely different atoms and are obviously very different materials. Sugar and alcohol are also very different from one another, yet they are made of the same atoms but in different proportions and joined together in different ways. Chemistry is about understanding the behaviour of the huge number of known chemical substances and exploring how they interact with one another, inventing and discovering new ones and manipulating them to make useful products.

Chemical Change

Apart from the elements, everything around us, including ourselves and all other living things, is made up of chemical compounds, many of them in a fairly continuous state of change. A good part of industrial activity is dedicated to channelling those changes along pathways useful to us as producers and consumers. We refine oil, smelt metal ores, treat sewage, ferment sugar to alcohol, make cheese from milk and convert a whole host of feedstocks into antibiotics, flavourings, industrial chemicals and other useful materials. All that work needs energy; indeed, the classic definition of energy is *a capacity for doing work.*

Energy is required for these chemical activities because the final products are more complicated and often purer when they are sold, than their raw materials. Effort is needed to put complicated chemical structures together, just as it is for building bridges or making cars. Energy is also needed for purification, that is, separating a product from the feedstock and any by-products, just as it is needed in the extraction of a metal from its mineral ore or separating the wheat from the chaff. High temperature and pressure, electric discharges, radiation and other sources provide energy for chemical processes in industry: none of these is directly useful for living systems. They have to get their energy in other ways.

Fuel, Energy and Feedstocks

Much of the energy used by human societies comes from burning fuel in boilers, motors and engines, either on site or at electricity generating stations. In chemical terms, burning a fuel usually means *oxidizing* the chemicals of which it is composed, combining it with oxygen from the atmosphere and liberating energy. In total there is more energy in the fuel and the oxygen before they interact in the process of burning than in the products of their combustion – the balance is released as heat and light or in other forms. Compared with the non-living world, biological systems need a great deal of energy. By inanimate standards, both their chemical compounds and their internal and external organizations are extremely complicated; building such highly complex structures is very energy-demanding. So living organisms need fuel for energy and many of them, including most of the microbes and all the animals, get it by oxidizing (burning) the chemicals in their food. Since those chemicals come from other living things, they are already complicated substances with a high potential energy content, entirely suitable as raw materials for animals and microbes to build their own bodies and to oxidize as fuels to supply themselves with energy.

The chemistry of biological oxidation is basically similar to any other but compared, for example, with the explosive combustion of petrol in a car engine, the rate of energy release in biological systems is low so living organisms do not become as hot as engines. But the biological process is far more efficient, with more useful energy being produced for each unit weight of fuel burned.

Green plants do it differently. Most of their energy comes not from oxidizing materials derived from other living things (although a few of them do that, too) but from the sunlight which the green pigment in their leaves is designed to trap, a process called *photosynthesis.* The sun powers the plants; the plants power the herbivorous animals; they in turn fuel the carnivores while many microbes live off the dead remains (and sometimes the living bodies as well) of all of them, including other microbes. The whole system goes round and round, driven by sunlight.

Energetics is obviously fundamental to life and much of the biochemical apparatus of living organisms is directly concerned with mobilizing and using energy, activities tightly integrated with all the rest of the organism's biochemistry. It is time to explore that biochemistry a little further because it is mostly there that biotechnology is based.

As well as needing a supply of fuel, living things have to have raw materials for building their own substance and for carrying out internal repairs. For green plants most of this need is easily met by carbon dioxide from the atmosphere. But neither animals nor most microbes (the group of organisms of greatest importance for product generation in biotechnology) possess within their bodies the capacity for using a feedstock as simple as carbon dioxide to make the range of chemicals they require for their own internal biochemistry. They therefore need more elaborate "food": other living organisms or complicated chemical products derived from them. The food each individual ingests, much of it chemically different from its own characteristic compounds, has to be converted into exactly the right building materials for its own needs. It is digested down to simple components, many of which have to be refashioned before later being assembled into the organism's own characteristic substances.

Biochemical Complexity

Biochemical compounds exist at two levels of complexity. Most of the body chemicals collectively contributing to the bulk of an individual are actually made up of large numbers of small units, or individual "building blocks". Thus, *proteins*, about which we will have a good deal more to say, are long chains made of small *amino acid* units joined together in a row. Many *carbohydrates*, like *starch* or *glycogen* ("animal starch") consist of variable length chains of individual sugar (*saccharide*) units. *Deoxyribonucleic acids (DNA)*, the compounds so important in inheritance which convey genetic information from parent to offspring, are also constructed of chains of units, in this case called *nucleotides*. Only the fats are not unitized in this way. Compounds made of long chains are called *polymers*; the word implies a series of multiples but does not specify precisely the number of units. Each individual unit (amino acid, sugar or nucleotide) is a *monomer* and other simple words describe chains of two, three or four units, etc. (*dimer*, *trimer*, *tetramer*, and so on).

There is a critical difference between *polysaccharides* (long chain carbohydrates) on the one hand, and proteins and nucleic acids on the other. The units in polysaccharides are either all the same or may comprise two or three different ones arranged in a simple alternating sequence. If the letters A, B and C represent three different monomeric sugar units, typical carbohydrates might be represented by:

–A–A–A–A–A–A–A–A–A–A–A–A–A–A–

or

–A–B–A–B–A–B–A–B–A–B–A–B–A–B–

or

–A–B–C–A–B–C–A–B–C–A–B–C–A–B–

Proteins and DNA are very different. The amino acids in protein chains are of 20 different sorts. Because the chemistry of each type of amino acid differs from that of all the others, and many different interactions are possible among the component amino acids within the protein molecule, the properties of the protein of which they form a part are governed both by the total number of amino acids in the chain and by their sequence in the linear array. It