Perspectives in Biotechnology

Edited by

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A. T. Bull and
G. Holt

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PREFACE

This book is the proceedings of a NATO Advanced Studies Institute organized jointly by LNETI, the National Laboratories of the Ministry of Industry of the Portuguese Government and The Institute for Biotechnological Studies in the UK. The ASI was held in 1985 on the beautiful peninsula of Tróia, once the site of a flourishing Roman salt industry.

The course was the first in the NATO "Double Jump Programme" specifically aimed to promote industrial and academic participation and cooperation. As such, contributions across the whole field of biotechnology were planned and the present volume represents perspectives from specialists in different areas. Biotechnology has been defined in a recent OECD publication as "the application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services" and the contents of this book, which often describe research from interdisciplinary groups, reflect this title. The value of the ASI was further enhanced by many first class poster contributions from the participants.

Looking at the development of biotechnology, three generations can be recognized. The first was based upon the empirical exploitation of micro-organisms; the second saw the introduction of scientific and engineering principles for industrial-scale fermentations; but the third, not constrained by nor dependent on the scientific experience of the past, is based on totally novel technology and particularly those of recombinant DNA methods. We are now embarked on the next major - and possibly last - industrial revolution. It was against this backcloth that senior academics, industrialists and many young researchers were brought together to explore developments in biotechnology - a stimulating experience for all concerned.

I and my fellow organizers and editors, Professors Archer, Bull and Holt, would like to express thanks to the Scientific Committee of NATO whose support made this meeting possible. Our deepest appreciation also goes to many other organizations and people who contributed to the Institute's success. There are acknowledgements on the following page. Finally, it is a pleasure to thank all the course lecturers and participants. I hope this volume will be a reminder to them of their visit to Portugal and a useful text to many unable to join us in Tróia.

José C. Duarte
Course Director, Lisbon

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The Organizing Committee:

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L. Archer
A.T. Bull
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BIOTECHNOLOGY: OPPORTUNITIES AND CONSTRAINTS

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DEFINING BIOTECHNOLOGY

During the decade since 1974 more than thirty national and international reports have been made on biotechnology and most of these have attempted to define the subject. We (Bull, Holt and Lilly, 1982) have chosen to define biotechnology as "the application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services". Such a definition is inclusive not only of actual processes in which the biological agent is used but of those processes also concerned with its preparation and with the processing of biological materials resulting from its action.

Despite the plethora of recent discussions it is worth reiterating that biotechnology is not a distinct discipline but a field of activity; neither is it an industry per se but a group of inter-related technologies that are applicable to a wide range of manufacturing and service industries. Whereas the ancient antecedents of biotechnology are well known, the scientific and commercial excitement of the "new biotechnology" has developed with quickening pace since the emergence of biochemical engineering, enzymes as industrial catalysts and, most recently, genetic engineering. Analysis of this new biotechnology reveals many of the problems that characterise the translation of scientific invention to commercial exploitation: technology push or market pull?; access to information and technology transfer; availability of finance; university-industry relations; roles of government; education, training and manpower provision; patent protection.

The basic conclusions presented in the OECD Report "Biotechnology: International Trends and Perspectives" (Bull et al., loc cit.) have remained valid. It "has proved to be remarkably accurate and has had a positive policy impact by alerting governments to problems" (OECD, 1986). Inevitably the benefit of hindsight leads to a reappraisal of certain issues and events since the Report's preparation argue that insufficient stress was placed on specific scientific issues such as plant biochemistry and molecular biology, protein engineering, membrane technology and bioelectronics. Nevertheless, the comprehensive check list of issues presented as a base for strategic planning (Table 1), and subsequently closely echoed by the US Office of Technology Assessment (OTA, 1984), is a useful point of departure.

Table 1. A Checklist for Strategic Planning in Biotechnology

1. Resources
   - Raw materials including feedstocks
     - water
     - minerals
     - energy
   - Land availability
   - Competing technologies
   - Manpower

2. Scientific and Technological Infrastructure
   - Education
   - Training
   - Research base
   - R & D priorities
   - Information transfer

3. Climate for Innovation
   - Invention - innovation time lag
   - Industrial base
   - Competition
   - Finance
   - Regulations
   - Patent laws
   - Social acceptability

4. Trading position
   - Commodity prices
   - Import-export balances, especially for food
   - Markets

5. Environmental Considerations
   - Land use
   - Effluent and waste, its location and management

From Bull et al. (1982)

Over the present decade the focus on biotechnology necessarily, and desirably, has shifted from the wonder of the new science to its commercial exploitation. The commercial realisation of the new biotechnology broadly has occurred in two phases. First, one that was dominated by small, narrowly based companies - in terms of the technology offered - that had "high tech" profiles and that concentrated on R and D rather than bringing products and processes to the market place. The second, present phase is much more orientated towards commercialisation where companies realise that, among other things, long term success will be built upon market-led developments, command over several or all of the necessary resources, and an international operation and structure. The NATO Advanced Study Institute, of which this book is the proceedings, was the first "Double Jump" programme in biotechnology and as such sought to provide a forum for university-industry-government discussions. This chapter does not purport to predict the detailed development of biotechnology. It is intended to provide a realistic background against which to explore future developments and as such it is concerned with (1) the relative positions of present day biotechnology-based industries, (2) the stimuli for innovation, (3) an analysis of the major industrial sectors, (4) the characteristics of the new biotechnology, (5) constraints on development, and (6) the determinants of successful biotechnology.

THE PRESENT SCENE

Attempts at global analysis of national biotechnology statistics have been made (for example, see OTA, 1984) but are outside the scope of this chapter. Instead brief reference will be made to the U.K. position which reveals many features common to industrialised nations.

In 1980, the contribution of the fermentation sector to the total sales of manufactured products in the UK was about 5% (equivalent to ca. £6500m). Although this sector is dominated by traditional drinks and foods, and by waste water treatment, the relative importance of particular fermentation products can best be assessed in terms of balance of trade figures (Dunnill, 1983; Table 2). We highlighted earlier import-export balance as a major determinant in strategic planning (Bull et al., loc cit.); some obvious considerations which emerge for British planning include:

- possible competition for strong traditional products (whisky);
- political restrictions preventing the improvement of trading position in commodities (sugar);
- need to maintain strong R&D effort to hold the present competitive position (antibiotics);
- opportunities for commercial development of patentable, high value-added products whose manufacture will be influenced particularly by genetic engineering (animal proteins).

Dunnill (1983) also draws attention to the price-volume relationship of biological products, the inverse nature of which has been long recognised in other manufacturing industries. Here the initial attraction of low volume, very high price products (particularly in health care) may have to be tempered by considerations of aggressive, world-wide competition (problems of patent protection; alternative routes to production; small scale production). On the other hand, innovations in the production of and adding value to commodities, such as baker's yeast and beer are likely to provide significant market opportunities.

Table 2. Net Balance of Trade for the UK in 1980

	Balance £M
Whisky	+ 741
Antibiotics	+ 120
Confectionery	+ 96
Vaccines	+ 7
Enzymes	+ 1
Lysine	- 1
Insulin	- 6
Glutamic Acid	- 6
Beer	- 17
Molasses	- 34
Wine	- 259
Sugar	- 290

From Dunnill (1983)

STIMULI FOR INNOVATION

The above snapshot leads naturally to a consideration of those factors that influence change and innovation in biotechnology. The reader is referred to an earlier analysis (Bull et al., 1979) for background information while the following is offered as an up-date of generally applicable influences.

Crises And Their Resolution

Food and population: although this is a prevailing factor in many parts of the world, the disastrous soya bean harvest of 1973 in the USA clearly promoted renewed interest in single cell proteins.

Energy: the increase in the price of crude oil during the 1970s catalysed enormous (and often ill-conceived) R&D and manufacturing projects for ethanol and other biofuels and chemical feedstocks.

Environment: the gradual appearance of "green" movements over the past 20 years has influenced thinking on waste management and pollution abatements.

Metals: the real, or artificially manoeuvred, shortage of "strategic" metals used particularly in the defence and electronics industries has focussed growing attention on biohydrometallurgical routes to metal winning.

Crises, however, notwithstanding their magnitude and impact, represent moments of danger or disaster but not infallible guides to the planning of biotechnology. Those crises outlined above largely have been resolved, albeit only partially or imperfectly, by factors outside biotechnology, e.g. developments in traditional agriculture, deep sea oil and gas recovery, and material science; political activity and inactivity.

Scarcity

Scarcity here refers to existing market products, such as amino acids, vitamins, steroids, hormones, enzymes, proteins, that are traditionally obtained from animal or plant sources and where there is a need to increase production. The latter has usually been achieved by developing a microbial process or substitute product.

Novelty

Novelty can be viewed in terms of products, services and technologies. The now classical group of novel biotechnology products are antibiotics and their introduction revolutionized chemical engineering and the industrial manufacture of biological materials. Other products in this context include microbial insecticides and monoclonal antibodies.

The novel technologies that have activated biotechnology over the past two decades are: industrial biocatalysts, heralded by penicillin acylase and glucose isomerase in the early 1970s; monoclonal antibody production; genetic engineering, and, subsequently, protein engineering. In particular genetic engineering or recombinant DNA technology has become a major design input with immense potential. Equally clear (now) is the fact that the full expression of genetic engineering in commercial terms is dependent upon (a) factors such as the development of second generation process technologies (for production, extraction and conformation); (b) on the realisation that the major technical problems have moved from DNA splicing to the maintenance of novel genetic combinations and the fidelity of foreign gene expression and translation; and (c) on the wider impact of the technology, in sectors other than health care, and its public acceptability. But, above all else, genetic engineering represents a dramatic technological discontinuity (Sharp, 1985) in the development of biotechnology.

Patterns of Disease

In industrially developed countries the pattern of human disease changed gradually from one dominated by infectious organisms to one progressively replaced by circulatory diseases, cancer and chronic degenerative diseases. On the other hand, infectious diseases continue to predominate in the Third World. In both cases human health care will remain as a, if not the, major instinct for biotechnological innovation.

Social Changes

Dunnill (1983) provides two interesting pointers to the relationship between social trends and biotechnology, both of which refer to changing lifestyles of women. One is the falling sales of baby foods in the UK due to a reduced birth rate and an increase in breast feeding; the other is the substantially increased demand for convenience foods due in large measure to the increased number of working wives.

Economic Changes

"While today's crisis may be unique in its details, its structured features are not unusual. In the past, analogous circumstances have produced instabilities in the market economy very similar to what we are experiencing today" (Mensch, 1979). Economists have produced various models of long-term trends. One of the most well-known is the Kondratieff-Kuznets-Schumpeter model in which economic trends since the Industrial Revolution in the West are depicted by cycles of prosperity, recession, depression and recovery. Extrapolation of this model brings us to the present point of depression and looked-for recovery. Mensch (loc. cit.) favours a model based on a series of intermittent innovative impulses that describe long periods of growth and relatively short intervals of turbulence. He argues that the cyclic model incorporates a deterministic recurrence of phase transition; his metamorphosis model does not, but instead allows for acceleration and deceleration of change. In times of depression the economy is more receptive of basic technological innovations; although some innovations are more likely to be successful than others, there is no determinism in the process. Many commentators agree that among the rush of basic innovations in the 1980s that will drive economic recovery those based in the biotechnologies will have major impact. In one sense, therefore, biotechnology is being espoused widely by governments, companies and investors almost as an act of faith.

THE MAJOR INDUSTRIAL SECTORS

In this section I wish to indicate the range of manufacturing and service industry activities where biotechnology is having and will have a decisive effect. The analysis is not intended to be either comprehensive or detailed but illustrative of opportunities. I have relied to a large extent on the excellent report of Peter Dunnill and Martin Rudd (1984) for statistics and informed comment and this source is recommended to the reader for further insights.

Chemical

Impact of biotechnology on the chemical industry may come from various directions. One long-term objective (post-petrochemicals) will be the provision of renewable feedstocks via ethanol-ethylene, for example. The industry is also concerned with substitute chemicals, especially those at present derived from petroleum. Among the targets are functional and structural polymers, surfactants, resins and fibres but, because of current great overcapacity, new products will need to possess novel properties (e.g. biodegradability, tissue compatibility) in order to replace existing products and to establish new markets. In general terms, large tonnage for chemical products are unlikely to be replaced by biotechnological alternatives this century. Much more attractive options occur in the speciality chemicals sector where the unrivalled capacity of biological processing to yield chiral compounds and to upgrade cheap materials to high value added products is very evident. In this context biocatalyst developments related to operations under non-physiological conditions (e.g. elevated temperature, low water activity) and to extending enzyme and cell half-lives are exciting much interest.

Health Care

The implications of health care for biotechnology have been alluded to above in reference to changing disease patterns. Without doubt health care can be the signal for some of the most rapid and massive responses for support as shown most recently by cancer and AIDS. Little wonder, therefore, that much of the new biotechnology is devoted to problems and markets in this sector. Among the new products emerging are: animal peptides and proteins (interferons, hormones, blood products); monoclonal antibodies (for drug delivery, diagnosis, purification); DNA probes for detecting inborn metabolic errors; vaccines; biomedical products (*in situ* biosensors, artificial skin, tissue compatible prostheses). Among traditional pharmaceutical products antibiotics are expected to remain very important. Similarly, novel pharmacological products of microbial origin are being discovered (immune regulators, neurological peptides) as a result of innovative screening procedures. The pharmaceuticals sector is subject to increasing international competition due to new entrants into the market (e.g. China) and the temptation of big companies to relinquish out-of-patent antibiotics with the effect of enabling competitors to develop a large manufacturing base from which to infiltrate more lucrative markets.

Agriculture

As Table 3 suggests agriculture is an ideal and immensely varied sector for biotechnological innovation. Opportunities exist world-wide and not infrequently the basic enabling technology is simple, low cost and effective. Plant breeding and micropropagation via tissue culture, for example, has burgeoned after initial scepticism. The targets here are diverse and related not only to performance in the field but to food processing. For example tomato processing in the USA represents a $500m industry and if the solids content of the fruits can be increased from 5 to 6%, $80m savings can be made annually in operating costs.

Food

In very many countries the food processing industries represent the oldest and largest component of the manufacturing sector but also have one of the lowest records of research investment (less than 0.5% of 1982 sales in the UK). Dunnill & Rudd (1985) express doubts about the rapid introduction of high biotechnology into the food industry because of the

Table 3. Biotechnological Innovations in Agriculture

Plant Breeding:	Disease and herbicide resistance Increased climatic and edaphic tolerances Increased lysine soya High polyunsaturated oils
Improved Plant Growth:	Soil inoculants Growth regulators
Pest Control:	Microbial insecticides Microbial herbicides
Animal Breeding:	Disease resistance Weight gain
Improved Animal Growth:	Bovine growth hormone Feed additives
Silage inoculants	
Vaccines:	Foot-and-mouth, colibacillosis

inadequate understanding of food structure and its relation to organoleptic properties. They believe that more immediate gains will come from innovations in process engineering and preservation. Other biotechnological goals of the food industry include:

(i) alternative and novel food ingredients: microbial polymers, colouring and flavouring agents, sweeteners, proteins, vitamins;

(ii) biocatalysis for the modification of food ingredients: high fructose syrups, interesterification of fats, detoxification; biocatalysis as replacements of traditional materials, e.g. rennin, meat tenderizing.

Service Industries

Under this heading will be considered waste management, energy, and services *per se*.

(i) Waste Management. Because of the very large volumes of very low value material involved, process costs have to be kept as low as possible and plant needs to be simple, reliable and long-lived. Hence, there are few major financial incentives for introducing high technology into this industry. The main effort has been made in improving existing systems via better process control, on-line monitoring and instrumentation. Biological developments are likely to focus on specific problems of toxic waste or social and operational inconvenience (e.g. deodourisation, clearance of pipelines and conduits) where inoculation of selected strains and the maintenance of controlled operational conditions may be important. Although many countries incur high annual costs for sludge disposal, the alternative economics of sludge utilisation have often been found wanting. The economics of product recovery or conversion are very susceptible to world market prices and the opportunities for utilisation usually depend on sludge quality, especially metal and phosphate contents.

(ii) Energy. The present author is among those who take a sceptical view of the application of biotechnology to energy production. There are, of course, local conditions and economic circumstances wherein fuels-from-