The International BIOTECHNOLOGY Handbook

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Foreword

This handbook presents a comprehensive picture of the international biotechnology industry in the mid 1980s. The industry has had its fair share of teething troubles and financial disappointments, but prospects for the new biotechniques to make a real contribution to industry and agriculture in the next decade are beginning to look up.

Although the book describes the scientific progress being made in biotechnology, the real accent is on practical economic issues – products on the market, major companies, and the standing of the industries in the main developed countries of the free world (USA, Japan and Western Europe). Other practical issues covered are the state of government regulation and patenting with regard to biotechnological products.

The book is in four parts:

Part One gives an introduction to biotechnology for the layman who may have only a vague idea, if any at all, of what this new science means. Chapter One briefly traces the historical developments which have led to man's imperfect but growing understanding of microbiological processes in the late twentieth century. Chapter Two follows this by outlining the main industrial products and processes with which biotechnology is involved today – again in simple terms for the non-expert reader.

Chapter Three examines in more detail (and necessarily in a more complex language) the products and processes which are the focus of current research in international biotechnology laboratories.

Part Two turns the spotlight on the national development of biotechnology in the major countries which are most likely to be the moving force in the next decade. Individual chapters are

devoted to the USA and to Japan, while Chapter Six summarises developments in Western Europe. These chapters also provide profiles of the major companies involved in biotechnology, whether they be small, research-based (or 'start-up') companies or the large industrial combines best able to exploit commercialisation of biotechnology.

Part Three, in contrast, examines the broader issues of the biotechnology industry – which confronts researchers and commercial enterprises in all countries – with the main focus on regulatory issues (Chapter Seven) and patents (Chapter Eight). This part of the book concludes with a chapter on market trends and prospects, a chapter which is a natural sequel to Chapter Three on current research. An individual chapter (Nine) is devoted entirely to the impact on medicine of biotechnology, because this is the sector of the economy which is already beginning to feel the impact of new products and processes based on this 'new' science.

Finally, Part Four is a reference section containing seven different sources of information on biotechnology, including a bibliography, press section, databases and, in line with the economic stress of the book, a section on current market surveys. The source lists are introduced by a guide to finding out more about biotechnology using these different sources.

Each chapter of the book has been researched and written by an expert contributor who specialises within the particular field concerned, whether it be market research, scientific research or information science (see List of Contributors). This means that each chapter has its own 'flavour', or a style suited to the topic being covered, whether industrial, scientific or commercial. The 'national' chapters (Four, Five and Six) have been written by contributors based in those countries, thus ensuring a difference of viewpoint in each chapter although the substance of the industrial coverage is the same throughout.

The format of the book does mean that some repetition of fact has been unavoidable. However, the reader will find that this repetition does serve to emphasise the most important aspects of biotechnology in the mid 1980s.

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Contents

1 Chapter One

Historical Development of Biotechnology

This section is in no sense intended to be a comprehensive history of the development of biotechnology – that book is yet to be written and a fascinating work it will be. However, by roughly tracing the ways in which humans have made use of (or rather co-operated with) microbes over the centuries, this complex subject can be put into some kind of perspective. Biotechnology divides into three parts: the early 'magical period' where discoveries made by accident were incorporated into daily life simply by following rules of thumb; a middle period beginning around the seventeenth century, when scientific explanations for these simple processes began to be established and followed; and the modern period when microbes have become the basis of great industries and modern techniques have given us new and far-ranging powers over micro-organisms.

1.1 Origins

Human beings have been making microbes work for them for a very long time. Oldest of all the useful products perhaps is wine, possibly as old as eight thousand years. Simon van der Weele, one of the few historians of the subject (so far), put it neatly:

> "Wine must be as old as pottery. – What do you do with a pot? You fill it with berries. Like most humans you forget one pot and the berries ferment. The first person to consume the contents had once again discovered wine. Vinegar is even easier, you just forget one pot of wine."

Sadly, history does not record even one of the many 'discoverers' of wine (unless Noah can be given this honour). Similarly, nobody knows who first added yeast to bread to make it 'rise'. The first time is pretty certain to have happened by accident. We know where, and roughly when, and we can make a guess about how.

The Nile Valley was the place and the time about five thousand years ago (during the reign of the Pharaohs). Certainly, the later Egyptians had bread and the Old Testament, somewhat later, is clear about the difference between 'leavened' and 'unleavened' bread. The difference, familiar to everyone who has tried baking, is in the lightness and texture that yeast gives to bread. When yeast is added to the dough mixture it begins to multiply (because, of course, it is alive). You must give it a little time to rest or 'prove'. As the yeast grows, or 'ferments', it gives off the harmless gas carbon dioxide. This is trapped as bubbles in the dough and results in the lightness and airiness that we know as the texture of bread.

Yeasts (there are many kinds) are naturally occurring one-celled microbes, and they are harmless and fairly common, floating around in the air. On the first occasion (in reality, like the wine, it must have happened many times in different places) a 'wild' yeast just happened to get into the bread mixture, perhaps from soured milk in which some yeast had already multiplied.

That batch of loaves must have tasted particularly good, and in a superstitious way maybe the baker saved a bit of that 'special' dough and added it to the next batch. Without really knowing why, he was 'seeding' the mixture with enough live yeast to multiply and aerate the next batch. This process went on down the centuries. Until pure yeast became commercially available, each batch was seeded with a little dough from the last.

The other great quality of yeast must have been discovered about the same time. This microbe lives on the sugars that are present in various quantities in most vegetable matter. In the right conditions it will grow and multiply incredibly quickly – this is known as 'fermenting'. As it grows, as well as giving off the carbon dioxide that makes such a difference to bread, it produces another much more interesting substance -- alcohol.

So brewing started, first as yet another household chore, and then semi-industrially, in the back sheds of pubs and taverns, and still later in specialised factories – breweries. As well as beer, these establishments sold another product: 'brewer's yeast', skimmed off their beer vats. And this in turn was sold to bakers and householders.

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The Egyptians were first again in this field. They produced a kind of beer from fermented cereals, but other primitive cultures produced their own versions. The materials fermented varied from asses' milk to various grains, barley and oats (the beer of many peoples and the 'ale' of the Vikings). Wine (from grapes, of course) was well known to the Greeks and Romans and spread across the world under their influence.

A number of other primitive biological processes were known to the ancient world. Notable among them are the manufacture of cheese and leather. Cheese is a fascinating substance. Originally it must have been just a way of conserving surplus milk, but later developed into the staple food (and delicacy) that we know today.

The key process in making cheese is coagulating (or solidifying) the liquid milk into the cheese solids (or 'curds'). Some unknown genius back in the mists of time must either have used a calf's stomach as a container for milk or gone through the remarkable thought process 'Calves live on milk alone – there must be something in their stomachs that turns the milk into a solid food.'

There is such a something – we now know that it is an enzyme called chymosin, about which more will be said. For many centuries this substance (then known as 'rennet') could be obtained only by boiling down calves' stomachs. Using rennet from this unlikely and unsavoury source, the entire cheese-making industry that we know today grew up.

More likely as a container than the calves stomach perhaps, was a leather bag or bottle. Tanned leather was an incredibly useful material during this period, not only for harness, straps and boots (for which it is still unsurpassed), but for bottles and goblets, clothes and armour. Other enzymes were used by the tanner to break down the stiffness of raw leather and turn it into a pliable and durable material. Like all the other users of microbes he had to work carefully and methodically, making sure, by meticulous ritual, that only the right bugs were present in his baths and vats. For there were, and still are, microbes that rot leather, make beer sour and turn wine into vinegar.

It is certain that the craftsmen and housewives of ancient history had no clear knowledge of why these processes worked. At best, there was a sort of semi-magical explanation for them. Today, with a fuller knowledge of just how complex these processes are, scientists have a mature admiration for so-called 'primitive' people who could develop, by whatever method, a fairly reliable means of producing good bread and cheese, beer, wine and supple leather.

Now, with advances in biochemistry and genetics, accurate instruments and powerful microscopes, we have more or less exact data on what happens in a vat of beer or a round of cheese. We can now control the processes more precisely and avoid some of the pitfalls in manufacture. With a few exceptions, however, we still make our bread and beer, and our cheese and leather by the methods developed centuries ago.

1.2 The Scientific Age

What we might call 'the age of innocence', during which mankind used microbes without really knowing what they were, lasted until about 1876, when Louis Pasteur identified some unwanted microbes that were spoiling the fermentation of beer. Beer and wine had gone bad before this, of course, but mishaps had been explained by the same kind of 'magic' as was thought responsible for the proper working of the process. When your beer went off, it was because of witchcraft, the evil eye, or even a change in the weather (which could have been correct if it radically changed the temperature at which the brew was made).

Microbes themselves had been seen and identified some two hundred years before by the Dutchman Antoni van Leeuwenhoek (1680), who invented a primitive form of microscope. What exactly they did, however, remained a mystery until Pasteur put forward his 'germ theory' and identified a number of bacteria and their functions. He was asked by Napoleon III of France, in 1863, to look into the reasons why wine (even then an important French export) deteriorated on its way to the consumer.

Pasteur introduced three very simple improvements in the approach to fermentation. The first, a rather obvious one, is that unless the wine is kept, not only in clean utensils, but also excluded from the air (and the many stray yeasts that abound in it) it will quickly turn into something else – usually vinegar.

This approach to hygiene led to the second innovation, the process that bears his name—'pasteurisation'. In this, wine, beer or any other product, including milk, is heated and held at a temperature just below its boiling point. By killing off most of the bacteria contained in the liquid, the onset of unwanted fermentations (which make beer or milk go sour) can be greatly postponed. We should distinguish this process, of course, from 'sterilisation', in which the liquid is raised above its boiling point

for rather longer. This can kill many more bacteria, but often has a harmful effect on the taste and structure of the product.

Pasteur's third innovation was to recognise the importance of oxygen to fermentation. When yeast is grown without sufficient air, it can only partly convert the available sugar into alcohol. Careful aeration of the fermentation vessels thus leads to stronger wine, and controlled stirring and aeration remain important features of modern fermentation techniques. There is, of course, a limit to this process. Alcohol, as far as the yeast is concerned, is a 'waste product', and when the concentration of alcohol in the wine or beer reaches around 18%, the yeast is poisoned. There is thus a limit on the alcoholic strength of naturally fermented liquor. Stronger liquors are, of course, obtained by distillation of fermentation products.

Unconnected with the work of Pasteur, but contributing greatly to our knowledge of genetics, was the work of the monk Gregor Mendel in the mid 1800s. Working in a garden, with several varieties of peas, he established precise rules governing the transmission of inherited characteristics. Mendel's contribution was an elaborate structure of 'rules' from which plant breeders eventually developed their methods of 'crossing' and hybridisation, and stockbreeders wrote their 'stud books'. What happened was now fairly clear. How it happened, the mechanisms involved in genetic transmission, was not discovered until the turn of this century.

In parallel with these research efforts was the beginning of the industrialisation of fermentation processes, the practical side of biotechnology. Breweries were now big business, as were distilleries, and the production of baker's yeast was taken out of the backstreet shop with the establishment of specialist factories.

The pressures of World War I also encouraged the production of industrial chemicals by fermentation. The best example of this is the production of acetone, an essential ingredient in cordite, for explosives. In 1914, Weizmann introduced the microbiological manufacture of acetone and butanol in the UK. As in the case of penicillin in World War II, the USA quickly contributed its facilities for large-scale production. Contemporary photographs show rows of fifty thousand gallon tank fermenters, the largest seen until then.

The foundations of modern biotechnology were laid in the first half of this century. The spectacular laboratory discoveries of recent years, the 'gene boutiques', have no real future if they

remain curiosities limited to tiny demonstration quantities. The techniques of large-scale commercial production and the accumulation over the years of expertise in fermentation and extraction have a very important part to play in the development of biotechnology into a real industry.

1.3 The New Era

In most fields of human endeavour, one can trace a progression of small developments and improvements, interspersed with occasional spectacular spurts. It is fashionable to call these 'breakthroughs' or 'quantum leaps', but in general these are only the outward indications of broad progress on many fronts.

The recent spectacular development of techniques of 'gene-splicing' (genetic engineering) are of such significance that it is usual nowadays to describe these processes as 'new biotechnology' to distinguish them from all that went before. Quite a lot, however, had gone on before, laying a foundation for this research and the industries that are growing around it.

Genetic research, applied to microbiology, had of course been in existence for many years before these new techniques were perfected. The practical side, however, had been much like stock-breeding, limited to careful selection of the best strains. Methods were primitive and painstaking, from cultures were made anything and everything, using soil samples from exotic places, bits of plant and animal tissue, and sometimes the accidental intrusion of yeasts and moulds from the air. Cultures were made by 'seeding' (sowing your sample) on a surface of jellified broth (containing agar) in a round, flat glass dish (a 'petri dish'). You then left it in a suitable place and watched what happened. 'Colonies' develop where microbes touch the agar surface and these can then be isolated and examined for useful properties. Simple it may be, but spectacular discoveries (penicillin, for example) have been made in this way.

Microbes have the advantage, of course, of reproducing many times faster than plants or animals, so many generations can be examined in a relatively short time. This rapidity also provides an opportunity to exploit variations that either occurred naturally or could be produced in relatively simple ways (irradiation, for instance, and by certain chemicals).

A 'mutation' or 'sport' (well known in the breeding of animals)

is an animal or plant that has a characteristic not apparently given to it by its parents. The results are entirely a matter of chance, some mutations are successful, some not. Such chance mutations are a key factor in Charles Darwin's theory of 'natural selection'. According to this, organisms with the more successful mutations (longer necks, specialised diets) had a small competitive edge over their fellows and prospered, gradually changing, or evolving, their species.

It had been known for many years, since the work of Mendel in the nineteeth century, that every life form contains within its cells the 'blueprint' for reproducing itself. Mendel laid out a structure of rules governing the transmission of this information, but the mechanisms involved had to wait for the more sophisti-cated techniques (and more powerful microscopes) available in this century.

This research began to suggest that the information was somehow encoded in the 'chromosomes' – tiny bodies visible as rod shapes in the nucleus of each cell. Every organism has a complement of these in varying numbers. Humans have 26 pairs, a crayfish has over 200, bacteria have only one, and no nucleus. Later studies showed that the chromosomes (the name simply means 'coloured shape') are themselves made up of even tinier units called genes. It was the patterns contained in these genes that in some way enabled the organism to replicate itself or 'breed true'.

It was found that the genes were composed of a complex chemical compound known as DNA (deoxyribonucleic acid). It was not, however, until as recently as 1953 that two researchers working at Oxford, Francis Crick and George Watson, finally uncovered the precise shape and function of the DNA molecule. This was the now famous 'double helix' – roughly the shape of a spiral staircase.

When the cell reproduces, the rungs of this staircase split down the middle of each tread and the two spirals that remain (with the half treads) act as a template for the formation of new complementary molecules – exact copies of the original, parent DNA. The threads of the staircase are composed of strings of units known as 'nucleotides', different kinds of nucleic acid. There are only four different types, but the 'staircase' is extremely long and the sequence of nucleotide 'bases' can easily convey a great deal of information. The best analogy here is the Morse Code. With just two different symbols (the dot and the dash), any message,

including, if you like, the works of Shakespeare, can be encoded. The arrangement of these nucleic acids, in specific sequences, carries all the detailed information necessary for the construction of a new organism – the genetic code.

GENETIC ENGINEERING

This slightly misleading term covers the recent development of techniques concerned with producing what are effectively controlled mutations – deliberate evolution.

The techniques, often colourfully called 'gene-splicing', are methods of constructively rearranging the genetic code to produce an organism with new, desirable characteristics. In the case of a simple microbe, this might involve introducing the ability to produce a certain chemical. Somewhere on the DNA molecule is the information ('genes') concerned with this desired quality or product. The 'engineering' is concerned with 'cutting out' that part of the string, and joining or grafting this into another organism.

This is not, of course, done with a knife, but chemically by using special enzymes. The discovery of this way to use 'restriction enzymes', by Stanley Cohen and Herbert Boyer in the early 1970s, supplied a tool that would cut the long DNA molecule into a fixed number of defined fragments. The enzyme does this by recognising and attacking certain specific nucleotide sequences in the DNA chain. There are now well over 300 of these enzymes in general use, each 'tuned' to a different sequence. 'Splicing' is done with another set of enzymes called 'litigation' enzymes, which can stick the fragments back together.

All this talk of 'cutting' and 'splicing' perhaps suggests delicate surgery, but it must be remembered that all these functions are in practice carried out chemically, in solution. The molecular biologist/genetic engineer often ends up with a 'soup' composed of fragments of the genetic code. Somewhere in there is the coding for the desired characteristic, but, unneeded sequences will also be present. There is a number of techniques that have been developed to help in the selection of those fragments he wishes to process.

If a DNA sample is placed on a plate of gel under appropriate chemical conditions and a weak electric current is passed across the plate, the fragments will start to 'migrate' in the direction of the positive pole. The smaller ones move faster, and after several

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