Keynote Address

OVERVIEW OF BIOTECHNOLOGY IN INDUSTRY

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by

Dr Brenner

First I would like to say that it is difficult to give on overview of Biotechnology in Industry in one hour. we have to stand very for back in order to get a closer view. The danger is that when you stand to far back we miss out the details and since the details are so important you cannot afford to miss the mark otherwise one will be speaking platitudes for most of the time. I'll have to be technical every now and then in my talk because I think that without a secure grasp of the scientific basis of the subject we will all be lost and I think it is very important that we must first of all know what we are doing in the subject and of cource later on we must know why we are doing it. The former is the scientific question and the latter is the applied question that is so remarkable as long as it applies in the social and economic objectors. I am really not totally qualified on the industrial side because on this large spectrum which ~~rays~~ ranges from fundamental research to Industry applications, I am ~~much at~~ more to the research end. However I do have opinions on the matter and I shall not hesitate to voice them during this talk. But first let me begin by making some general remarks on biotechnology as it is now and this is because it has come to be largely identified in the public eye to one particulat technique namely that on gene cloning. I think if you ask most people on what is biotechnology, they say Biotechnology is genetic engineering and of course I think it has a much wider scope and of course a much longer history than merely the last 8 years.

Biotechnology is simply the application of living cells or their components to industrial processes, of course many examples aboard and many common place nature processes involving particularly microorganisms have been harnessed by man since the dawn of time and especially in subjects like waste treatment, food production, may of the thing that have been mentioned. We have ssen the application of Biotechnology for a very long time. I'll call this traditional biotechnology because it is empirical, it is an art rather than a science with many tricks and much special knowledge learnt from practice and it is still an art for I think most of the lower value higher voloume industrial production the form of the usual food products - alcohols, beverages daisy products and so on.

Sometime ago one should mention, there was a triving appplication of these traditional processes to what would be how be called bulk industrial chemicals. But the development of the petrochemical industry over the last fifty years in particular, caused many of these processes to become economically non-competitive and the industrial fermentation for bulk chemicals essentially became a sunset industry rather than a sunrise industry. So much so that some years ago a survey revealed that the only major chemicals being made by fermentation were ethanol and citric acid and everything else have been replaced by chemical processes. The major moves in oil prices over the last decade or so have seen these questions opened again and there bave been many studies comparing biotechnological and chemical methods for the production of bulk chemicals and fuels and in particular you all know Brazil has instituted a massive scheme for ethanol production from biomass to be used as full in the form of

gasoline (substitute) supplement. However I have to point out and I think all of you know that many of these processes sure requires large amounts of energy for example ethanol has to be distilled and the economics of the process may not be easy eventhough Biomass may be relatively cheap e.g. it has been calculated that the agricultural wastes produced in America which is largely in the form of cellulose could in principle be converted to ethanol by biotechnological process and this could replace about ¼ of the fuel used in automobiles in the US. However the cost would be prohibitive and that would largely be the cost of collecting the wastes, transporting it to centres of production and redistributing it again. And it is this very important factor that many scientists do not bother to take into account that really make many of these processes economically inviable. I also like to remind you of one other thing that I believe is very important in assessing the value of this. It has been said that biotechnology processes have the advantage of proceeding at low temperatures and low pressures unlike chemical processes which usually require high temperatures and pressures but that also means that they proceed for more slowly and biotechnology processes therefore occupy a much larger area than an equivalent chemical plant for the same treatment and that of course has consequences in terms of investment. Furthermore all biotechnology processes operate in aquous solutions unlike many chemical processes that can also operate in the gaseous phase and and the product is diluted with water and that gives you problems of purification, drying which further increase the problem size and make the process more complex more difficult to achive better economy boundaries. It is therefore even

today more economical to make ethanol by the oxidation of ethylene rather than setting up a large biotechnological process for its production and the same appears to be true for other chemicals such as methanol, acetone, acetic acid and so on. This is an area of technology which depends on the interaction of a very large number of technical and economical variables and the answer to this complicated question needs to be constantly reviewed as the weights of the different factors change and as as you know the weights of the factors have changed very much in favour of chemical processes because of the present situation feedstock such as oil. You will notice that all the chemicals I've have mentioned have a few carbon atoms 1, 2 or 3 and are simple instructure - they are linear molecules.

There is a rough and ready rule in biotechnology which is that the price of any compound goes up more or less directly with the number of carbon atoms which is also a reflection of the complexity of the chemical structure so that many of the products with large numbers of chemical atoms are special chemicals and these include many of the pharmaceuticals and thing now come to the high value end of the range because of their complexity and therefore command higher prices everthrough their volume are considerably lower the chemicals which I mentioned before and which could been seen as being based on traditional fermentate processes, their production is gauged int he form of millions of tonnes sometimes billions of tonnes whereas the chemicals we are talking of now might be in the range of a few to thousands of tonnes a year in production. New way of these are being

made and can be made by biotechnology processes and indeed there are certain sectors of this production in which there is no other process but a biological process to make them e.g. in the production of complex secondary metabolites and this includes antibiotics.

This is of course the area in which everbody is interested in because of its high value low volume type. It also corresponds to the field of science based biotechnology and I propose to call the part we going to deal with classical Biotechnology - we have processes that depend on traditional Biotechnology which in the main is not science based and now we are going to deal with this biotechnology that has become science based and has developed essentially over modern time. It is in this field that we the scientist and engineer intervene directly in the process and try to remould it rather than merely use it. This has been as is in the lay application of traditional fermentations. Both are natural phenomena which we may control but we do not modify, we do not intervene in the process itself. In this field of science based biotechnology we intervene in the processes. For science based biotechnology, we must distinguish 2 distinct phases the more classical one which is based largely on natural product chemistry and biochemistry in the widest sense particularly enzymology and the modern phase which is based on genetics and molecular biology. Now this distinction is important not only historically but it is very important conceptually and technically as I went to by now to make it clear. In summary, in the first case we operate with the protein components of living cells, these are essentially the enzymes and the products they will make, whether these are a complicated organic molecule like penicillin or a

food additive like glutamic acid or even polymers like polyhydroxy-butyric acid or polysaccharides. In the second case we do not work with the protein directly but we work with the material that specify the protein i.e. we intervene at the level of the genes. I think this is very important because you have to think that if you have a factory that is manufacturing TV sets. There are 2 ways in making modification to the TV sets - one is to get to the factory floor and alter each TV set, that will be operting at the level of the protein which we are now at, the other one is to get into the office of the factory where the blue prints are kept which tell people how to make TV sets and alter the instructions there and from that part on that factory will produce the modified TV sets I think that it is very important to distinguish between operating on the working machinery, of the cells and working on the specification of the working machine. It is not merely a quantitative difference but an absolute qualitative difference and requires a completely new approach to the subject. Let me now try to give you a very general picture of how one must look in order to appreciate what the general problems are going to be let me take for illustration, a bacteria cell and look at what I'll call its 'ife style' its molecular life style what is the molecular life style of a bacterial cell. A bacterial cell is a very small object. It is 2 microns $^{(10-3)}$ by 1 micron. Inside this tiny object something like 3000 chemical processes go on simultaneously in the same spot. However that object reproduces itself every 20-30 minutes - produces 2 like it which again carry out the comprehensive chemical processes. Now if you ask a processing engineer, a chemical engineer I say how could I run a factory in which I have 4000,

of bulk chemicals and fuels; ~~[illegible]~~ and Brazil has ~~embarked~~ on a massive scheme for the production of ethanol from biomass to be used as a fuel in the form of gasoline supplement. But many of these processes still require large amounts of energy, for example in distillation of ethanol and ~~absorption~~ other ~~[illegible]~~ The economics of the process may not be easy. For example, ~~agricultural~~ agricultural waste ~~which~~ could be converted into ethanol which is largely cellulose could, in principle, be converted into ~~the source~~ ethanol by biotechnological process and it has been estimated that the waste in the US thus ~~could supply~~ could substitute for about 1/4 of the fuel consumed by motor vehicles. But the overhead ~~and~~ collecting the waste, and transporting it to production centres can make is so large as to make all of this process uneconomical. We shall have to come closer to the threshold of resource depletion to have any of these processes established on any scale. There is an additional factor that ~~also affects~~ complicates the issue. It has been said that biotechnological processes ~~proceed at~~ have the advantage of proceeding at low temperatures and pressures than the ~~these in~~ chemical industry; but this also means that they proceed far more slowly and a biotechnology process ~~therefore needs to~~ occupies much larger areas than ~~those~~ a chemical plant; furthermore, all biotechnology

processes operate in aqueous solutions and the product is ~~diluted with large~~ diluted with water with problems of purification and drying; increasing the plant size further, ~~with~~ and making the process more complex. It still appears more economical to make ethanol by the oxidation of ethylene rather from setting up biotechnical processes for the production, and the same seems to be true for other chemicals such as (methanol) acetone, acetic acid, propanol and so on. ~~We will note that the~~ But this is an area of technology ~~with a large~~ which depends on the interaction of large number of technical & economic variables and the answer needs to constantly reviewed as ~~the~~ weights of different factors change.

You will notice that all the chemicals mentioned here (and are simple) have a few carbon atoms one, two, three. There is a rough and ready rule in biotechnology that the price goes up directly with the number of carbon atoms which also reflects the complexity of the chemical structure. Many of these products are special chemicals and many pharmaceuticals; they are at the low volume high value end of the range and many are made or could be made by biotechnological processes and this is, of course, the area everybody is interested in. It also corresponds to field of science based

biotechnology ~~as opposed to the~~ and is the ~~area~~ field where we intervene directly in the process and try to remould it rather than merely use it as in the ~~more traditional~~ applications of traditional fermentation. For science based biotechnology I ~~would~~ think ~~like to divide~~ that there are ~~two division~~ have been two distinct phases; a more classical one based on natural products chemistry and biochemistry, particularly enzymology, and the modern ~~one~~ phase which ~~evolved~~ is based on genetics and molecular biology. ~~It is important to distinguish~~ ~~It is important~~ This distinction is important not only historically but also conceptually and technically ~~also~~ as I hope I can now make clear. Basically, in the first case we operate with the protein components of living cells ~~such as~~ essentially ~~enzymes~~ which could be small molecules such as enzymes or the products they synthesize ~~like~~ (glutamic acid, penicillin or ~~sugar~~ polymers such as polyhydroxybutyric acid or polysaccharides; in the second instance we work with the material that specifies the enzymes, namely the genes*. It is still the enzymes and their products that we want, but we intervene directly at the gene level. Classical biotechnology, as I have called it, has of course used genetics in the sense of strain selection and improvement by the exploitation of natural processes such as mutation and recombination, but intervention has been at the level of the phenotype. I happen to be great believer in these ~~new~~ genetic engineering

methods; ~~[illegible]~~. but the gene cloning methods also allow us to cross genetic barriers far more readily than they are abrogated in Nature. They allow us to extend _horizontal_ transmission of genetic information which in Nature is largely vertically transmitted.

The application of gene technology to processes involving microorganisms is only just beginning and will, I think, be an enormously ~~fruitful field area scientifically and~~ exciting and fruitful both scientifically and technically. Ironically it comes at a time when the thrust of research in ~~[illegible]~~ prokaryotes is on the wane in the advanced countries as they move more into research on complex eukaryotic organisms. For example, ~~strept~~ the streptomycetes are ~~the~~ a very large family of bacteria from which many antibiotics ~~[illegible]~~ and other secondary metabolites have been obtained. Little is known about their genetics and biochemistry; the biosynthesis of antibiotics and the characterization of the enzymes that perform ~~the~~ the many steps is hardly begun and there are ~~very few people who work~~ not many people who work in it. I am sure that colleagues who follow me will cite many other cases ~~[illegible]~~ of bacteria of major industrial, agricultural and medical importance. In addition, microorganisms will remain the important ~~[illegible]~~ ~~[illegible]~~ vehicle in which to make the products ~~[illegible]~~ for genes removed from other organisms, and a knowledge of ~~the~~ physiology of bacterial growth and

the ~~physiology of~~ regulation of bacteral physiology is going to be increasingly important as the Technology advance. I would ~~like to~~ advise countries ~~to~~ who wish to acquire a Science base for biotechnology to ensure that they give prority to ~~educ~~ training and research in this field where can be centered relatively ~~rather~~ deeply and I believe competitively.

~~Up to this point~~ So far I have talked about microorganisms but there is another area of biology developed and ~~now~~ ~~discussion~~ more complex organisms and I shall now move on to the more complex organisms ~~by introducing~~ and also introduce other techniques — largely in cell biology and developmental biology.

both in plants & animals:

~~Perhaps~~ What is complexity? On the outside, it is seen as multicellularity, specialization; ~~but~~ also the organism has a developmental pathway and unlike microorganisms there is separation of germ line and soma. ~~Over the last year or~~

DNA complexity

Completely different bases of DNA genes. Structure in higher organisms but probably not ~~as~~ as much novelty as arguably might have been believed. Because of junk DNA. both in and outside genes. Note I say junk not garbage | garbage you throw away, junk is useless but you keep it.

Can grow cells of organisms — cell lines both in plants and animals. Plants can regenerate whole organisms from somatic cell cultures. But the cells ~~make~~ can remain in differentiated stage and make products. Animal cell culture not exploited as expensive. but short term, & long term used briefly in interferon. need human cells if want for human products. Now will be largely replaced by cloning and expression in other organisms. ~~But animal cell culture will be needed for that production~~ ~~Illustrates insulin and interferon~~ ~~We have a situation where the~~
But animal cell culture will be needed for products that need special processing. ~~Talk about~~
Hybridoma making antibodies best produced this way:
- ~~...~~ this is good example of new products replacing old. Gradual evolution. and many later applications purification behind even in therapy
- Plant cells — only beginning treat like microorganisms ~~maybe~~ is single cell cultivation alternative for high value product to ~~plant~~ field plants. Uses existing ~~...~~ methodology.

~~...~~ —

Most striking advance is cloning and expression of human polypeptide products in bacteria + yeast.
— (mention insulin, growth hormone and difficulties

malaria

(vaccine)

Discuss interferons how it arose are they useful?
Interleukins, speed of technology but we are now possessed of reagents for which there is no clinical use!
Main benefits are going to be in research & understanding roles of regulation pathways in man & other complex animals. perhaps then. In particular genetics approachable.
This has already had impact in human genetic disease. discuss. (Importance to Thailand).

~~Hybrids~~ What of the future? Mythological animals
Yes in plants going much faster than expected.
Harder in animals:
As we became more intensive (disease resistance important)
exploration of other ecological niches.
Novel field designing enzymes protein computers?
v far still lots to learn very difficult hi level of expertise + large range — should be for ~~us~~ science.

Conclude with relation between science + industry
~~[illegible]~~ research community
is a spectrum, ~~[illegible]~~ in the creation, transmission and application of knowledge. But ~~can~~ must have all 3.
Special problems of the less developed countries: How to cross the barrier — higher + higher entry fees but ~~[illegible]~~ struggle to set up the ~~basic~~ services. Need a training centre — (prokaryotic biology) + technology

several thousand chemical processes, some are in chanins may which are branding, many which come together, he will tell you 'totally impossible' because you could not control them. What he means is that you would not buy a computer which is big enough to deal with all the information that will be sent back to the computer to calculate the optimun for the next step. This is because computers are in fact stupid and biology to do it justice is stupid at least by the way they work with them. And the reason is very simply that if you have a system in which the control is centralised and the information then goes to one central operation which then have to give orders to all the periphery it in general will swallow itself up swallow all its power in calculating all its own administration systems. This is what happens to almost all computers. They spend an increasing amount of their computing power in deciding what they have to do rather than in doing it. Now biological system, bacteria are certainly not impossible disregarding what the engineers tell us, they exist, they are very efficient and they do not use that centralised control, instead we have a set of parallel processes that go on simultaneously within the cell and they depend not on ways going from one process to another but on a broad course system so that one molecules that is a product of one enzyme step is throuwn out into the medium and by diffusion it will find itself everywhere in the cell. For some enzymes which have no affirmity for the small molecules, they simply ignore them but for those that have a specialised binding side i.e. the one that will identify, recognise the small molecule. They will act. We do not have information, if you call them that, routed along fixed line, we simply have a broad

course system. If the message is not relevant to you the enzyme, your ignore and if it is relevant you action it so that's the first step. The bacterium does not have a winning problem of getting everything from one place to another so there is no pipes so that is the first thing you do not have to worry about. Secondly it operates under local control i.e. you'll have a pathway and the product will inhibit the first steep in the pathway so that if you have too much product then it will be automatically damped down and if there is too little it will automatically come up.

This technology has advanced to the stage where it is possible to make use of chemical sythesis to enhance the output. There is not much limit to the production but what is really limiting is what the product is used for. Much of medical advances in biotechnology is to make products available in abundance for which people are looking for diseases rather than having diseases for which people are looking at products.

Although those look like the commanding heights in medical biotechnology, I think that there is much to gain, much to learn by looking at the microorganism and in enhancing and exploiting by genetic engineering the things we know about in those organisms.

Presently there are no genetic engineers, in the world. We do have some genetic mechanics. The reason is that an engineer has a design and also the implements for the design. He plans and understands the constraints within which the plan will work. We are not at that point as we do not have enough knowledge. We have yet to design molecules, new enzymes. I do not see us doing this for quite

sometime yet except for some trivial changes. I think we should work with bacteria and tackle the problems with it first before taking on more complex organisms.

My final remarks are on the relation between science, technology and industry. There is a controversy in the advanced countries on where, one begins, where the other ends, who has responsibility and for what powerful research institutions of the advanced countries and even then, some of them.

Cell biology and Developmental biology are very important areas of science when we move into the more complex structures, the multicellular organisms. There are more things to explan and understand. Multicellulars organisms separates the germ line from the some line i.e. a bacterium in the germ line is mixed up with the some line. When a bacterium divides and reproduces, the parent disappears to give rise to 2 daughters but when a multicellular organism reproduces, the parent do not disappear. The organism that is formed is a complex of many specialised functions and structures. This is obviously an area we have to understand as we are going to deal with many organs - plants, animals and including ourselves.

An important concept in developmental biology is that it do not allow us to plan. In other words no bacterium can sit in the primitive soup 2 billion years ago to say I better not have that enzyme because in 2 billion years I am going to have muscles and that will forbid me to have acton. That is totally impossible why I am thinking about evolution.

The techniques on which biotechnology is based are exactly the techniques which we can use to analyse man and to advance the science. The techniques will feedback to increase the power of analysis. An important part of this from the technical point of view is to grow separate cells of the organism, both in animal and plant tissue culture. One method of genetic engineering of cells is the hybridoma technique - the fusion of cells, one which produces useless protrin product with another usually an animal cell, which produces useful products e.g. antibodies and confers upon that product the ability to reproduce indefinitely in tissue culture. Unlike plant cells where there is a possibility to manipulate and regenerate them into a new plant, the manipulation of animal cells is more complicated. This being due to the higher degree of cell differentiations. We must therefore pay far more attention to the way the product is integrated into the physiological economy. For genetic engineering in the field will take a long time as we know very little about this area and more work has to be done.

There are of course technologies based on cell culture e.g. in the production of inteferon and secondary metabolites for pharmaceutical use. The fact that we can make use of gene technology has a tremendous impact in biotechnology especially in the medical field e.g. in the diagnosis and identification of people with genetic diseases. These will be remarkable advances in the use of research materials as diagnostic methods in man.

The gene technology also allows us to get sequences corresponding to various products by introduction into bacterial cells and

manufacture them. I have opinions on it. I that there is a community of people here who are concerned with the creation, transmission and application of knowledge. One must not ask the wrong people to do the wrong things e.g. one of the problems is because of the jump. Many simple techniques that depend on sophisticated molecular knowledge have come from the laboratory into practice very quickly indeed. Because of this, molecular biologists who are particularly academic has now been thrust very much into the application area and I think very few of them are equipped to make the requisite judgements that the technical and at the economic levels. I think that some of us should be allowed to contibue with the intervention of new science, because if that is strangled we will strangle future technology. Because without that impetus and the training of people to collect new knowledge you will lose the capacity for innovation in the long run. It used to be argued that countries do not need to do the basics, it suffices to subscribe to journals and you just read the journal and you get the information for nothing. The danger with it is that after sometime, the people will not understand what is in the journal. The characteristic of the exploring sciences is that to know them you must be a participant.

The 3rd world and less Developed Countries have enormous barriers to cross in biotechnology which is based on high level science and high level preamble.

The way to succeed in biotechnology is to start at a level where you can assimilate and make it the base for the future investment scientifically, also directed at the social, economical,

technical problems that you have but not the advanced countries (or rather in those that they are not interested in e.g. Malaria).

In the case of transmission of Information, there is an immerse volume of literature on biotechnology. The problem is that of assimilation for the individual. The solution is to have a commune of people who read each the relevant sections and communicate verbatim, groups that are large enough to do research and also to encompass the diversity of interest that you need to ensure progress especially in technology that is to come. This will involve such areas as Cell Biology, Developmental Biology and this urgently needed.

In conclusion, while concentrating on the practical questions on how to apply Biotechnology here, you must not forget about the need for a scientific platform on which is to be based my advice which you may or may not take is that procaryotic biology could provide a proper and fruitful area of investment here.

KMP/dm

I do not have an easy task in opening this seminar to give you an overview of biotechnology in industry in one hour. We have stand quite far back from the subject to see all of it and also to encompass all of the recent scientific advances, but I do not want to be so far that details are missed because without these we will talk in platitudes. During my talk I shall therefore ~~[illegible]~~ need to become quite technical, because I think that, without a secure grasp of the scientific basis, ~~[illegible]~~ of the work we will ~~[illegible]~~ not know what we are doing; but equally so that we know <u>why</u> we are doing things we need to have ~~[illegible]~~ clear ~~the~~ social and economic objectives. ~~Everybody knows that there is a fatal [illegible] [illegible] technology for technology's sake, "sweet" technology~~ I am less qualified to judge in this area because in the spectrum that ranges from ~~from pure~~ fundamental research to industrial application I occupy the research end of ~~[illegible]~~ the field. ~~I will make some comments on the more applied aspects but~~ ~~[illegible]~~ are others in the ~~[illegible]~~ seminar who are more qualified than I am there ~~will I hope be~~ able to help us move on the ~~matters~~ applied problems but of course mine I have opinions on these

I want to begin ~~by~~ my talk proper by making some general remarks on biotechnology itself, ~~because [illegible]~~ ~~[illegible]~~ because it has come to be too closely identified with one particular ~~technique~~ novel technique of gene cloning. It has, of course, a much longer history ~~than~~ so than 8 years. It ~~[illegible]~~ involves the

usually microorganisms

application of living cells or their components to industrial processes. Many commonplace natural processes involving microorganisms have been harnessed by man, both for waste treatment and food production; the biotechnology of soya bean is an old and widespread one in this part of the world. A considerable Traditional biotechnology is empirical, an art rather than with many tricks and special knowledge learnt from practice and not yet fully accounts for most of the lower value, high volume industrial production in the form of alcoholic beverages, dairy products, and other food products. Biotechnology is rapidly developing. Same time ago there was flowering application of fermentation to bulk industrial chemicals but the development of the petrochemical industry caused many of these processes to become economically non competitive and industrial fermentation became a sunset industry; so much so that some years ago a survey revealed that only two of these processes major chemicals were being made by fermentation — ethanol and citric acid. The major moves in oil prices over the last decade or so have seen many of these questions opened again and there have been many studies (there are many studies) on these questions comparing biological and petrochemical based methods of

Let me illustrate this briefly by considering a bacteral cell and its life style.

Discuss added genetic elements, episomes and viruses
Brief discussion of cloning in bacteria addition of functions.