PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Panel Discussion

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Panel discussion

B. S. Hartley, F.R.S. (Chairman) (*Centre for Biotechnology, Imperial College, London*). Can I ask members of the panel to introduce themselves and the interests of their companies?

J. L. Meers (*J. & E. Sturge Ltd, Selby, N. Yorks., YO8 8EF, U.K.*). Our company is primarily involved in citric acid and monosodium glutamate and has extended its interests in recent years into enzymes. We are selling a range of enzymes to diagnostic kit manufacturers and into the food industry. These are largely fermentation enzymes, although we are also selling a number of enzymes from plant and animal extracts. I'd like to comment later on some of the things that have been said about markets and commercial factors in diagnostic enzymes.

M. H. Nielsen (*Novo Industri A/S, Bagsvaerd, Denmark*). Novo has two main areas of activities, i.e. pharmaceuticals and industrial enzymes. In the pharmaceutical area our main product is insulin, which is sold all over the world. In the field of industrial enzymes Novo is specializing in microbial enzymes for many different industries, of which the following are the most important: detergents, starch, dairy, alcohol, brewing, wine and juice.

C. Bucke (*Tate and Lyle Ltd, Philip Lyle Memorial Research Laboratory, Whiteknights, Reading, U.K.*). Most of you know Tate and Lyle as a sugar company, but our interest in enzymes results from what turned out to be a rather brief involvement in the British glucose-from-starch industry. We started with the intention of using glucose isomerase as an opportunity to get into immobilized enzyme technology. We thought in 1974 that glucose isomerase could probably be immobilized better than it had been by others, so we saw an opportunity to get into that discipline. That interest has continued and we are still doing a lot of immobilization work, particularly of amyloglycosidase for use in the starch industry. We have also begun to sell small amounts of it in the United States. We are interested in the immobilization of other enzymes for carbohydrate conversions, and, as you realize from my paper, we are also very interested in using immobilized cells to do carbohydrate conversions. We have considerable other interests in the use of enzymes.

G. Näher (*Boehringer Mannheim G.m.b.H., Werk Penzberg, Penzberg, West Germany*). I am in charge of biochemical production at my company's plant at Penzberg. As most of you will be aware, our work is mainly in the field of highly purified enzymes rather than technical enzymes, and their applications mainly in diagnostics.

P. J. Strijkert (*Gist-Brocades N.V., Delft, The Netherlands*). I am in charge of the biotechnological R&D of the company in Holland. Besides having a pharmaceutical division, we have an enzyme division, and an antibiotics and steroids division; I have already previously mentioned the yeast division. In enzymes, which is the feature of this meeting, I would say that the company is a fermentation industry in the first place and produces all the enzymes for industrial use.

H. G. Volger (*Shell Biosciences Laboratory, Sittingbourne, Kent, U.K.*). I am in charge of the biotechnology research in Shell. As many of you know, Shell is an energy company working in oil, natural gas, coal, metals and as a petrochemical producer. We are not at present using enzymes in our products and processes. However, we are looking at biotechnology, as an additional toolkit apart from the normal chemical approach, to achieve our business objectives. Hence in our research we are definitely looking at enzymes and microbial cells, but at this moment we have no products and processes based on enzymes.

A. T. James (*Unilever Research, Colworth Laboratory, Sharnbrook, Bedford, U.K.*). We are interested and involved in the use of isolated enzymes as production tools for food components. Some are already in production, others are in pilot plant and some are in feasibility study; I should also add enzymes for certain specified chemicals and of course enzymes in certain cleansing products. We are also involved in immuno diagnostics and are deeply interested and involved experimentally in enzymic control by recombinant DNA, in both plants and microorganisms.

B. S. Hartley. At this stage my intention was that this distinguished panel should be asked some awkward questions from the floor, particularly questions that they don't want to answer! To start the ball rolling, I would like to ask two coupled questions. I made a statement right at the beginning of this symposium that any enzyme could be produced by genetic engineering as cheaply as the cheapest industrial enzyme. How many and which of the panel agree with this statement, and if so has this realization affected your research plans at present or are you still thinking about it?

A. T. James. In many continuous processes for the production of valuable substances by enzymes, the cost of the enzyme is almost irrelevant. For example, we have one process in pilot plant at the moment where the enzyme reactor is, of course, the central component. Together with the upstream processing, the downstream processing, fractionation and recycling, the enzyme reactor costs 7% of the total capital of the plant and 5% of the revenue. So there is no point in us requesting the enzyme suppliers, 'will you give us an enzyme at one tenth of the price?' It's irrelevant to the overall costing of the plant and I really think it should be understood that continuous reactors, whether they be fermenters or whether they be enzyme reactors, often represent a very small proportion of a production plant. I think that is responsible for many of the misunderstandings that exist between academic groups and industry. Academic groups rightly concentrate on the reactor because that is their interest, but in terms of the total economics the reactor is not the major cost component.

Anon. Could I answer that? Maybe prices for enzymes for industrial use are only relevant for competition between enzyme producers but they are very relevant to the feasibility and hence the profitability of the process. One should bear in mind that when you produce 10 g of glucose isomerase, the user of that enzyme can treat 15000 kg of glucose with it, so that makes the price rather relevant for the process.

M. H. Nielsen. Your first question was 'is it possible to make any enzyme you want very cheaply by gene technology?' It might be possible, but I believe it will take 10 to 15 years to develop

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that technique. Today it is claimed that you can increase the yields very easily, but it is not so easy when you really work with it. Our present production strains have been mutated for 20 years and are very high-yielding, so it is very difficult to increase the protein synthesis in the microorganism. Perhaps newly isolated and not mutated strains can be increased in yields much more rapidly than by the old technique. But what we see as one of the big advantages – Professor Hartley mentioned it himself yesterday – that is, that you have access to a bigger part of the microbial world. With this technique you can take, for example, a pathogenic organism producing an enzyme and by transferring the gene into a safe organism, you can produce the enzyme without risk in a normal fermentation and recovery plant. Of course there are also chances of increased yields. You also asked how this influences our R&D policy. I must say there has been too much science fiction in the gene technology discussions. We read in the papers that everything could be solved by genetic engineering. I think that biotechnology is a multidisciplinary technology and gene technology is just one of these disciplines. If you don't have all of them you can't do anything at all with the technology. You need classical microbiology, fermentation technology, chemical engineering, protein chemistry and also toxicology. But it *has* influenced all the biotechnology companies. We have ourselves established a gene technology department that works very closely with our pharmaceutical and enzyme technology people.

J. L. Meers. Just to take a slightly different point, I think there is a good deal of confusion about the actual volumes of enzymes or the value of enzymes that are sold. We have to get that reasonably clear if we are to assess the case for spending the kind of money that the genetic engineering companies seem to think they are worth for doing any experimentation on gene products. I think Professor Atkinson's first slide may have misled people, because when you alk of enzyme markets of around $800 M or indeed markets for specific enzymes in the U.S.A. of more than $20 M in the diagnostic industry, I think we have to be very clear. The gentleman from Boehringer Mannheim may be better placed to answer this than I, but I am fairly sure that those are the figures for the final packaged kit product and bear very little relation to the enzyme sales. In fact, if those figures are correct as related to kit sales, I am fairly sure that the contribution of the cost of the enzymes for those kits – and hence to the cost of the analysis that was under discussion – must be less than 5%. So any reduction in costs brought about by genetic engineering is not going to be that dramatic in that particular industry for example. If you are talking about many hundreds of thousands of pounds that companies like Biogen might see themselves requiring to do this research, you're very unlikely to recoup the cost in terms of profits on the sales of diagnostic enzymes. The cleverness of diagnostics lies elsewhere, as I think other speakers have said, than in the genetic engineering.

G. Näher. Dr Meers is absolutely right. What was on Professor Atkinson's chart was the total market of kits. Now, in test kits, the enzymes are a comparatively small share of the total cost – the same as active substances in pharmaceuticals. If you buy penicillin by the ton, it's quite cheap. If you buy it in ampoules, you pay quite a bit more. The market for diagnostic enzymes is very limited, and actually at the present time it is rather decreasing due to automation and due to miniaturization. If you shift from manual to automated systems, you will decrease the consumption of enzymes by at least 75%. For the time being innovation in diagnostics is

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mostly aimed at the improvement of existing methods or at other diagnostic principles like immunoassays, which make very little use of enzymes in terms of quantity.

T. Atkinson. Could I reply to Dr Meers's statement? I did try to make it clear that the prices marked on that slide were the price of the kits and not the price of the enzymes. But I would like to point out that if the enzyme didn't exist, the kit wouldn't exist and neither would your profits. Your profits are made on the kit, not on just the sale of the enzyme. The prices for bulk enzymes, as people from other industries know, are extremely low. In diagnostics it's the value of the kit that is critically important and that has to be taken into account, not just the cost of the enzyme in the kit. Royalties on enzyme patents are invariably paid on the price of the diagnostic kit, not the enzyme.

A. T. James. Yes, you are quite right on that issue, but you are talking to enzyme manufacturers here, you are not talking to manufacturers of diagnostic kits. An enzyme in many of these processes is rather like a transistor, and if the transistor can be put to work in some novel device; that is where the skill lies, and it is a great skill.

There has been a certain tendency, I notice in many of the papers, to dismiss scale-up as if it were simple and easy. Going from fundamental research and background research into process development can be very costly: once you get into pilot plant work, your costs go up by a factor of 10 to 20 before you put any capital into your actual operating plant. Add to this the problem of then having to educate a sales force when you get into a totally new field – which much of the diagnostic field is. Many of the figures you put up are projections: they are not actual sales but projections assuming that the devices will actually fulfil the market demand. Let us hope they will; there is certainly no technological reason why they shouldn't fulfil that. But the great deal of skill is in producing the diagnostic system, trialling it and so on.

T. Atkinson. To take your second point first, the slide figures are actually 1980 sales figures direct from the U.S.A. Furthermore we have Boehringer Mannheim and Boehringer Ingleheim represented here on the panel, who both manufacture diagnostic kits and who are not just simply enzyme manufacturers.

J. L. Meers. This is perhaps not getting us too much further, but I want to make it clear to Professor Atkinson that the point we are responding to is the original question: how much difference would genetic engineering make to the scene? I think the main point here is that cleverness in patenting it and excluding everyone else from getting in on the act, particularly the application, is probably more important in this business than the actual price of the totality of the kit manufacture. Speaking as a kit manufacturer then, the price of the enzyme is important like everything else, but it is not so important that genetic engineering will sweep and revolutionize the business.

J. Patterson (*University of Strathclyde, Glasgow, U.K.*). One of the places where gene technology has been successful has been in modifying the physiology of microorganisms, and as Professor Lilly said today, the physiology of some of the microorganisms used in fermentation is not very well understood. Some of the organisms that you pick up from the wild are very strange unstudied organisms. Does industry think that the Government should pay for the kind of basic

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microbial physiology studies using gene technology, or does industry also play a part in this kind of approach?

B. S. Hartley. I can answer that before anybody does: industry will be absolutely sure that the Government should pay for all academic research!

J. L. Meers. That's a rather over-simplified approach really, because of course industry pays for all of it in one way or another doesn't it? So really it's just a question of how you actually split the money. You either pay it in taxes and it pays for the Government's expenses, or you pay directly. But I think it's worth remembering the actual size of the enzyme market. It is sobering, actually, to think of the number of people interested in enzymes research and development, when the scope and scale of the enzyme business is not really all that big. If you were to add up all the R&D that has been done over the last 20 years, that would absolutely swamp the industry. The actual profits and the size of the turnover worldwide in the enzyme business could never support all of the research that has gone on in universities here and elsewhere. So it just wouldn't have happened. The whole industry would have collapsed under the weight of it all.

R. Spier (*Animal Virus Research Institute, Pirbright, Woking, Surrey, U.K.*) I have had recent cause to examine the Japanese policy *vis-à-vis* their attitude to biotechnology. I'd like to ask our distinguished panel as industrialists:

(*a*) What do they think of the Japanese approach to developing enzyme technology in order to be able to corner the enzyme market?

(*b*) What do they think of the Japanese attitude to the interactive development with both government and the universities?

(*c*) Are they really going to get their house in order and mount an effective challenge to what seems to me to be an equivalent Japanese strategy to that which took over motor-bikes, transistors, cameras, you name it!

M. H. Nielsen. I was in Japan just three weeks ago to investigate that, and I must say I am very, very impressed by the Japanese activities in that field. They feel they are the fathers of biotechnology, and that they have lost their leadership. They want to have it back in 5–10 years from now and they are very determined to have it. There is a very close relationship between industrial laboratories, governmental institutions and universities. For example, in waste cellulose utilization they have given a lot of money to two companies who have made it a priority, and they are also giving high priority to gene technology. I think this is a real challenge to the western world with regard to biotechnology. Also they work 20 hours a day!

R. Spier. So, sir, do some of the genetic engineering people in the U.K.

A. T. James. The Royal Society and the S.E.R.C. recently sent a group over to Japan to look at Japanese biotechnology. I was a member of that party and there were one or two striking things about that visit from which I think we can learn. It has already been said that the Japanese Government identifies reactors as a major area, together with all its subsets of sensors, of which we have been talking quite a bit today – both enzyme reactors and fermenters – and they have poured a lot of money both into industry and the universities. The pattern there is

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for many in universities to be directly interested and knowledgeable about industrial processes, so that they tend to do research into areas which they can see have some potential. We got the impression also that once that work had got to a patentable stage, the Government patented it; then the patent was handed to a company who paid royalties back to the Government if they exploited and utilized it. They have also kept up fields of work which have tended to become a bit unfashionable in the U.K. and the U.S.A. and perhaps in parts of Europe too; for example, detailed continuous study of microbial metabolism and control has been kept up. They have a much larger range of culture collections than there are in the U.K.; most University departments have quite big culture collections, which gives them, for all other aspects of work, quite a powerful tool to play with. They are very well organized, but they are weaker in molecular biology compared with us. I would say that so far as recombinant DNA work is concerned, the Japanese Government has had very stiff regulations such as to switch everybody off from getting into it. This was relaxed very shortly after we were there. It was very noticeable that already you could buy 'off the peg' in Japan prefabricated P3 facilities; they were rapidly being installed. But they recognize that they are behind in that area and I would say they are behind in immunology as well. But in overall fermentation expertise, as has already been said, they are very, very good.

R. Spier. May I come back for a second? Is it clear that the Japanese intend to mount a challenge to dominate this particular area of the market? Is U.K. industry sufficiently fast on its feet to make use of the available potential just alluded to? Is it prepared to make use of this potential by getting together and drawing up the same kind of national strategy, so as to be able to really do something original which could dominate the market from a technological point of view? After all, an extra 1% yield is enough to give you an edge to take over the market.

A. T. James. Well, may I answer for the S.E.R.C. biotechnology panel, and its connection with industry? The setting up of the cooperative award system, which is a direct coupling between a company and selective University departments, is one way of getting this close interaction. But so far as a national plan is concerned, that is quite difficult to formulate because it means putting together the interested ministries, of which there are several. The actual troops – what I refer to as troops are research scientists and development people – are of course within the universities, within the research councils' permanent laboratories and within industry, so one has to have some national plan of putting all those together in a concerted way. At the moment, there is the A.R.C. in one particular set of areas, the M.R.C. in another and the S.E.R.C. operating almost across the board. The plans of the individual companies, I would have thought, are fairly well set. A lot of thought has gone into biotechnology; it hasn't been going on for only five minutes. Indeed, if you look at the previous history of the Japanese who have been heavily involved in fermentation technology for 25 years, they are dominant in amino acid production, but they are not dominant in antibiotics production – very powerful, but not dominant. So a lot of Government money on a very large scale has gone in for a very long time, whereas we are not in that situation in Europe as a whole. As you say, we need to get this national alliance and across Europe as well through the E.E.C. But a lot of work *is* going on to put these things together to try and get some national developments. Having recognized where the weaknesses are, we have gaps, which we have recognized in the universities' support. There are areas which are not supported enough and the groups are not strong enough. They all need

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development and encouragement, so the S.E.R.C. has determined the policy of going out and encouraging, not just being in the passive waiting queue, for grant applications.

F. E. Young. I'd like to ask a question from a different direction, which comes from being both an educator and a person who chaired the Microbial Genetics Study Section of the National Institutes of Health during the last year. I see two things happening in the United States that I'd be interested in comments on. I'm fully aware that industry cannot pick up the support of research. We estimate in the States that at present it is 5% and that the maximum that it can go to is 15% of the total research dollars. So we are not looking at a major influx from industry, but I'm concerned on two issues.

First, we are not seeing young people move into careers in research. In the United States and in Europe the support for fundamental research is decreasing and our young people are concerned that this is not a good career. Also there are fewer university posts. Industry is expanding, but most agree that this is not going to pick up many of the people that might go into these fields.

Second, there is very little cross-training between the chemical engineering components that are required for larger-scale apparatus and scale-ups; the understanding of physiological processes and medicine; and what used to be called molecular biology – now transmuted into a 'sexy' word, biotechnology. I wonder what your visions are for ways to couple some of the opportunities that we talk about here with the nadir of enthusiasm of young people for going into higher eduation?

J. L. Meers. I can only speak a little for what is going on in the U.K.; there are other speakers from other European countries. It seems to me that what has happened in the last 10 years distinguishes it from the 10 years before when this kind of issue was important to me personally. It seemed then that everything was expanding and plenty of opportunities were presenting themselves within the universities, which were expanding. Indeed industry was generally fairly buoyant and profitable and companies were expanding, so there were plenty of opportunities in research. What has tended to happen recently is that many companies like ourselves have reduced their numbers as a whole, not necessarily in research, and of course the universities have not expanded either, so this has reduced mobility. This has reduced the number of opportunities for people that were previously in research to move into production or commercial jobs, because there simply hasn't been the mobility and people have tended to stick rather firmly to the job they have got. That has reduced the flow of people out of research, and I suspect a number of companies are tending to keep people within research departments longer than they might have done 10 or 20 years ago. Hence there are fewer opportunities for bright people to come into companies, and I imagine the same is happening in universities too. That is what is happening here, and I wouldn't be surprised if it was happening in other countries. I can't really speak of the vision of young people in universities to which you were referring, but perhaps it's also influenced by the opportunities that are very difficult to come by now.

C. Bucke. Yes, I agree with a lot of what Dr Meers has said. At the same time, I get the impression that the people we are interviewing for the few posts we have available are of considerably higher calibre than they were 7 or 8 years ago. There are still some disciplines also where there is movement through a company or out away from research: those are chemical engineers and

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the fermentation technologists. So the overall discipline that really is lacking is microbial technology, as Professor Lilly said this morning; that is an area where we still need lots of people. I have got a hobby horse, it reveals one of my little frustrations. I agree with Professor Hartley as I think he said in his introductory talk yesterday that there could be a lot more enzyme work done leading to the production of chemicals – getting biotechnology into the chemical industry as opposed to pharmaceuticals. You can find an enzyme that will do more or less anything. The problem is persuading the chemist that that is true, and it is very difficult to persuade him, because if he has a new idea and he knows the reaction he wants to do, he can go away and do a little feasibility study – whether the reaction works or not – which will take him perhaps a week. Somebody wanting to do the same thing with a new enzyme has got first to find an organism that will do the job. He has to get the enzyme out and do further studies to demonstrate the feasibility of the process, which might take 3–6 months. If biotechnology is going to get anywhere in the chemical industry, then chemists have got to be given more knowledge of biological techniques and the time and concentration they take than they have now. A greater cross-fertilization of disciplines is necessary.

H. G. Volger. Yes, I'd like to look at this question from a slightly different point of view. The first question is, what does the company need from research staff? That does not necessarily mean that the people have to be actually specialized in a certain field. What the research group of the company actually needs, apart from a number of specialists, is people who have a good overview of basic research and also of process research; not from a typical engineering point of view, but from the actual details of factors that are important in the overall cost of a possible process. People that know the most important costs and factors and can address that question with scientific and technological insight. There has to be an attitude among those who wish to make a career in research in companies to look from a much wider point of view than that of their Ph.D. topic, which they have mastered very well. That's a point I'd like to make strongly.

Secondly, the question about microbial physiology and what basic research should be done. When basic research is of vital importance to a company, the company will do it on their own with the help of academic consultants if they can afford to. When they need it and it doesn't pay off to do it in-house, then there has to be an interaction of a company and a fairly good academic group who are knowledgeable in their area. In that case I'm in favour of that company spending money in terms of post-docs to help that group, getting back a certain amount of knowledge, techniques and so on.

C. R. Lowe. Can I ask each of the panel members for their views on what they consider to be the major limitations to the development of enzyme technology, and speaking as an academic, what they would like to see us do about it?

J. L. Meers. A major problem with enzymes remains one that has often been stated: although there has been a great deal of excitement for a long while, what really is required are major new applications for enzymes. These are somewhat lacking. There are a lot of ideas floating around, much being talked about, and plenty of research, but it's quite a while since a really significant large tonnage enzyme hit the scene. I mean something quite new. It isn't through lack of looking for it. I'm sure we all on the panel have been digging very deeply to find totally

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new things that could scoop the pool, and I trust that many people in universities have been thinking about that also. We all have our ideas and crystal balls, but there has not been much since glucose isomerase that has been very significant as a large tonnage enzyme. The market is well satisfied with good products rather well made by those companies involved.

M. H. Nielsen. I think that new developments within this technology are very capacity-demanding; that's one of the limitations. It takes a lot of capacity to develop a new product or process and all the easy ideas in enzyme technology have already been used: the more difficult ones take a long time to bring to a solution. Another limitation is toxicology investigations; all the investigations demanded can delay marketing of new products by 2 to 3 years. But I do not agree with Dr Meers that there is a lack of ideas. There are lots of ideas and we'll find new enzymes like glucose isomerase. As I tried to say yesterday, we face three big problems: the fuel problem, the food problem and the fertilizer problem. I think we have sufficient brains and resources to solve these three problems, which are decisive to the future of the human race.

C. Bucke. I think there is a need for a really good thermostable lactase. All the enzyme companies offer lactase, but none of them seems to be really quite what's wanted. What can be done by academia is to take a rather greater interest in industry and then speculate a bit; think about the sort of things that industry might want, try some of the wild ideas. Can you convert galactose to glucose or galactose to fructose? I shouldn't really have said that, but there's an idea for you! Twenty-five years ago you would have been laughed at for suggesting that you could convert glucose into fructose. There are *some* wild ideas that are worth trying. If something is going to be used in the food industry then it's going to be fairly attractive to make that material by using biological catalysts rather than by chemical means. For example there are opportunities in looking at high-intensity sweeteners like aspartame, which was originally made chemically; now we hear it's being made by enzymic processes. That process is likely to be superseded by producing an aspartame polymer as a result of genetic engineering though it still has to be hydrolysed correctly. There are other examples of materials which are really 'twinkles in the eye' of the food industry, and where biotechnology might get in. So if academia uses its imagination about what might be needed, it could probably find tasks to do – and support from industry to do it.

G. Näher. It makes a very great difference when you develop a completely new process based on enzyme technology instead of trying to change an existing procedure just for the sake of enzyme application. An example of this is the great success of glucose isomerase for the production of high-fructose syrup. Another similar possibility might be the utilization of cellulose by means of cellulase.

Dr Lowe and Professor Mosbach gave interesting papers this morning showing what could be done with immobilized enzymes. They even showed in principle how to overcome the co-factor problem. As producers of pure enzymes we are interested in this kind of work. However, if you pursue this with a chemical company, if you try to change existing processes to using enzymes instead of conventional catalysts, you won't get far. It costs a company a tremendous lot of money to change a process and therefore they are quite anxious to avoid such changes. For this reason biotechnology can become effective only in the long term.

Of course, there are some novel syntheses, in particular stereospecific steps, feasible only with

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enzymes, which will be accepted faster by industry. But for commercial large-scale processes a lot of work still has to be done in chemical engineering and also in convincing the chemists of the benefits of enzymic processes.

P. J. Strijkert. From another point of view I would like to add that I too am convinced that for a substantial extension of the use of enzymes we should look at the chemical industry. But then you will quickly come to the conclusion that there will not be reactions that need simple enzymes like hydrolases, but more complicated reactions like oxidation–reduction. We had a lot of interesting talks on the subject, but I must repeat that for bulk conversions in chemical industry it will be necessary not only for the enzyme to be cheap, but for the whole reaction to be cheap, as with a reaction that needs cofactor regeneration. I really think that we shall not come to where we should come by the way Professor Mosbach told us he was going at the moment. He was trying to solve the problem in a very elegant way and so we can learn a lot from it. It is a complicated problem and he admitted that he liked working on complicated problems, but I think for the type of reaction that industry needs is a good, simple economic solution. Therefore I think we should go about it quite another way: we should really look for this type of reaction without the need for expensive cofactors and see what we can do with tailor-made enzymes and cheap cofactors.

H. G. Volger. What chemical companies are looking at is the kind of chemical conversions they would like to achieve. Some are simply not possible for a chemical catalyst, so you have to put these on the list. Some are multi-step reactions that cost a lot of money; you put those on the list. It may be difficult to get your product pure because you are making a mixture. When you have listed goals in chemical conversions, you look at the kind of tools available in principle in biotechnology. If it is a reaction where there is no difference in redox systems, where you might use enzymes without a cofactor, then I would advise starting straight away unless these are relatively simple non-enzymically. When you need a redox enzyme system with a cofactor, then the most difficult and challenging problem is to regenerate the cofector cheaply. Not that this is not possible, but it has to be done in a very low-cost way to compete with the types of system used in redox chemical conversions.

A. T. James. Yes, I agree with much of what has been said. If you look at the rough costs of production by fermentation, which seem to be in the region of £200–300 a ton of raw biomass, then add any fractionation upstream and downstream and so on, you are up around £1000 a ton. That's the sort of level that one would look at, either for isolated enzyme processes, or even for a fermentation whole-cell process, whatever the type of cell. My feeling is that we have gone almost as far as we can with the exploitation of lytic enzymes generally, whether they be proteases, lipases or carbohydrases. The next stage, which was referred to in many of the papers in this symposium, is reactions of addition, elimination, hydration of double bonds, isomerization and so on, all of which are now worth studying. Those reactions, which include naturally a very complex electron transport system, seem almost always to be done best with an intact cell. Nevertheless there is a very large number of such reactions and if we could handle the enzymes conveniently we could expand the field of chemical exploitation very much more. There are many fields from lubricants, adhesives and so on, where one could usefully take some naturally occurring biological materials, such as some carbohydrates or fats, and carry out

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some quite interesting transformations to give higher-value products. There is an enormous amount yet to be done.

K. Mosbach. Here's to my love of complicated systems! But sometimes they pay off. For instance Pharmacia are making money now from these coenzymes for enzyme purification. The requirement for low-cost regeneration for coenzymes is definitely true, but not in all cases. For enzyme replacement therapy in medicine, the cost of the coenzyme would be irrelevant. The major criterion is to confine the coenzyme together with the enzyme within a bead which you inject or have in an external bypass. The cost is *totally* irrelevant.

I noticed particularly in the last session that we academics were put on the defensive. You say that we play around, unaware of the major costs. It is good for people not aware of these problems to put them into perspective. Then some more positive replies and suggestions came and I would like to have more such dialogue with you commercial people. We who are more adventurous – we have no investment captital, but we have investment interest and energy – 20 hours a day some of us even! Tell us the ideas you have. You want to have this compound transformed, like galactose to glucose. You want to have this chemical made this way. Then we can start thinking, 'can we use current enzyme technology, can we do changes of specificity by genetic engineering, can we make synthetic enzymes mimicking enzyme reactions?' We need these suggestions and then I think most of us will be happy to try to get our fingers wet even if it is a 5 year project. A way of better communication has to be found.

R. Spier. This is something that is at the level of my original question, so if you don't mind I'll cobble something on to the end of it. There seems to be an essential problem in communication. Can one reasonably expect communication between people who are seeking to develop things for their own exclusive use, basically with secrecy in the background and for their own monopolistic exploitation? This is the way it works, this the way it's set out. Can one really expect them to come forward and say, 'these are the things we would really love to have', and then have some academic come along and say, 'well here's how you do it', and the world then knows about it? It is not going to work that way. I think to some extent one has to find a formula that may look, not necessarily at the next 5 years, but at the next 25 years and perhaps go beyond the point where immediate self-interest is involved. One has to take a national interest and put it to the companies. If they are going to be beaten by Japan, which is going to take a long-term programme, what are we going to do to counteract this? What kind of concerted effort, a strategically developed effort, are we going to have to mount? I think that's the only thing we can do, bearing in mind that we are in fact being threatened by a very heavily organized, highly interactive and clearly motivated operation.

B. S. Hartley. I regret that I must bring this valuable discussion to a close, though there is much that I and others would like to have said. The conclusion I bring away with me is the same that caused some of us to organize this meeting. What is desperately necessary is more communciation between academics at the frontier of technology and industries at the sharp end of the market place. Industry needs our specialist knowledge and creative science. We need their wisdom about markets, process costs, sales opportunities and financial and regulatory constraints. It is not enough for academics to sit back and wait until they are approached to produce constructive solutions to these problems. We need a continuous dialogue of looking at

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the problems that industry has, the opportunities that a particular company sees and the new ideas that we have. If all these things come together at one particular moment of time, it is marvellous, but almost unique. Generally one has an idea in search of a market, sometimes we have a market in scarch of an idea, sometimes we have a technology in search of both. When these three things come together we have money, but putting them together needs work. I thank you all for the work you have put in to make this a useful meeting.

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