PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Industrial Microbiology: A View from Whitehall [and Discussion]

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Industrial microbiology: a view from Whitehall

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New developments in biological sciences have major effects on macrobiology (forestry and farming) as well as on industrial microbiology. Governments may give more attention to the former (because it can produce quicker results) rather than to the latter (whose very great potential may take longer to realize). Even so, they can and must provide a favourable trading environment for microbiology. As regards general measures, microbiology creates new demands for improving the efficacy of the patent system (adequacy of the period of useful protection; applicability and validity of patent law to microorganisms) and benefits from monopoly law (justifiability of consortium research and development). There are fewer new problems from trading legislation, and none from limited liability. Regarding specific measures, toxicology and safety law are crucial.

New skills and skill combinations are needed, including easy exchange of information between research teams and with other biologically orientated industries, e.g. process plant, brewing technology and medical industries.

1. Introduction: past government actions

This opening paper is not a U.K. Government view, or 'official' in any way. It is a personal view of the way in which governments of many countries have played or may be expected to play a part in this crucial subject, which has been important for a very long time and is now rapidly rising in significance, perhaps comparably with microelectronics, control technology, robotics and artificial intelligence. As a personal matter, this is a welcome opportunity to think again about the subject in which I did research, as a graduate student.

As a start, it is necessary to compare the strengths and weaknesses of microbiology, as a production process, with those of macrobiology (agriculture and forestry) and of non-biological methods based on non-renewable resources. It is on these comparisons, as conventionally perceived, that the climate for your work will set. They tend to indicate that progress in microbiology, however important and promising, may not be always quick or easy. The new science that is the source of the new possibilities can be applied to macrobiology as well as to microbiology, and will strengthen both. Further, macrobiology and oil-based chemistry are very well established and, despite escalating oil prices and the totally obvious long-term need for conservative husbandry, will provide very exacting economic standards and competitive resistance. Some current writing about microbiology, in concentrating on long-term strength, may be underestimating the immediate obstacles to be overcome, and generating some over-optimism about immediate results.

Three potentially large cost barriers have to be overcome by the new industrial microbiology: those of the capital cost of the production unit, of the removal of water, and of proving safety. If we leave aside the significant but somewhat less important field of speciality chemicals for non-biological purposes, there are two major areas for consideration: bulk products, such as food or materials for clothing, furnishing, cars, etc., and potent substances for medicine or

agriculture, needed in smaller volume. Table 1 shows the obvious features of the three technologies in relation to these three barriers. In all countries the agriculture, forestry, and petrochemical lobbies are very powerful and, even allowing for conservation and myopia, have very strong cases in relation to normal government time scales (which, to be fair, are lengthening), but not to the figure of decades that interests this meeting. So democratic governments will often be difficult to persuade that public funds should be used for the big entry fees of industrial microbiology. Finally, it may well be that the governments that so far have done most to provide a favourable climate for manpower-efficient petrochemistry, farming, or forestry will not be those most receptive to microbiology. Just possibly, more authoritarian governments in developing countries might be kinder. The inertial factors there are less.

TABLE 1. INDUSTRIAL MICROBIOLOGY: RELATIVE COST BARRIERS

	plant capital	drying and finishing	proving safe
(*a*) Bulk products (food, fuel, materials)			
petrochemistry	medium: throughputs and selectivity intensively improved	water not used: separation intensively improved	increasing
macrobiology	low (trees and crops need no containment): machinery not dear; already optimized	often low (outdoor drying)	lower because of tradition and familiarity
microbiology	still high: dilution large; mixing aeration etc. sometimes complex; despite high growth rates throughputs not high	drying still expensive	high because of suspicion of novelty and because of unfamiliarity
(*b*) Low volume biologically active products (medicine and agriculture)			
petrochemistry (synthetic pharmaceuticals and agrochemicals)	production equipment cost usually low	formulation the only important element	escalating rapidly
macrobiology (insect control methods, plant- and animal-based medicinals and insecticides)	animal, vegetable and insect sources: collection costs high but plant cost small	similar for all	may stay low (familiarity)
microbiology (antibiotics, vaccines, polypleptides etc.)	small	—	will escalate rapidly

TABLE 2. SOME PAST GOVERNMENT AND GOVERNMENTAL INSTITUTION ACTIONS

(*a*) *Beneficial*

(i) wartime penicillin programme
(ii) collaboration in semisynthetic penicillin development (Italy)
(iii) recognition, patenting and licensing of cephalosporin (N.R.D.C.)
(iv) maintenance of culture collections
(v) development of agricultural microbiology
(vi) education, training, basic research

(*b*) *Difficulties*

(i) single cell protein in Sardinia (B.P.)
(ii) workload planning at Porton Down
(iii) fluctuations in public authority attitudes to experimental work on recombinant DNA
(iv) problems of reconciling old and new fructose sweeteners

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Against this backcloth, we may illustrate past activities in development by governments. Table 2 reminds us that governments do best for science and its application (*a*) where objectives are clear (as in wartime) and (*b*) where there is public consensus (such as exists in relation to protection against most narcotics, but not in relation to tobacco or alcohol). So, where there are complex or confused objectives and absence of consensus, we must expect trouble.

There is one further area, which I shall leave aside, that of spillover from defence work in the various countries where it may be going on. At some stage, such work, whatever its moral or legal position, could somewhere be commanding substantial resources and generating very important findings, and should not be forgotten.

2. Economic and trading environment

(*a*) *General matters*

The tradition of democratic government is to seek, wherever possible, general methods of achieving good trading conditions, rather than a mass of specific arrangements. This limits bureaucracy and makes it much easier for industrial firms to know where they are. The classic instances are the patent system, limited liability provisions and the law relating to monopolies. To these must be added, in recent decades, measures, such as G.A.T.T., for preserving a high degree of freedom in international trade. It is worth paying some attention to each of these matters.

(i) *The patent system*

With the increase in the average cost of carrying new pharmaceutical or microbiological invention to permitted commercial practice, the efficient functioning of the patent system has become of greater importance; although markets are larger, the time remaining between commercialization and the expiry of patents has now shrunk to no more than a few years out of the total patent life of 16–20 years. Manufacturers comment that this is making it progressively more difficult to earn sufficient money during this period to cover long lead time research and development costs. No one denies that the newer techniques involve more substantial toxicological problems, which take longer to clear, but, if, as in the U.S.A., the toxicological system is run on an adversary basis, it can be argued that delays become unreasonably and unacceptably protracted and, in due course, erode the willingness of the private sector to do research that is in the general interest. It may therefore be that the lengthening of patent lives will come to be discussed more often in the years ahead, and it is also important that President Carter has recently sent a message to Congress, recognizing the value of regulatory achievements, but suggesting that a number of measures, listed in table 3, might be considered to strike a better balance between technical progress and regulatory constraint. This matter has also been thoroughly discussed in the recent Department of Commerce consultations on industrial innovation (Department of Commerce 1979). The private sector has played a key part in medical and microbiological advance, and there is no mechanism at present in prospect for replacing the patent system as a means for underpinning such research and development. Proposals from the Third World, through U.N.C.T.A.D., for substantially reducing patent protection, will therefore be resisted by the private sector in the biological industries, and it will also be exceedingly important to find means whereby the patent system, or something akin to it, can be applied in the new area opened up by recombinant DNA and other technologies.

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The patent system is clearly running into some difficulty when attempts are made to cover microorganisms or their methods of manufacture. Here are some important issues.

(1) A basic requirement for the grant of a patent is that of novelty. Can a microorganism be novel? Can it be newly made, like a chemical compound, or did it pre-exist in nature? Can you patent a living thing? Two recent cases concern this matter. First, *Streptomyces vellosus* was patented by the Upjohn Company for production of the antibiotic lincomycin, on the basis that the inventors produced a pure sample whereas the organism grows naturally in mixed cultures (Bannister 1979). The precedent was, interestingly, in the production of pure semiconductors (Szabo 1973). Secondly, American G.E. patented strains of *Pseudomonas* that carry one or more R-factors (plasmids that determine metabolic pathways to degrade hydrocarbons and so give a potential for cleaning up oil spills) (Bannister 1979). The U.S. courts have yet to reach a final verdict, but a U.K. patent was granted in 1976. The U.K. stance is that human intervention (e.g. creating a mutation) is sufficient to allow a patent. To take a product from natural sources is insufficient.

TABLE 3. CARTER PROPOSALS FOR BALANCING TECHNICAL PROGRESS AND REGULATION

(i) regulatory agencies should publish long-term plans so that legislation is not inconsistent or unreasonable
(ii) future regulation should specify standards of performance (goals) and not the means of achieving them
(iii) regulatory overhead costs can:
make a product uncompetitive
increase market concentration
(iv) anti-trust policies need rewriting to recognize:
worldwide market practices
acquisition of market share by improved products
(v) there should be a relaxation of price and entry regulation to encourage innovation (in, e.g., railways, cable television, civil aviation) and competition

(2) A process could be patented that generates a specific microorganism, access to which (in the public domain) may lead someone else to further development, based on that organism, that also turns out to be useful and profitable. There is no protection under the present systems for the holder of the original patent, who may well have spent considerable sums of development money.

(3) The patent law and the Budapest Treaty (Industrial Property 1977) require that a product that is to be patented must be placed in one of a number of specified national culture collections. Once the patent is published, then there is free access to the culture, which can be specified by its reference number in that collection. The very nature of microorganisms means that they can be generated in very large quantities from an initially small and dilute sample from a culture collection. Again, the results of an invention are immediately available to commercial competitors and infringement may be virtually undetectable. This may already be causing firms to refrain from patenting their products, relying instead on secrecy as their protection.

(4) The curators of culture collections are concerned about their responsibility if cultures die or are mistakenly acquired before the patent is published.

(5) The non-reproducibility of a patented process constitutes grounds for invalidation; this is likely to be more important in biology. This matter arose in proceedings between American Cyanamid and Berk Pharmaceuticals in 1976.

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(ii) *Limited liability, monopoly law, freedom of trade*

The use of limited liability companies is a second general method for providing a reasonable trading environment, and does not yet seem to offer any new problems. Monopoly law, needed in order to prevent too high a concentration of power in established businesses, can, in countries where monopoly behaviour is inherently held to be illegal, without reference to the question of public interest, bear down on the conduct of research and development by consortia. As is well known, this is the case in America, and in continental Europe, although in U.K. the criterion of the public interest is allowable as a justification for the existence of a monopoly. Again, the current Department of Commerce (U.S.) studies of innovation have raised the question whether the U.S. Department of Justice should do more to recognize the value of consortium activity in the field of research and development. Presumably, the same issue may arise in due course in continental Europe.

Measures for international freedom and fairness of trade can also have an effect on microbiological technology and its profitability. This is because export prices are normally expected to be in line with domestic prices, so that any form of price control in the home country can have considerable effects on the worldwide income of an innovating company and can create large profits for trading or retailing agencies in countries where the market will bear a higher price than the innovator's home market.

(*b*) *Specific matters*

These include product toxicology, process and experimental safety, animal experimentation, maintenance of collections of biological material, and a wide variety of small matters.

As regards product toxicology, some of the difference between U.K. and continental and U.S. practice stems from the greater U.K. reliance on experience and common law, rather than on codified and laid down legislation alone (Code Napoleon). The controversy in this area lies between the innovators themselves, who, on the whole, prefer the British system, and the 'public interest groups', who often claim that their activities stimulate the right kind of innovation, and trade stemming therefrom, rather than stopping innovation. As for other standards, there is considerable overspill from the standards procedures in the biggest markets or from the more energetic standards-oriented countries like the Federal Republic of Germany to those in other parts of the world. This can sometimes favour the producers whose home operations are in the big markets. At present, the balance of argument tends to lead toward the more pragmatic U.K. approach.

The issues of safety at work and safety of experimentation raise a number of new factors. Individuals vary in their sensitivity to synthetic chemicals, whether as products, intermediates, or starting materials; this complicates the setting of environmental standards for factories. The variability, however, is much worse for biological materials, as became clear during the period when biological detergents were produced. It is likely that the screening of workers will present special problems in some of the microbiological industries that will become important over the coming decades, and this will provide a considerable incentive for automation. This, in turn, will increase capital intensity and therefore, the 'patient money' problems referred to below. Experimentation hazards from self-replicating material are, of course, not new (smallpox being a case in point). But, after the initial alarm about the wider possibilities arising from gene transplantation into relatively prevalent organisms normally harmless to human hosts, the need for containment has now, to some extent, been dealt with. It is, however, likely to remain an

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area of continuing concern, and it will be very much in the interest of the new technology for high standards to be voluntarily maintained. This, too, will increase the expense of work. It is probably reasonable to comment that the delays occasioned by discussions during the past two years will, in retrospect, not appear oppressive or excessive and may well have been beneficial. The problems of long delayed action arising from any form of genetic damage will raise exactly the same kind of controversy that exists about carcinogenic hazards, with the resolution of arguments being even more difficult and some of the issues attracting a good deal of publicity.

TABLE 4. SOME MAJOR COLLECTIONS OF LIVING ORGANISMS

Industrial Culture Collection, Aberdeen, U.K.
Central Public Health Laboratory, Colindale, U.K.
American Type Culture Collection, Rockville, Maryland, U.S.A.
German Collection of Micro-Organisms, Munich
Japanese Federation of Culture Collections of Micro-Organisms based at Tokyo University
Central Bureau vor SchimmelCultursbaarn, Amsterdam, Netherlands
Russian National Collection, Moscow

Animal experimentation is another area in which continuing argument can be expected. The number of animals involved is substantial (100 million worldwide annually, 5 million in the U.K. in 1977). The purposes of experiments vary widely, and, inevitably to some people, some of the experiments will seem trivial in relation to the animal sacrifices involved. There seems to be no alternative to a case-by-case approach, with licensing arrangements along the present lines, but with some lay representation. The U.K. attitude to animals is more sympathetic than elsewhere, so that this may be a case where we, in this country, have a particular problem.

Table 4 shows some of the more important collections of biological material, both in U.K. and elsewhere. At present, these are not particularly expensive, but the new technologies are likely to create a greatly increased value for biological diversity (new variants, modified species, etc.). Alongside considerable expansion in private collections, there are likely to be enhanced needs for bigger, better maintained and more accessible public collections. During the next decade or two, therefore, we must expect considerable discussion of the proper level for this kind of activity.

3. AVAILABILITY OF RELEVANT SKILLS AND SCIENCE

At this point, we need to recognize that biotechnology embroils at least three major areas, as shown in table 5. The relevant skills for each of these areas is different, but, taken together, they cover a wider range than almost any major area of technology. The necessary collaboration between different skills will be difficult if the geography of laboratories and plants is not carefully thought out; perhaps we should have a 'DNA Valley' somewhere in the U.K. The level of specialization and skill needed in each subject is large, so that the problem cannot be solved by hoping for large numbers of multi-dimensional polymaths, although, of course, some such people will be needed to create communications and to draw things together. High standards of teamwork will be needed in particular projects, but there will be great benefit if teams in different projects can exchange experience. This will be particularly true for the public sector institutes concerned with toxicology collections and so forth and for the private sector groups.

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Some further points are as follows.

(*a*) Few universities offer courses for full time undergraduate biochemical engineering in the U.K., and those that do so run courses based on chemical engineering, biology or food technology. It is arguable that a biochemical engineer could be produced from a fundamental study of either engineering or a biologically orientated subject.

(*b*) There is a real lack of industrial experience upon which to base objectives and structure for undergraduate courses.

(*c*) Bioengineering courses are not fully subscribed, and industrial requirements are few. Table 6 gives the number of advertisements in the *Diary of the Institution of Chemical Engineers* up to a few years ago. There is no reason to expect it to be very different now (Emery 1975).

TABLE 5. SOME SKILLS RELEVANT TO BIOTECHNOLOGY

chemical engineering	genetics	economics
	botany	politics
mechanical engineering	zoology	moral philosophy
	physiology	
control engineering	chemistry	
	biochemistry	
electronic engineering	physics	
	mathematics and statistics	
sterile engineering	toxicology	
	pharmacology	
	colloid sciences	

TABLE 6

year	number of advertisements
1969	10
1970	5
1971	9
1972	5
1973	7
1974	10

ratio of $\frac{\text{academic}}{\text{industrial}} = \frac{2}{3}$

4. 'PATIENT MONEY'

In all the major areas of biotechnology, there are reasons why the period between the formulation of a project (whether on the basis of an invention or a market perception) and financial break-even will be a long one. For the large-scale production technologies, such as those of fuel alcohol and of single cell protein animal feed, the delay is the already familiar one associated with scale-up and product toxicology (although this will not be severe for fuel alcohol and related projects). Consequently, the outward cash flow curve will go a long way into debt before it turns horizontal and the money can be recovered; furthermore, the recovery of the debt will depend very substantially on public sector policy for the pricing and availability of alternative materials, whether these are oil, or nuclear fuel (for fuel projects) or soil or fish meal (for animal feed). The idea is, of course, that the free market, whether in products or in financial loans, should be equal to the task of financing the cash flow. Unfortunately, the uncertainty in the product markets, and the extent to which these are manipulated as a matter of national policies, must make banks and normal lending agencies somewhat hesitant about the large sums

involved and the large risks. Large production, therefore, is an area where only governments or the biggest firms can afford the 'patient money' entry fee, and there will be continual proposals for public sector involvement.

In the smaller volume, high value polypeptide or protein and related markets, it may well be that a very wide variety of materials can shortly be made available, in reasonable quantities, but it is far from clear which of these products can safely be used in therapy, diagnosis, etc. We must therefore again expect rather long delays between the beginnings of expenditure and financial break-even, with the building up of cumulative debts, perhaps not quite as large as those for the bid productions, but still large enough. The attractiveness of this market is already bringing in money from some private investors in the U.S., and from large companies in Europe. But there are likely to be some areas where, for one reason or another, the risk is too great for the private sector, but where there are long term prospects of important markets, so that some countries will put in government money, and thereby threaten to pre-empt the field if others do not do likewise. We may therefore expect that the issue of patient money will be a lively one during the years to come.

5. Strengths in related industries (table 7)

Alongside the wide range of skills that are needed, there are industries that employ these skills, and whose presence or absence will, therefore, considerably affect the health of the biotechnology sector. For example, any country with a healthy chemical process plant industry is likely to be brisker and nimbler in putting together the plant for biotechnology. Similarly, good performance in the brewing and food technology industries will help. Big natural product industries (forestry, agriculture etc.) will cut both ways. On the one hand, there may be powerful lobbies that will resist some of the new technologies because they threaten existing procedures and businesses; on the other hand, the technical capabilities will be helpful.

Two other industries of importance are those of medicine and of control technology. Without high medical standards, the prospects for protein and polypeptide technology in a given country would be rather dim; similarly, the conduct of the new kinds of enzyme and microbiological processing are likely to be very demanding in all kinds of control, including the control of sterility.

Table 7. Some related industries

process engineering
pharmaceuticals and chemicals
control engineering
computers and software

6. Important opportunities: selectivity

Alongside those already mentioned, it must be noted that other microbiological technologies will develop hand in hand with those being discussed at this meeting. These are listed in table 8, and the form of their interaction varies greatly in complexity.

It will be important, in countries like the U.K., where resources are limited in relation to the large potential expenditure in fields such as this, for mechanisms to be developed whereby there is adequate concentration of effort on a selected and manageable portfolio of projects. This will

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mean stopping some projects that are attractive but less so than those that are chosen. At present, our methods for doing this when there are long lead times are far from satisfactory, either in private or in public sectors.

TABLE 8. SOME OPPORTUNITY AREAS

waste reutilization
microbiological leaching of metals
immunology and medicine
fine chemicals
fuel
photosynthesis

7. CONCLUSIONS

We can thus sum up as follows.

(*a*) Industrial microbiology, greatly enhanced in power by new science, has very great potential comparable with that of microelectronic control.

(*b*) Its rate of economic acceptance depends on the rate of cost and price increases in conventional industrial technology based on non-renewable resources, or on actions by governments to tip the balance.

(*c*) Simultaneously, 'industrial macrobiology' (forestry and farming) is also advancing fast, driven by the same new science. This technology has the great advantage of not requiring containment or artificial drying, both of which are very dear.

(*d*) At present, governments are more inclined to help macrobiology, which is more familiar and also creates more employment, but is best in warmer climates (e.g. in Brazil).

(*e*) Governments have, in the past, played a considerable and constructive part in microbiology, with some conspicuous problems.

(*f*) In creating a good economic and trading environment, attention must be paid to various aspects of patents and regulatory systems and to trade patterns.

(*g*) The skills and sciences needed for effective industrial microbiology are exceedingly diverse and their integration needs new approaches to extend the existing procedures traditionally based on specialism and limited alliances.

(*h*) Development times will be long and much patient money will be needed, provision of which will create problems.

(*i*) Strengths in related industries, e.g., plant and process engineering, containment technologies, fermentation technology, will be a crucial contribution.

(*j*) The range of areas of opportunity is very large, so that, where (as in U.K.) resources are limited, there will have to be selectivity.

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Discussion

J. L. Meers (*John & E. Sturge Ltd, Denison Road, Selby YO8 8EF, N. Yorkshire, U.K.*). I feel that the Common Agricultural Policy of the E.E.C. increases the cost of our agricultural raw materials for the fermentation industry. For example, consider the production of lactic acid from sugar. The E.E.C. price of sugar is in excess of £200 per tonne compared with a present world price of around £93 to £95 per tonne. Despite rebates of around £19 per tonne for industrial use, it still pays to make lactic acid by fermentation outside the E.E.C. and import it into Europe. In short, this policy of high agricultural prices in Europe is inhibitory to research.

D. S. Davies. I accept that this is true at present, and this policy will clearly have an effect on project selection. However, production of high potency materials, such as pharmaceuticals, should not be significantly affected.

E. G. Beveridge (*School of Pharmacy, Sunderland Polytechnic, Sunderland SR1 3SD*). The U.K. government has a particularly bad record in support for industrial microbiology. They have entered very few ventures, and then only at a very late stage of development; an example of this is the involvement of the N.R.D.C. in the development of the cephalosporins. Furthermore, they are actually withdrawing their support from this type of research, as witnessed by the transfer of the Microbiological Research Establishment (Porton) to the Public Health Laboratory Service and the shortage of funds for the maintenance of our National Culture Collections. This contrasts with the attitudes of the governments of Brazil and West Germany.

D. S. Davies. I cannot give the view of the Government and my personal opinion will be of little use.

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