Introduction

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INTRODUCTION

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The Seminar on Biotechnology in Europe and Latin America (SOBELA) took place in Brussels, 27-29 April 1987. Unlike many recent meetings in biotechnology this was not an opportunity to display the latest developments, but more importantly a chance to exchange information and prepare commercial agreements based on the transfer of skills and technology in the biosciences.

The meeting opened with important statements of interest and goodwill by key scientific and political figures from Europe and Latin America. Later, businessmen and scientists from the two sides of the Atlantic described the infrastructures that support biotechnology activities in their respective regions. It emerged that there was real scope for two way exchange of skills, materials and equipment.

The Commission of the European Communities, CEC, and various multinational groupings in Latin America were able to compare and contrast the effectiveness of their enabling programmes. In both areas regulation and legislation raise barriers to the free exchange of skills and commodities resulting from biotechnology. In both areas collaborative ventures are breaking down such barriers, albeit too slowly. Both areas perceive the greatest competitive challenges to their biotechnology industries to come from the USA and Japan.

Since April 1987 the stock market has become a less than safe investment and the US dollar is no longer a safe alternative to gold. These developments will have long lasting effects on the ease of raising capital and the success of exported products from Latin America. More pressure will be applied to Latin American governments to provide the means to enable the development of an internationally competitive industry. European biotechnology has moved rapidly from the position described in 'Industrial Biotechnology in Europe', edited by Duncan Davies, (CEPS, CEE, 1986) in which Europe was perceived to be failing to compete. In the past year there has been a flurry of supportive and concertation measures at both national and Community levels.

Why SOBELA?

Europe and Latin America have social, cultural and linguistic ties, which for many years have supported significant commercial exchanges. The European Community is Latin America's second biggest trading partner (after the USA) and the biggest supplier of development aid.

The present problems of the Latin American economies lead many Europeans to ignore the wealth of natural resources and the size of potential markets. The good educational infrastructure and the presence of modern technology and science-based industry offer considerable scope for mutually profitable exchanges in the area of biotechnology. Despite sometimes being included amongst the nations of the 'Third World', Latin America has made significant contributions to developments in biotechnology and may have acted as a stimulus to action in European biotechnology.

Existing training schemes funded by the European Community and its Member States do much to enable skilled management and senior scientific personnel to keep ahead of the latest technological developments. Biotechnology also depends on the availability of highly skilled technicians for whom fewer international training programmes are accessible. The absence of such personnel is a serious hindrance to the development of the biotechnology industry in Latin America. SOBELA participants meeting at informal events had the opportunity to discuss, without commitment, the nature of potential collaborations in this and other areas of interest to the biotechnology industry.

In the absence of a formal biotechnology link between the European Community and Latin America, SOBELA provided a forum for dialogue. The presentations, summarised in the following pages, presented existing national initiatives in industry and in the public sector. It will be immediately noticeable that this was not a scientific seminar, but more importantly perhaps, an overture for collaboration in industry and the underlying science, mediated by diplomatic goodwill and influence. How can European/Latin American collaboration in biotechnology serve national priorities?

The example of Brazil's ambitious Gasohol programme so impressed France's President Giscard d'Estaing during his 1977 visit, that he commissioned a report on French options in biotechnology. The report, Sciences de la Vie et Societé' by Gros, Jacob and Royer (1979) initiated the

chain of events that lead to the first 'Programme Mobilisateur', designed to establish France as a leading contributor to the new technology, and participant in the markets of the emerging 'bioindustries'.

The United Kingdom and other European states in turn began the implementation of hastily contrived programmes, designed to salvage national position or pride in an emergent industry that seemed once again destined to be dominated by the USA and Japan.

The example cited may in one case have acted as a spur to development in Europe, but in general the direction of technology transfer is predominantly in the opposite sense. What can Europe and Latin America do for each other? What are the perceived needs of these two widely different groups of nations? Firstly we shall examine what we mean by biotechnology.

The Scope of Biotechnology

Very broadly, biotechnology may be defined as the purposeful application of biological science, thus encapsulating most aspects of current and traditional agriculture, food production and health care, narrower definitions of phrases such as 'new biotechnology', forms specifically upon the more prominent modern techniques of genetic engineering, monoclonal antibodies, and their applications.

Biotechnology has a prehistory, which predates the keeping of records or experimental details. Into this area must fall the first examples of cheesemaking, beer and wine manufacture and some aspects of traditional medicine. The transition from tradition to science took place around the end of the 18th century. At about that time the scientific method was becoming respected, the microscope was becoming a serious research instrument and the value of careful measurement was becoming realised. The quantitative approach saw fruits in the researches of Mendel and the flowering of organic chemistry, although a century was to pass before those disparate strands could be drawn together in the new biology.

Until the second world war many basic organic chemicals were made by fermentation and subsequent purification. Glycerol, acetic acid, citric acid and many other solvents and acids were extracted from stirred tank fermenters using molasses as a raw material. In Japan monosodium

glutamate production from strains of aspergillus was the first pure product of the fermentation industry, other than alcohol.

Microbiological development in the same period had been rapid as had the growth of medical genetics, but perhaps the most critical discovery for modern biotechnology was the discovery of penicillin action by Fleming in 1928. The stimulus of the second world war created a need for the large scale production of antibiotics. Because of the development of several different strands of appropriate technology it became possible to achieve the growth of moulds and filamentous bacteria in highly defined and controlled conditions. In 1940 Florey and Chain succeeded in isolating and purifying penicillin in a manner which allowed mass production. The development of downstream processing can be traced to this period.

The perfection of the hybridoma technique for the production of monoclonal antibodies resulted from the work of an Argentine scientist carried out in a British laboratory. César Milstein with Georges Köhler went on to share the Nobel prize.

In Latin America it is possible to say that much large scale use of biotechnology remains at roughly the stage reached in Europe by 1945. There are relatively sophisticated brewing and food technologies and increasingly a degree of competence in medical technologies such as vaccine manufacture. The inclusion of state of the art skills will hopefully be one of the results of some of the ambitious programmes described in this presentation.

There is a real danger that biotechnology is being presented as a new industry. This is quite clearly not the case. Biotechnology is a set of enabling technologies which will find application in the existing bioindustries, i.e. the several sectors of activity based upon the applications of life sciences and/or the use of materials of organic origin. It is quite fair to say that some aspects of biotechnology have allowed the launch of new companies such as Genentech or Celltech, which rely exclusively on the new technology for their sales. The outlets for their products quite clearly label those companies as newcomers in the pharmaceutical industry, rather than harbingers of a completely new industrial sector.

Modern biotechnology has the potential to change profoundly the nature of several major industrial sectors. This potential has as its foundations two very different sets of skills. Firstly, there exists an

assemblage of biological and engineering skills built up over centuries of experience in the fermentation industry. Secondly, and in the public eye, more prominently, modern molecular biology has allowed the tailoring of genomic material and cells to serve specific goals. The first biotechnology revolution occurred, not in the 1970s, but in the 1940s when the industrial scale production of antibiotics necessitated radically new developments in fermentation technology and downstream processing.

In the course of the Seminar Professor Da Silva, working in Paris at the Pasteur Institute, used the example of vaccine production to identify four generations of biotechnology.

Generation	Vaccine Type	Technology used
Fist	Traditional	Eggs/in vivo extract
Second	Polio, Mumps, Rabies	Cell culture isolation of virus
Third	Hepatitis	Genetic manipulation
Fourth	AIDS?	DNA/Peptide synthesis

Europe is currently experimenting with Fourth Generation vaccine production, while Latin America is locked into the Second Generation. Can it become economically justifiable for Latin America to acquire its own Third and Fourth Generation capacity?

From the viewpoint of a commercial entrepreneur, biotechnology serves to make money from biology. Growing public concern for the environment and public health risks, has in some cases limited the application of biotechnology. Such issues as the erosion of the earth's ozone layer and CO_2 build up in the atmosphere have sensitized the public to possible harmful effects of scientific and technological innovation. It is to the credit of the biotechnology industry in Europe and North America that their own policing standards have disarmed most critics. Biotechnology has succeeded in building up an environmentally responsible image, although as Mrs Viehoff emphasised, there is no room for complacency. The environmental record of the Latin American bioindustry will come under dose scrutiny if its products are to be launched on the European market.

Like any innovative industrial activity, biotechnology is underpinned by an investment in Research and Development, R&D. The R&D financing comes either from the private sector, the public sector or a mixture of both. In the following chapters specific examples of European and Latin

American experiences will be presented, however certain general principles can be outlined here. Industry is concerned with making money in the medium or short term. R&D in biotechnology is very expensive and in industrial laboratories must be aimed at process improvement or product development, linked to astute market analysis if profits and long term success are to be achieved. In the case of modern genetics, applied industrial research is supported by the results of public sector research, published in open sources.

To take a very obvious example. The structure of DNA, resolved by Watson and Crick in 1953, underpins the whole of modern molecular biology, which is one of the foundation stones of biotechnology. The discovery of DNA structure was made possible by public sector funding. The synthesis of human insulin by a yeast or bacteria would be unthinkable without knowledge of DNA structure. Human insulin is sold by many reputable companies, who could not dream of financing a research programme that might give commercial results only after 25 years. Yet it was only in 1988 that the first genetically engineered insulins appeared on the market.

The European Commission has been deeply involved in discussions about the nature of fundamental research, precompetitive applied research and competitive industrial research, as applied to the biotechnology area. Fundamental research in Europe has historically been a matter for national funding programmes, while competitive research is quite properly the domain of industry. The middle ground is a difficult area in which all available goodwill must be coordinated so as to realise public sector/private sector collaboration. In Latin America collaboration in the Andean Pact states and between Argentina and Brazil is tackling specific goals perceived to be of regional benefit. The European Commission has attempted to tackle this middle ground through the Biotechnology Action Programme, BAP, which will be described later. Future European Community programmes will concentrate on providing enabling technology for the European bioindustry in order to enhance international competitiveness. The nature of European/Latin American collaborations may depend to some extent on the willingness to compromise such competitiveness in relations with the Latin American states.

Ten years ago very few firms could think of a commercially justifiable reason for having molecular geneticists on their staffs. It would now be considered foolhardy for a European pharmaceutical company not

to employ such people. Later on, contributors to this volume will show why this is not always the case in Latin America.

At present the agricultural industry is waking up to the promise of biotechnology. In ten years it will be unthinkable for a major seed supplier not to have a molecular genetics team. Dr Sargeant, working in the European Commission, showed that it is likely that the very nature of agriculture and land use may be changed by developments made possible by biotechnological research. Such consequences might be of more immediate relevance to agriculture in the developing world, including Latin America.

In Western Europe, the United States and Japan, the main thrust of recent industrial activity in biotechnology has been orientated to the production of therapeutic products and diagnostics, both in the health sector. The public perception of biotechnology has been strongly influenced by issues as diverse as AIDS, the recent availability of highly publicised new wonder drugs, thrombolytic agents for heart attack victims and the dramatic application through forensic science of 'genetic fingerprinting'.

What can Biotechnology Offer?

The first impact of biotechnology has been in the area of human health. The public has seen remarkable progress made in the treatment of viral diseases and cancer, using the twin technologies of molecular genetics and cell fusion. Molecular genetics gave rise to genetic manipulation and cell fusion gave rise to the 'magic bullets' of monoclonal antibodies.

Products resulting from DNA cloning and expression in micro-organisms include: insulin, lymphokines, clotting factors and thrombolytic agents. Monoclonal antibodies have been the basis for simplified diagnostic tests and the hope of a cure for several cancers. Monoclonal antibodies can be used as guided missiles, carrying a 'warhead' of toxin or radioactive element to a specific target, such as the cells of a malignant tumour.

There is a great deal more to biotechnology than the health care sector. As a set of technologies it is poised to offer benefits to a number of industrial sectors including: Food, Environment, Agriculture and Animal Health, Chemicals, Mining, Energy and, of course, Human Health.

Despite the conspicuous successes of some health care applications, some goals have proved unexpectedly difficult to realise. Plant

biotechnology, for long the Cinderella of the biosciences is hastily constructing a carriage to get to the ball! Despite the early delays, the pace of discovery in this area is now remarkable.

The prospects of controlled nitrogen fixation by incorporating the genes of bacteria into flowering plants have proved difficult to realise. The complexity of the problem was underestimated by the naively phrased publicity which portrayed molecular biology as a universal solution in search of problems to attack. The hopes for alcohol from wood have also evaporated as enzymatic means of lignocellulose degradation have proved impracticable as a commercial process. Responsible scientists had always pointed out the difficulties involved, but the media, conditioned to a science which realised the impossible, would not accept such stark realism.

Political pressures are also significant. Debate has raged on the introduction of an EEC sponsored bio-alcohol programme, portrayed as an alternative to adding lead to petrol. Backed by several agricultural and fermentation companies, but strongly opposed by producers of industrial alcohol and more cost-effective lead substitutes, the ultimate decision looks set to be made as much on political grounds as on economic: finally, the argument was resolved by the decline in the price of oil and the strengthened Community commitment to budget discipline.

The Latin American countries with their vast genetic resources could well harbour microbiological resources that might offer solutions to some industrial process problems. Screening and identification of natural resources is an aspect of biotechnology that is often overlooked in Europe and North America. The potential reward in terms of useful biological activities is immense. Microbial screening using fairly traditional technologies is a key area in which Latin America can make a contribution to European biotechnology. A recent expedition to Brazil by staff of the Cranfield Institute of Technology, UK, underlined the importance of resources held in developing countries. The expedition hoped to collect samples from the Amazonian forest, with a view to understanding the rapid turnover of vegetable life on a very thin topsoil. Genes locked in Amazonian organisms could play an important role in the energy and environmental industries in years to come. Obvious applications in the environment sector include sewage treatment. The growing problem of urban sprawl in the developing world, makes sewage control a major issue in environment and public health.

Mining has received comparatively little attention from the public, but micro-organisms have been developed that are capable of concentrating minerals of commercial value from normally unworkable deposits. The same techniques could scavenge environmentally dangerous elements such as Cadmium or Mercury.

Biotechnology can do more than exploit existing markets. As old markets are eroded biotechnology has the potential to create new markets and revenues. In the context of SOBELA we must address the question of how biotechnology can serve the common interests of Latin America and Europe. Cynics will find it easy to say that major European companies will exploit Latin America. Collaboration should be approached with caution so as to distribute the benefits equitably between partners. The contributions of the following chapters show that indeed we do have something to learn from each other in terms both of science and models of cooperation.

European Biotechnology

Most European states have taken action at government level to improve competitiveness in the area of biotechnology. National programmes and coordinating bodies have until recently had little interchange of views. Even the European Commission has had comparatively little success in coordinating national strategies in biotechnology. Despite thirty years of community it is not generally appreciated among European governments, to what extent the European Commission works on their behalf in the harmonisation of regulations and the elimination of barriers to trade and free movement of personnel and skills. The probable impact of the 1992 target date for the removal of internal barriers to trade is gradually being appreciated by European industrialists, thanks to an information campaign orchestrated at national levels.

Total public sector biotechnology spending in the EEC member states may not be far short of that spent in the USA – estimated at $2.7 billion in 1987 by a report from the Congressional Office of Technology Assessment. Partly because of duplication and fragmentation of effort and largely because of differences of commercial opportunism and the absence of a real Common Market, Europe nonetheless lags behind both the USA and Japan in the commercial exploitation of biotechnology.

The funding of new ventures has been easier in the USA than in Europe. Seedcorn capital, venture capital, tax concessions and the entrepreneurial tradition are particularly North American attributes. Europe however has less often had to write off investments in failed ventures. The most conspicuous examples of failure in Europe have involved US companies operating without a tightly defined business plan. In the past two years European entrepreneurs have established a substantial pool of venture capital, with several specialist funds able to evaluate ventures in biotechnology. The United Kingdom has Europe's most sophisticated venture capital market, modelled on the USA, but characterised also by European conservatism. Some analysts now say that there are more new funds in Europe than the USA, although the pool of American funds, especially in the area of seedcorn capital will continue to be larger for the foreseeable future.

Europe probably has much to offer Latin America by way of advice on business start up schemes. If this can be integrated with some of the existing programmes and experience, it may be possible to fund suitably targeted biotechnology start-ups in Latin America.

In Europe two very different types of company have played a role in the new biotechnology. In the first instance medium to large companies, with diverse products and a long established tradition in product sectors ranging from engineering and chemicals to ethical products, have adopted the new technologies as a logical extension to their portfolios. More recently a second kind of company has emerged, backed by risk capital, small to medium sized, with a very few but very high technology products. Whereas in the USA such small companies dominate the biotechnology sector, in Europe it is the old, traditional, medium to large companies that dominate.

The larger companies in Europe, such as Elf-Aquitaine, Hoechst, ICI, Unilever etc. have added rDNA technology to their research programmes in health care and agriculture. In the UK and Netherlands university/industry partnership has played a major role in transferring appropriate technologies. Many of the resulting small firms, which succeed by attracting investment, become in turn targets for acquisition by the larger companies with a more conservative approach to new technology. Large companies are often unwilling to gamble on untested technology, but happy to pay the going price for proven products.

Even for the largest companies the regulatory and legislative barriers that exist in Europe are a major headache. A large company will have a regulatory affairs department far larger and more expensive than a USA company of the same size that focuses only on the internal USA market.

Latin American Biotechnology

In Latin America as in Europe, manufacturers of ethical products have had to face a number of different regulatory regimes. The cost of overcoming different national requirements has proved prohibitive for many smaller companies. In Europe as in Latin America, multi-national negotiations are moving ahead with the desire to provide a unified regulatory system. SOBELA might prove a launch point for European/Latin American negotiations in this area.

The SOBELA meeting demonstrated the steps taken by Latin American countries to rationalise, regroup and pool skills in this important area of high technology. Biotechnology has been the focus of an almost unprecedented dialogue between the Latin American states. Typical results of this dialogue include Argentinean/ Brazil collaborations, Andean Pact collaborations and an increasing Mexican involvement in South American biotechnology.

Whereas there are a number of interesting biotechnology start-ups funded by private or state organisations, it is notable that the local market is already being assaulted by the established multinationals. Many middle sized European, Japanese and N American firms are establishing marketing structures in Latin America. Several are contemplating the establishment of manufacturing and R&D facilities. These companies in particular must be encouraged to enter into a constructive dialogue with the nascent domestic biotechnology companies. This route might also be the most appropriate if European companies are to avoid the pitfalls of inadequate patent protection. It is difficult for companies to defend their intellectual property rights if they are far away from the market or competition concerned – even where such protection is legally guaranteed. Several small European companies have lacked the financial resources to defend infringements of their intellectual property rights in the USA.

The SOBELA Meeting

Introductions by several distinguished speakers confirmed the extent of goodwill among the participating states. The subsequent presentations gave an overview of the status of biotechnology in Europe and Latin America. Speakers from both sides of the Atlantic affirmed their governments' commitments to collaboration and several presenters were able to speak of specific examples.

Dr Pereira da Silva explained that biotechnology cannot be regarded as a panacea for the problems of a developing economy, although its application to well defined problems could yield very significant benefits. Many of his recommendations could be summarised by saying that what Latin America, and other developing countries, need is the establishment of bilateral accords with developed nations which permit training and the creation of a domestic infrastructure capable of supporting the benefits to be wrought by biotechnology.

The following chapters consider the state of biotechnology in Europe and Latin America. To what extent are the goals of collaboration likely to bring tangible benefits to participants?