BIOTECHNOLOGIES: RESPONSIBILITIES, PRIORITIES AND CONSTRAINTS

JOSEPH H. HULSE, VICE-PRESIDENT RESEARCH PROGRAMS
INTERNATIONAL DEVELOPMENT RESEARCH CENTRE

Presented to: Inter-Center Seminar on IARCs and Biotechnology
27 April 1984, IRRI, Los Banos, Philippines

BIOTECHNOLOGIES: RESPONSIBILITIES, PRIORITIES AND CONSTRAINTS

Presented to: Inter-Center Seminar on IARCs and Biotechnology
27 April 1984, IRRI, Los Banos, Philippines

By: Joseph H. Hulse, Vice-President Research Programs
International Development Research Centre

BIOTECHNOLOGY: BANE OR BOUNTY

"I look upon all the world as my parish" wrote a famous 18th century evangelist. One wonders how many of his converts became biotechnologists.

In an earlier paper I reviewed briefly several definitions of "biotechnology" and suggested that the word seems disposed to embrace all aspects of applied biophysics, biochemistry and microbiology, together with a fair sprinkling of organic chemistry and chemical engineering added for good measure.

In spite of the short history of its more novel attributes, papers to this meeting show evidence of some quite remarkable progress, much of potential benefit to agricultural sciences.

Biotechnology has proved a doughty competitor with space exploration and advanced electronics in attracting the attention of the popular press, whose judgement of its potential impact ranges between unbounded optimism and deep concern for the future of the human race. The pessimists, who appear to be in the minority, see the biochemical manipulation of life processes as the ultimate revelation of Mary Shelley's Dr. Frankenstein. They seem to share Mrs. Shelley's view that those who unlock the secret of heredity and learn how to create life artificially may not cherish their synthetic progeny with the tender loving care and caution they deserve.

At the other extreme are those who predict boundless benefits, any attendant risks being purely conjectural and improbable.

The following are recent quotations from two different Asian newspapers:

> "Biotechnology has been identified as the growth industry of the future because it holds the promise of a single technology that could meet all man's needs."

While welcoming the reporter's enthusiasm, his concept of a single technology comes close to a *reducto ad absurdum*.

The views expressed in this paper are those of the author and not necessarily of the International Development Research Centre.

The second journalist writes:

> "The use of genetic engineering in the West to mass produce crops may render (Asian) agricultural produce - including rice - uncompetitive in the international market. Because of recent advances in genetic manipulation technology, the United States is able to produce more, better and cheaper crops in less time than Asian countries can produce them with ordinary agricultural techniques."

On the other hand, a senior American professor of biology has stated that:

> "Science has become too potent and it is no longer enough to wave the flag of Galileo (in its defence). People seriously wonder if, through our cleverness, we shall not blunder into worse dilemmas than we seek to solve."

The professor is concerned that genetic engineering might inadvertently provide deadly weapons to enable the anarchists and the tyrannical in our society to imprison our liberty and threaten our existence.

An eminent Canadian geneticist and science educator has sounded yet another warning:

> "Because implications of the new (recombinant DNA) technology are enormous, I sound a cautionary note based on historical precedent...there will be unexpected and detrimental effects of the new DNA technologies. I say that without direct documentation but confident from history's lessons that there are no problem-free technologies and no fool-proof systems. Remember, it is fallible human beings...who designed and used the systems in the first place...Precautions often slow down research and biotechnology in an area characterized by incredible speed and competitiveness. If you are in competition and have to accomplish something in a short time, then paying attention to what you consider unimportant precautions is not going to be a high priority. I am not convinced that Canadians have come to grips with the difficult issue of how to enforce safety regulations."

Notwithstanding its prophets of doom, biotechnology has enjoyed a relatively favorable press, particularly when compared with nuclear physics. Perhaps we should remember that 20 years ago nuclear fission was being heralded as the ultimate solution to mankind's increasing demands for energy in addition to benefits offered by induced mutation to gamma gardens; to the control of cancer; and to the elimination of waste and spoilage from all post-harvest food systems through radiation sterilization.

....3

Not all of these promised benefits are readily evident in today's world.

While welcoming the generally favourable publicity given to biotechnology both by reputable science writers and the more popular press, greater attention seems to be devoted to scientific principles and techniques than to the overall comprehensive management of biotechnological research and development: in particular to the resources needed to pursue to the point of demonstrable human benefit all the many options presented in the biotechnological smorgasbord.

THE EXPANDING AGENDA

The component platters offered in the biotechnological smorgasbord increase with every related conference, symposium and statement of national science policy. The following are lists of subjects recommended for research and development in developing countries, the first from an international agency, the second from a major international conference.

The international agency recommends research be pursued on:

1. Genetically manipulated bacteria to produce energy and fertilizer from biomass;

2. Development of human and animal vaccines;

3. Improvement of traditional and novel fermentation technologies;

4. Improved agricultural plant and animal products using genetic engineering;

5. Drugs and pharmaceuticals for all tropical diseases;

6. Tertiary oil recovery from petroleum wells.

The above presents a disarmingly simple list which obscures a vast, complex and formidable hidden agenda.

The international working group presented an equally daunting list, its suggested priorities being:

A. Biological conversion of agricultural and industrial wastes and by-products:

   The conference listed over 30 such by-products but since these included such general descriptions as straw, oilseed cakes, fruit peelings, cannery effluent, slaughterhouse waste, lumber and paper mill waste, and oil refinery hydrocarbon waste, a more specific list would likely be longer by several orders of magnitude.

....4

In pursuit of the conversion of wastes and by-products the working group recommended the following:

(i) Systematic identification and classification of all wastes and by-products;

(ii) Analysis of constituents;

(iii) Identification of the most suitable microorganisms and fermentation processes to achieve economic conversion.

Given the immense natural variation and the rapid changes in chemical composition which biological materials undergo post-harvest and post-mortem in the tropics, together with the thousands of identified and as yet unidentified bacteria, moulds and yeasts that might be examined, this recommendation alone if taken to its logical conclusion could occupy several generations of the world's microbiologists and chemists.

B. The second priority was given to research to gain greater scientific understanding and control of traditional and novel food fermentations.

This clearly deserves serious consideration since one would be dealing with foods that are already accepted, that have been consumed over many centuries and therefore present less potential obstacles to commercial marketing and concerns for human safety. Indeed, the products of panary, alcoholic and lactic fermentations have been consumed for many thousands of years. In spite of this immense history of human experience and the very sizeable research investment over the last 100 years into the technologies of breadmaking, alcoholic beverages and cheese making, these industries are still guided as much by the empiricism of the educated thumb and experienced taste apparatus, as by sound scientific knowledge.

C. The next recommended priority was for embryo, tissue and cell culture research to produce secondary metabolites of commercial value. The international working group listed 54 classes ranging alphabetically from alkaloids to vitamins.

Once again, when each of these general classes is separated into individual substances, the list increases many fold. Little mention was made of the extensive manufacturing and marketing experience, resources and facilities needed to convert laboratory research results into viable industrial technologies.

Furthermore, unlike those primary proteins which are the immediate products of a single gene, are not the antibiotics and other secondary metabolites polygenically controlled? While

recognizing recent progress made by the fusion of cells from different Streptomyces species, most of the increases in antibiotic yields have resulted from conventional selection among random mutants combined with improved fermentor design and operation.

D. The fourth priority was given to the microbiological generation of industrial chemicals. Specifically mentioned were alcohols, aldehydes, ketones, glucose and fructose from waste cellulose and lignocellulose. There is logic in such a recommendation in that the three essential components of woody plants: cellulose, xylan (a hemicellulose), and lignin, are nature's three most abundant polymers. The international working group specifically recommended that cellulases from Trichoderma, Xanthomonas and Cellulomonas spp be immobilized to permit continuous conversion of cellulose and hemicellulose to fermentable saccarides.

As is well known, the lignocellulosic complex consists of microfibrillar bundles of crystalline cellulose which provides the skeleton of the fibre surrounded by a matrix of cross-linked xylan and lignin which holds the structure together. It is the lignin/xylan compound which prevents penetration by acids, micro-organisms or enzymes.

The first problem is to separate the crystalline cellulose from the amorphous hemicellulose and the lignin. Significant attention has been given to wood rot funghi and other lignocellulytic organisms but to my knowledge, no microbiological fermentation process starting with lignocellulose as it comes from the woody plant has been successfully elaborated to any commercial scale. In fact, some of the microorganisms described appear to take the cellulose all the way to carbon dioxide which is not particularly useful either as feed or fuel.

A promising means of separation which has been experimentally applied to various species of wood, straw stalks and bagasse relies upon explosive decompression to separate the cellulose from the hemicellulose and lignin. Steam at high pressure is injected into the wood chips or chopped straw. As the temperature is raised to about 234^{o}C, the constituents undergo morphological change: first the lignin, then the hemicellulose and finally the cellulose soften and the chemical cross links are so weakened that when the pressure is suddenly released the liquified lignin and hemicellulose are sufficiently disassociated from the cellulose fibres that the three can be separated, the lignin in ethanol or methanol, the xylan by mild sodium hydroxide.

It is claimed that if the process is accurately controlled, the three fractions emerge relatively pure and chemically reactive. The lignin is thermoplastic and can be chemically

....6

converted to a variety of products or used without further degradation; the two carbohydrate fractions must be separated and hydrolized by enzymes, microorganisms or mineral acids.

While this explosive decompression technology has been known for some time, it does not appear to have been widely exploited commercially and there is probably still much to be learned about the production economics.

Furthermore, the proposed conversion of cellulose by immobilized cellulase will also call for a significant research program. As mentioned in my earlier paper, in North America much publicity has been given to the conversion of dextrose to the much sweeter fructose by immobilized glucose isomerase. Fructose is now widely preferred over sucrose in soft drinks and many confectionery products. It should be mentioned however that in spite of the attractiveness of fructose to the soft drink and confectionery industries it has taken nearly 10 years to fully establish the industrial technology and to increase production from 0.3 to 3.0 million tonnes per year in the United States. Research is still in progress exploring bacterial rather than fungal sources of isomerase and in improving the carriers upon which the enzymes are immobilized. The various techniques of immobilization include: micro-encapsulation, gel entrapment, covalent bonding to various porous and solid surface polymers, in packed columns, fluidized and trickle beds. Other techniques are still coming.

Consequently, the commercially acceptable conversion of lignocellulose to useful industrial chemicals will necessitate a sizeable investment in applied research and process development, together with an equally comprehensive investigation of the production economics and marketing potential, aspects which tend to be overlooked in much of the biotechnological literature.

E. The working group's fifth priority envisages an impressive range of pharmaceuticals to be generated and eventually manufactured by genetically manipulated microorganisms. In addition to such familiar biochemicals as human insulin and the various interferons, the working group proposed research on hormones for tissue generation, pain and appetite suppressants and ovulation stimulants together with a long list of enzymes and vaccines for the treatment and prevention of a great many human and animal diseases.

One commentator on the working group's recommendations suggested that greater attention be given to vaccines for animals than for humans since the former offer greater potential profit. It was argued that if the vaccines are successful, human beings require relatively few and infrequent doses to acquire immunization. On the other hand, farm animals are slaughtered and

therefore every new animal needs individual immunization. It was also mentioned that the safety requirements for animal vaccines are much less exacting and therefore the cost of bringing them to market is lower than for human vaccines.

THE DRUG DILEMMA

A particular word about pharmaceuticals may be in order. As populations get older and richer, their concern with health and fighting off disease becomes increasingly evident. In spite of George Bernard Shaw's dictum, most of us would probably like to live forever.

In 1980, the estimated value of pharmaceuticals throughout the world was about $75 billion and one agency has forecast an increase to more than $250 billion by the end of the century, of which the LDCs' demand will be about one-third. The U.S. enjoys about one-tenth of the world market ($7.5 billion) of which close to 20% are drugs derived wholly or partially from microorganisms. Antibiotics are the largest class of microbiologically derived drugs, representing roughly 10% of the total world pharmaceutical market.

Over 25 years, the fermentor yields of penicillin have increased from a few milligrams to over 20 grams per litre. The improvements result in part from genetic selection among random mutants combined with significant improvements in fermentor design and operation. It is probable, in the short term, that improvements in antibiotic production will result more from established microbiological methods than from genetic engineering. Unlike those primary proteins which are the immediate products of a single gene, antibiotics are secondary metabolites and thus are the ultimate products of actions of anywhere up to 30 genes. However, the progress made in generating new and modified antibiotics through protoplast fusion of different species of Streptomyces has already been mentioned.

Though the research interest and investment is considerable, relatively few drugs of any kind, produced by the genetic engineering of microorganisms, have yet reached the commercial market on any scale. Developing countries clearly need to develop greater self reliance in the production and distribution of essential drugs. Nevertheless, the constraints for most of them are very great indeed.

The International Organization of Consumers Unions has repeatedly drawn attention to the selling of drugs in developing countries that are restricted or banned in the industriallized countries in which they originate. A recent report illustrates how anabolic steroids and other dangerous drugs can be bought without medical prescription in many developing countries. The report states:

....8

> "Many developing countries have few or poor regulations covering what information must be provided about drugs offered for sale, few quality control checks, health systems too burdened to identify which drugs are really needed, and medical authorities with such limited access to information that they rely heavily on product advertisements. Worse, prescription drugs can be bought over the counter in many parts of the third world."

Industrialized countries such as Canada have established extremely rigorous testing protocols by which to establish the suitability of new drugs for use by humans. Canada's Department of Health and Welfare protocol starts by stating: "All drugs produce toxic effects...The ultimate objective is to evaluate the probability that the drug will not produce significant damage under specific conditions of use." The testing protocols include among a long list of extensive evaluations of primary and secondary pharmacological actions: Determination of acute and long term toxicity; carcinogenicity, and mutagenicity; possible effects upon reproduction and teratology; and potential genetic damage.

It is not surprising that the established pharmaceutical companies estimate that clinical trials of each new drug cost $20 million or more. The larger drug companies with established research and manufacturing facilities provide for 8 to 10 years and up to $100 million in investment to bring a new drug to the market. The largest pharmaceutical companies invest more than 12% of their sales income on research and employ large, highly trained sales forces to market their drugs.

The demonstrated possibilities of employing genetically manipulated microorganisms to produce insulin, growth and reproductive hormones normally extracted from the organs of dead animals, have stimulated the rapid rise of a new type of commercial technological enterprise. Several of these companies metamorphosed from university laboratories that had developed a high degree of competence in the production of bacteria instructed by genetic manipulation to make specific proteins to order.

Successful biotechnology companies such as Biogen, Cetus and Genentech have succeeded largely by collaborative arrangements in which larger established companies assume the responsibility for futher development and marketing of the biotechnologically derived drugs. Several of the biotechnological research enterprises are now seeking to expand their scope of operations into manufacturing and marketing. In addition to the larger profits realized from the manufacture and sale of drugs, the biotechnological research enterprises have come to recognize the difficulties in being remote from the market place. Success in the pharmaceutical industry

....9

requires more than exceptional research competence. It calls for skill and experience in expanding from a test tube or a small batch fermentor to a full-scale manufacturing technology. It needs a constant direct feedback from the production factory floor; from the market place; from the medical profession engaged in clinical trials; and from those who prescribe and distribute its products.

To metamorphose from a research facility to an integrated production and marketing enterprise requires a very large injection of risk capital in addition to a sizeable increase in competent experienced staff. It seems possible that changes in U.S. tax laws may enable the biotechnological research companies to acquire some of their risk capital from wealthy private individuals who can write off their investments as tax losses.

FROM THE LABORATORY TO THE MARKET PLACE

But what useful lessons does this experience offer to those developing countries who do not have access to the human, material, manufacturing, marketing experience and facilities needed? Many government owned laboratories find difficulty in developing products and technological processes that are adaptable and profitably exploitable by commercial industries whether the latter are privately or parastatally owned. Without an integrated marketing and market research facility, research laboratories cannot easily develop products and processes that are commercially viable or which can be exploited to serve a human need or a user demand.

Illustrative of the investment in time and facilities needed is the experience of a Canadian public company which, for about 60 years, has manufactured and sold insulin, together with a long and expanding list of vaccines and biologicals for prophylactic and therapeutic use.

About four years ago the gene for human insulin was transferred to and expressed itself in a bacterium. The final broth from this bacterial fermentation contains a pro-insulin precursor which, after isolation, undergoes a series of 10-15 chemical modifications before the human insulin analogue reaches the desired degree of potency and purity. It has taken more than four years from the time the insulin gene expressed itself in the bacterium to reach the present advanced laboratory scale of development. It will probably be another two to three years before full commercial production is attained. The work has been carried out by a staff of over 15 scientists and medical professionals, many with more than 15 years post-doctoral experience. The investment necessary has been close to $10 million. A sizeable further investment will be needed before scale-up to full production is accomplished.

....10

As the Director stated, the research is not the most difficult component. The greatest investment and risk lies in the scaling-up to production level; maintenance of fermentation efficiency; establishing quality control and integrating the whole process with the marketing and distribution infrastructure. Where no marketing infrastructure exists, it has to be created.

Given the progress made by the same Canadian organization in the isolation and injection of pancreatic cells into the spleenic vein (these cells then act as living pancreatic cells capable of releasing insulin in response to the host body's demand), the genetically engineered process of producing human insulin described above may become obsolete in about a decade.

FARMING VERSUS PHARMACEUTICALS

This audience, meeting in an international research centre devoted to agriculture, may feel that I have devoted a disproportionate amount of time to pharmaceutical research and said little about agriculture. My justification is that the high publicity profile enjoyed by biotechnology in general and the many benefits promised by its advocates will inevitably result in intensive competition internationally and nationally for the essential yet very limited resources that are available. If history is any guide, a much greater volume of research and development funds will be dedicated to the health than to the agricultural sectors. The major drug manufacturers invest more than 10% of their sales income on research. The chemical industries allocate between 1% and 3% and the food industries in Canada roughly 0.12% of their respective sales incomes on research. The annual 1983-84 budget of the Government of Canada's Department of Health and Welfare is $21.1 billion, that of the Department of Agriculture is $1.1 billion.

For the industrially developed countries the basic scientific tools of the biotechnology trade are generally widely known. But after a desirable new gene has been stiched into a generally amenable bacterium many production problems need to be overcome before a technologically sound fermentation process is ready for large scale production and commercial exploitation.

The topics to be addressed at this meeting of IARCs at IRRI do not suggest an urgent need to revisit Asilomar. Nor is there need for most of us to carry in our back pockets the relevant provisions of the U.S. Federal Register governing gene transfer among dangerous pathogens. Nevertheless, genetically engineered pathogens for the biological control of prevalent agricultural pests may not be so very improbable in the future. Certainly during the massive invasion of cereal plots by rats in the Sahelian countries a decade ago, a rodent equivalent of myxomatosis would have appeared very welcome.

....11

Recently IDRC engaged a consultant prior to convening a small working group to discuss opportunities for tissue culture research. A copy of the report will be sent to all participants at this IRRI/IARC meeting. The following are a few of the main observations:

Neither tissue culture nor any other of the ingenious techniques lumped under the heading "biotechnology" will foreseeably preempt the established skills of plant breeders, agronomists, pathologists, entomologists, or soil scientists.

Meristem culture could be adapted to a much greater range of tropical plant species. For species of a woody habit of growth, meristem culture remains largely unexplored. Wang and Hu have described a process for potatoes which progresses from the meristem tip via plantlets to more than 30,000 miniature tubers in a period of four months.

In relation to meristem culture the Canadian group recommended more work on genotypic variations, nutrient needs, incubation conditions and cryogenic preservation.

To further exploit callus culture it was recommended, especially for the gramineae and leguminosae, that more attention be given to embryoids, to a better comprehension of the genetic instability, chromosome loss, and declining capacity of calli to regenerate over time.

In the realm of protoplast culture, research is needed to understand why transformed cells and the products of heterokaryon fusion often fail to generate viable seed. Are embryonic and juvenile tissues in all instances the most valuable sources of totipotent protoplast?

Given the encouraging experience with Brassica species in Canada, pollen and anther culture offer a potentially effective route to homozygous lines. The problem of albinism is well recognized but the group wondered if "cultural ability" is a heritable trait and whether one might screen cultivars within a species for superior anther culture potential. The group expressed mixed feelings about the applicability of tissue culture to early screening for stress tolerance. The group was not optimistic about early selection for tolerance to drought given its polygenic complexity.

The complete report will be distributed later in the summer of 1984.

RESOURCES AND CONSTRAINTS

The highly favourable publicity given to biotechnology and the many theoretically possible products and processes it offers

....12

suggests to the developing countries an almost limitless abundance of opportunities for better health, more food, sufficient energy, and profitable industrial development and employment. One hopes sincerely that at least a few of these benefits will be realized by those in greatest need.

But much of the literature says little of the resources needed, the investments made, the risks attendant, and the very difficult choices among alternatives for the allocation of very meagre resources. Even the most beneficially endowed nations cannot pursue simultaneously all that biotechnology purports to offer.

Before starting any research and development program, the $64,000 question for all biotechnological companies is: Which market should they choose and which product is going to satisfy the greatest need and give the greatest return on investment?.

It is unnecessary to emphasize to this audience that management consists of choosing priorities among many alternatives, of allocating the physical, material, economic, human and other essential and available resources in pursuit of the priority objectives. For almost all of the developing countries the institutional, industrial, economic and human resources available to them are so meagre that it is not particularly helpful for international agencies or international working groups to offer them a totally indigestible smorgasbord menu of biotechnological abundance.

For most developing countries it is not a question of how many different pharmaceuticals and microbiological conversions can be examined in the laboratory but in what manner can their under-privileged populations hope to gain any predictable benefit from biotechnological research and development. Should they give biotechnological priority to agriculture, health or industrial chemicals? Should they first seek licensing or some other form of cooperative arrangement with established institutions or companies in other countries?

THE LIMITING HUMAN RESOURCE

Though all of their essential resources are strictly limited, the most seriously limiting for most developing countries is a suitably qualified and experienced cadre of research scientists and development technologists. How many of the low income countries with more than 20,000 of population per qualified physician and over 13,000 per qualified nurse, can seriously consider diverting their few medically qualified people from their urgent day to day tasks to biotechnological research and development?

....13

Tables 1-19 show the proportions of new graduates in the various disciplinary sectors in the principal geographic regions of the world. These are total graduates, probably including many at a technical college diploma level among which the proportion of those with research degrees will be relatively small.

Though total numbers are increasing, in most regions of the developing world the proportions in agriculture and natural sciences appear to be declining. Among 50 selected developing countries natural sciences fell from 21.6% to 16.8% of the total graduates between 1970 and 1980. Similarly, the proportion of agriculture graduates declined from 3.7% to 2.9%.

In 1970 Canadian universities graduated roughly 972 people at the PhD level in the natural and physical sciences. By 1980 doctoral graduates in these disciplines had fallen to 872, while arts graduates at the PhD level had more than doubled (Table 19). During the next five years more senior agricultural scientists will retire from Canadian universities and the government service than will be replaced by new PhDs. Though Canada needs roughly 150 new PhDs annually, the eight faculties of agriculture are at present graduating only 70. These trends, evident in other industrialized nations, may well serve to encourage an accelerated brain drain from developing countries.

PRIORITIES FOR THE IARCs

Table 20 shows the public sector investment in agricultural research in various regions of the world. It should be remembered that whereas in most developing countries agricultural research is financed almost entirely by government and development agencies, in the industrialized countries there is a sizeable investment from the private sector.

It is not only the developing countries who will be called upon to make difficult choices from the biotechnological smorgasbord. The IARCs, individually and collectively, are faced with a very thought provoking set of issues. The contribution from the CGIAR members to the IARCs core and special programs have not increased very greatly in recent years. The general decline in donor support of development assistance (apart from the international arms bazaar), together with the relatively low rate of investment in agricultural research in all regions (Table 20), present difficulties for both developing countries and the IARCs. It requires that the IARCs reexamine their priorities and answer some critical questions such as:

1. **Who precisely are the clients for the products of the IARCs' research activities?**

....14

The general answer is: "National agricultural research systems". But what exactly is the scope and limit of each system and how deeply and broadly can an IARC penetrate or react with each national system?

2. **What products of biotechnological research related to agriculture can the various and widely different national systems accept, adapt and use?**

3. **Will the IARCs develop and demonstrate new and improved techniques of embryo, somatic tissue, pollen and anther culture and if so, to what states of refinement?**

4. **Will the IARCs pursue the products of these techniques to a stage of improved germplasm that farmers can plant, together with demonstrations of appropriate accompanying agronomic practices?**

5. **Will the IARCs seek to offer training, technical advice and assistance in biotechnology appropriate to the very many levels of scientific skill and resources among the LDCs?**

6. **Will the IARCs concentrate first upon the more scientifically and agriculturally advanced of the LDCs - those best able to adapt and profit from new research and advanced technologies?**

7. **Who will undertake the basic cellular biochemistry and other molecular biology research essential to the greater comprehension and solution of many existing and evident biotechnological problems?**

8. **Will basic research be subcontracted to universities and/or private research institutes, or will the IARCs do it themselves? In either case, will the IARCs be seeking a significant increase in their budgets or will they be reducing investment in their more traditional breeding and agronomic research programs?**

It is worthy of note that a relatively new North American research company is assembling an international team of close to 20 highly qualified biological scientists to pursue advanced techniques for plant breeding devoted almost entirely to two crops. Their horizons for delivery of significantly improved genotypes is a decade into the future.

In the past a vigorous discussion has taken place concerning the IARCs' and LDCs' relations with the International Union for the Protection of New Varieties of Plants (UPOV) and the means by which to protect the IARCs' new crop varieties from restrictive explotation by commercial seed companies. This is not the time or place to attempt a comprehensive review of proprietary ownership of

....15

novel products or processes of biotechnology. Suffice it to say the whole subject is confused. Some authorities define a patentable variety as one that is new, sexually reproduced, distinct, uniform and stable. The U.S. now permits patenting of asexually generated plants. Several countries permit the patenting of genetically manipulated microorganisms. In the broader context and among different countries the options may include patenting of the product, the process of production, or the end use.

I am told that one of the leading American biotechnology research companies (GENETECH) is reported to have applied for over 1400 patents. Only 80, most for methods of production, have been granted.

IDRC is supporting two relevant projects with the International Centre for Law in Development: (a) Plant breeding and plant breeders' rights in the Third World; and (b) Law and biotechnology. FAO is proposing a major new initiative in the conservation and free availability of essential genetic resources, the scope of which and its potential impact upon the CGIAR family in general and the IBPGR in particular have yet to be determined.

CONCLUSION

It seems readily evident that the potential opportunities and the expectations aroused in human hearts and minds in the short term greatly exceed the resources available to many developing countries for the biotechnological research and development that seems so inviting. The many fascinating opportunities for biotechnological development and the difficulties by which they are constrained will not be realized or overcome purely by laboratory research. The subject is highly complex and deserves a broader spectrum of understanding than it has so far received.

It is hoped that this meeting will stimulate the TAC and the Centre Directors immediately to begin a coordinated and collective plan to determine both short and long term priorities for the IARCs. The plan will need to envisage very precisely what products of biotechnological research within or sponsored by the CGIAR/IARC family will serve the greatest need, and more specifically, whose need is to be served. The priorities, I would suggest, should be directed by careful consideration of what essential needs can be best satisfied and opportunities better realized by biotechnology than by the longer established research methodologies.

Collectively, the TAC and Centre Directors need to determine which essential research can best be undertaken in-house and which requires the direct collaboration of other scientists elsewhere. They will need to offer extensive advice to developing countries about the resources needed and the probable time required to realize any desired objective through a biotechnological process.

....16

Many developing nations will need guidance on the resources they need in order to adapt, modify and apply whatever products of biotechnological research the IARCs propose to offer to them.

More important, the TAC, the IARCs and the CGIAR need to develop a logical, carefully constructed plant for the next decade: a plan which prescribes what the IARCs collectively and individually must pursue, what cooperation with research agencies outside the CGIAR is essential, and the manner in which this cooperation will be developed, coordinated and financed. No mean task, but one that is vital if the promised benefits are to be fully realized.

As a final thought, may I offer a dictum from Sir Francis Bacon: "If we start with certainties we shall end with doubts; but if we begin with doubts and work patiently we shall end with certainties".

TABLE 1.

COUNTRIES INCLUDED IN SURVEY OF GRADUATES

(All data used was 1969/70 and 1979/80 unless otherwise indicated)

SOUTHEAST ASIA

HONG KONG
MALAYSIA
SINGAPORE (1981)
SOUTH KOREA (1981)

SOUTH ASIA

BANGLADESH
INDIA (1968)(1978)
NEPAL
SRI LANKA

EAST AFRICA

BURUNDI
ETHIOPIA
KENYA
MALAWI
MAURITIUS (1971)
MOZAMBIQUE
TANZANIA
UGANDA (1971)
ZAMBIA

WEST AFRICA

BENIN
CONGO
GABON (1973)
GHANA
MALI
NIGERIA (1973)(1981)
SENEGAL
TOGO
UPPER VOLTA (1973)

MIDDLE EAST

ALGERIA
EGYPT
IRAQ
JORDAN
KUWAIT
MOROCCO
SAUDI ARABIA
TUNISIA
TURKEY

LATIN AMERICA

BARBADOS
CHILE
COLOMBIA (1981)
CUBA
ECUADOR (1981)
GUATEMALA
GUYANA
HONDURAS
JAMAICA (1972)
MEXICO
NICARAGUA
PANAMA
PERU (1971)
URUGUAY (1981)
VENEZUELA

CANADA

TABLE 2.

GRADUATES/YEAR BY FIELD OF STUDY - SELECTED DEVELOPING COUNTRIES*

	1969/70		1979/80	
	NUMBER	PERCENT	NUMBER	PERCENT
ARTS, SOCIAL SCIENCES, HUMANITIES, LAW, BUSINESS	414,390	66.9	1,233,581	72.9
NATURAL SCIENCES, HEALTH SCIENCES, MATHEMATICS	133,955	21.6	283,865	16.8
ENGINEERING	48,310	7.8	125,015	7.4
AGRICULTURE, FORESTRY, FISHERIES	22,778	3.7	49,869	2.9

*See Table 1.

Source: UNESCO Statistical Yearbook (1975, 1983)

TABLE 3.

GRADUATES/YEAR BY FIELD OF STUDY BY REGION

SOUTHEAST ASIA REGION*

	1969/70		1979/80	
	NUMBER	PERCENT	NUMBER	PERCENT
ARTS, SOCIAL SCIENCES, HUMANITIES, LAW, BUSINESS	31,119	57.0	82,356	55.3
NATURAL SCIENCES, HEALTH SCIENCES, MATHEMATICS	8,670	15.9	15,737	10.6
ENGINEERING	10,447	19.2	42,552	28.6
AGRICULTURE, FORESTRY, FISHERIES	4,332	7.9	8,272	5.5

*See Table 1.

Source: UNESCO Statistical Yearbook (1975, 1983)

TABLE 4.

GRADUATES/YEAR BY FIELD OF STUDY BY REGION

SOUTH ASIA REGION*

	1969/70		1979/80	
	NUMBER	PERCENT	NUMBER	PERCENT
ARTS, SOCIAL SCIENCES, HUMANITIES, LAW, BUSINESS	311,896	70.9	893,861	79.1
NATURAL SCIENCES, HEALTH SCIENCES, MATHEMATICS	100,260	22.8	193,445	17.1
ENGINEERING	18,202	4.1	28,991	2.6
AGRICULTURE, FORESTRY, FISHERIES	9,662	2.2	13,664	1.2

*See Table 1.

Source: UNESCO Statistical Yearbook (1975, 1983)

TABLE 5.

GRADUATES/YEAR BY FIELD OF STUDY BY REGION

EAST AFRICA REGION*

	1969/70		1979/80	
	NUMBER	PERCENT	NUMBER	PERCENT
ARTS, SOCIAL SCIENCES, HUMANITIES, LAW, BUSINESS	2,618	66.7	6,701	62.0
NATURAL SCIENCES, HEALTH SCIENCES, MATHEMATICS	636	16.2	1,736	16.0
ENGINEERING	336	8.6	668	6.2
AGRICULTURE, FORESTRY, FISHERIES	336	8.6	1,713	15.8

*See Table 1.

Source: UNESCO Statistical Yearbook (1975, 1983)

TABLE 6.

GRADUATES/YEAR BY FIELD OF STUDY BY REGION

WEST AFRICA REGION*

	1969/70		1979/80	
	NUMBER	PERCENT	NUMBER	PERCENT
ARTS, SOCIAL SCIENCES, HUMANITIES, LAW, BUSINESS	4,963	69.7	19,819	74.0
NATURAL SCIENCES, HEALTH SCIENCES, MATHEMATICS	1,288	18.1	4,400	16.4
ENGINEERING	426	6.0	1,256	4.7
AGRICULTURE, FORESTRY, FISHERIES	439	6.2	1,321	4.9

*See Table 1.

Source: UNESCO Statistical Yearbook (1975, 1983)

TABLE 7.

GRADUATES/YEAR BY FIELD OF STUDY BY REGION

MIDDLE EAST REGION*

	1969/70		1979/80	
	NUMBER	PERCENT	NUMBER	PERCENT
ARTS, SOCIAL SCIENCES, HUMANITIES, LAW, BUSINESS	41,404	59.7	109,536	64.9
NATURAL SCIENCES, HEALTH SCIENCES, MATHEMATICS	12,523	18.1	27,602	16.3
ENGINEERING	10,272	14.8	19,775	11.7
AGRICULTURE, FORESTRY, FISHERIES	5,139	7.4	12,007	7.1

*See Table 1.

Source: UNESCO Statistical Yearbook (1975, 1983)

TABLE 8.

GRADUATES/YEAR BY FIELD OF STUDY BY REGION

LATIN AMERICA REGION*

	1969/70		1979/80	
	NUMBER	PERCENT	NUMBER	PERCENT
ARTS, SOCIAL SCIENCES, HUMANITIES, LAW, BUSINESS	22,390	50.3	121,250	58.6
NATURAL SCIENCES, HEALTH SCIENCES, MATHEMATICS	10,578	23.8	40,945	19.8
ENGINEERING	8,627	19.4	31,773	15.4
AGRICULTURE, FORESTRY, FISHERIES	2,870	6.5	12,892	6.2

*See Table 1.

Source: UNESCO Statistical Yearbook (1975, 1983)

TABLE 9.

GRADUATES/YEAR BY FIELD OF STUDY

CANADA

	1969/70		1979/80	
	NUMBER	PERCENT	NUMBER	PERCENT
ARTS, SOCIAL SCIENCES, HUMANITIES, LAW, BUSINESS	52,298	74.4	73,878	73.4
NATURAL SCIENCES, HEALTH SCIENCES, MATHEMATICS	8,809	12.5	11,870	11.8
ENGINEERING	5,212	7.4	8,547	8.5
AGRICULTURE, FORESTRY, FISHERIES *	4,000	5.7	6,285	6.3

*Includes Biological Sciences

Source: STATSCAN Computer Printout, March 1984

TABLE 10.

UNIVERSITY GRADUATES PER MILLION POPULATION

SELECTED DEVELOPING COUNTRIES*

	1969/70	1979/80
ARTS, SOCIAL SCIENCES, HUMANITIES, LAW, BUSINESS	370	860
NATURAL SCIENCES, HEALTH SCIENCES, MATHEMATICS	120	198
ENGINEERING	43	87
AGRICULTURE, FORESTRY, FISHERIES	20	35
TOTAL	553	1,180

*See Table 1

Source: UNESCO Statistical Yearbook (1975, 1983)
World Population Trends 1950-2000, UN Dept. of International Economic and Social Affairs (1979)

TABLE 11.

UNIVERSITY GRADUATES PER MILLION POPULATION

SOUTHEAST ASIA REGION*

	1969/70	1979/80
ARTS, SOCIAL SCIENCES, HUMANITIES, LAW, BUSINESS	650	1,400
NATURAL SCIENCES, HEALTH SCIENCES, MATHEMATICS	181	267
ENGINEERING	218	723
AGRICULTURE, FORESTRY, FISHERIES	91	141
TOTAL	1,140	2,531

*See Table 1

Source: UNESCO Statistical Yearbook (1975, 1983)
World Population Trends 1950-2000, UN Dept. of International Economic and Social Affairs (1979)

TABLE 12.

UNIVERSITY GRADUATES PER MILLION POPULATION

SOUTH ASIA REGION*

	1969/70	1979/80
ARTS, SOCIAL SCIENCES, HUMANITIES, LAW, BUSINESS	489	1,101
NATURAL SCIENCES, HEALTH SCIENCES, MATHEMATICS	156	238
ENGINEERING	28	36
AGRICULTURE, FORESTRY, FISHERIES	15	17
TOTAL	688	1,392

*See Table 1

Source: UNESCO Statistical Yearbook (1975, 1983)
World Population Trends 1950-2000, UN Dept. of International Economic and Social Affairs (1979)

TABLE 13.

UNIVERSITY GRADUATES PER MILLION POPULATION

EAST AFRICA REGION*

	1969/70	1979/80
ARTS, SOCIAL SCIENCES, HUMANITIES, LAW, BUSINESS	32	62
NATURAL SCIENCES, HEALTH SCIENCES, MATHEMATICS	8	16
ENGINEERING	4	6
AGRICULTURE, FORESTRY, FISHERIES	4	16
TOTAL	48	100

*See Table 1

Source: UNESCO Statistical Yearbook (1975, 1983)
World Population Trends 1950-2000, UN Dept. of International Economic and Social Affairs (1979)

TABLE 14.

UNIVERSITY GRADUATES PER MILLION POPULATION

WEST AFRICA REGION*

	1969/70	1979/80
ARTS, SOCIAL SCIENCES, HUMANITIES, LAW, BUSINESS	56	170
NATURAL SCIENCES, HEALTH SCIENCES, MATHEMATICS	14	38
ENGINEERING	5	11
AGRICULTURE, FORESTRY, FISHERIES	5	11
TOTAL	80	230

*See Table 1

Source: UNESCO Statistical Yearbook (1975, 1983)
World Population Trends 1950-2000, UN Dept. of International Economic and Social Affairs (1979)

TABLE 15.

UNIVERSITY GRADUATES PER MILLION POPULATION

MIDDLE EAST REGION*

	1969/70	1979/80
ARTS, SOCIAL SCIENCES, HUMANITIES, LAW, BUSINESS	343	691
NATURAL SCIENCES, HEALTH SCIENCES, MATHEMATICS	104	174
ENGINEERING	85	125
AGRICULTURE, FORESTRY, FISHERIES	43	76
TOTAL	575	1,066

*See Table 1

Source: UNESCO Statistical Yearbook (1975, 1983)
World Population Trends 1950-2000, UN Dept. of International Economic and Social Affairs (1979)

TABLE 16.

UNIVERSITY GRADUATES PER MILLION POPULATION

LATIN AMERICA REGION*

	1969/70	1979/80
ARTS, SOCIAL SCIENCES, HUMANITIES, LAW, BUSINESS	164	672
NATURAL SCIENCES, HEALTH SCIENCES, MATHEMATICS	77	227
ENGINEERING	63	176
AGRICULTURE, FORESTRY, FISHERIES	21	71
TOTAL	325	1,146

*See Table 1

Source: UNESCO Statistical Yearbook (1975, 1983)
World Population Trends 1950-2000, UN Dept. of International Economic and Social Affairs (1979)

TABLE 17.

UNIVERSITY GRADUATES PER MILLION POPULATION

CANADA

	1969/70	1979/80
ARTS, SOCIAL SCIENCES, HUMANITIES, LAW, BUSINESS	2,456	3,069
NATURAL SCIENCES, HEALTH SCIENCES, MATHEMATICS	414	493
ENGINEERING	245	355
AGRICULTURE, FORESTRY, FISHERIES *	188	261
TOTAL	3,303	4,178

Source: STATSCAN COMPUTER PRINTOUT - March 1984
World Population Trends 1950-2000, UN Dept. of International Economic and Social Affairs (1979)

*Includes Biological Sciences

TABLE 18.

UNIVERSITY GRADUATES PER MILLION POPULATION

	TOTAL		AGRICULTURE FORESTRY & FISHERIES		NATURAL SCIENCES HEALTH SCIENCES MATHEMATICS	
	1970	1980	1970	1980	1970	1980
ASIA						
Bangladesh	972	306	4	18	164	67
India	668	1,579	17	17	160	269
Singapore	1,805	2,249	2	-	413	276
Sri Lanka	307	245	3	7	50	53
AFRICA & MIDDLE EAST						
Egypt	927	1,916	118	204	164	314
Ethiopia	41	85	2	33	7	9
Kenya	55	162	4	16	7	39
Mozambique	14	11	2	1	3	4
Nigeria	80	223	5	11	16	40
LATIN AMERICA & CARIBBEAN						
Colombia	257	1,062	31	32	60	159
Cuba	350	2,595	22	174	122	214
Peru	429	1,043	31	61	68	151
Jamaica	1,103	1,946	36	30	169	445
CANADA	3,302	4,178	188	261	414	493

Source: STATSCAN COMPUTER PRINTOUT - March 1984
World Population Trends 1950-2000, UN Dept. of International Economic and Social Affairs (1979)
UNESCO Statistical Yearbook (1975, 1983)

TABLE 19.

GRADUATES BY LEVEL AND TYPE OF DEGREE - CANADA

	1970		1980	
	No.	%	No.	%
BACHELORS				
Arts	46,132	76.2	63,577	73.6
Science	14,391	23.8	22,833	26.4
MASTERS				
Arts	5,766	68.4	9,435	75.9
Science	2,658	31.6	2,997	24.1
DOCTORATE				
Arts	400	29.0	866	49.8
Science	972	71.0	872	50.2

Source: STATSCAN Computer Printout, March 1984

TABLE 20.

PUBLIC SECTOR INVESTMENTS IN AGRICULTURAL RESEARCH (1980)

	AGRICULTURAL PRODUCT VALUE %
LOW INCOME DEVELOPING	0.5
MIDDLE INCOME DEVELOPING	0.8
SEMI-INDUSTRIALIZED	0.7
INDUSTRIALIZED	1.5
CENTRAL PLANNED (Excluding China)	0.7