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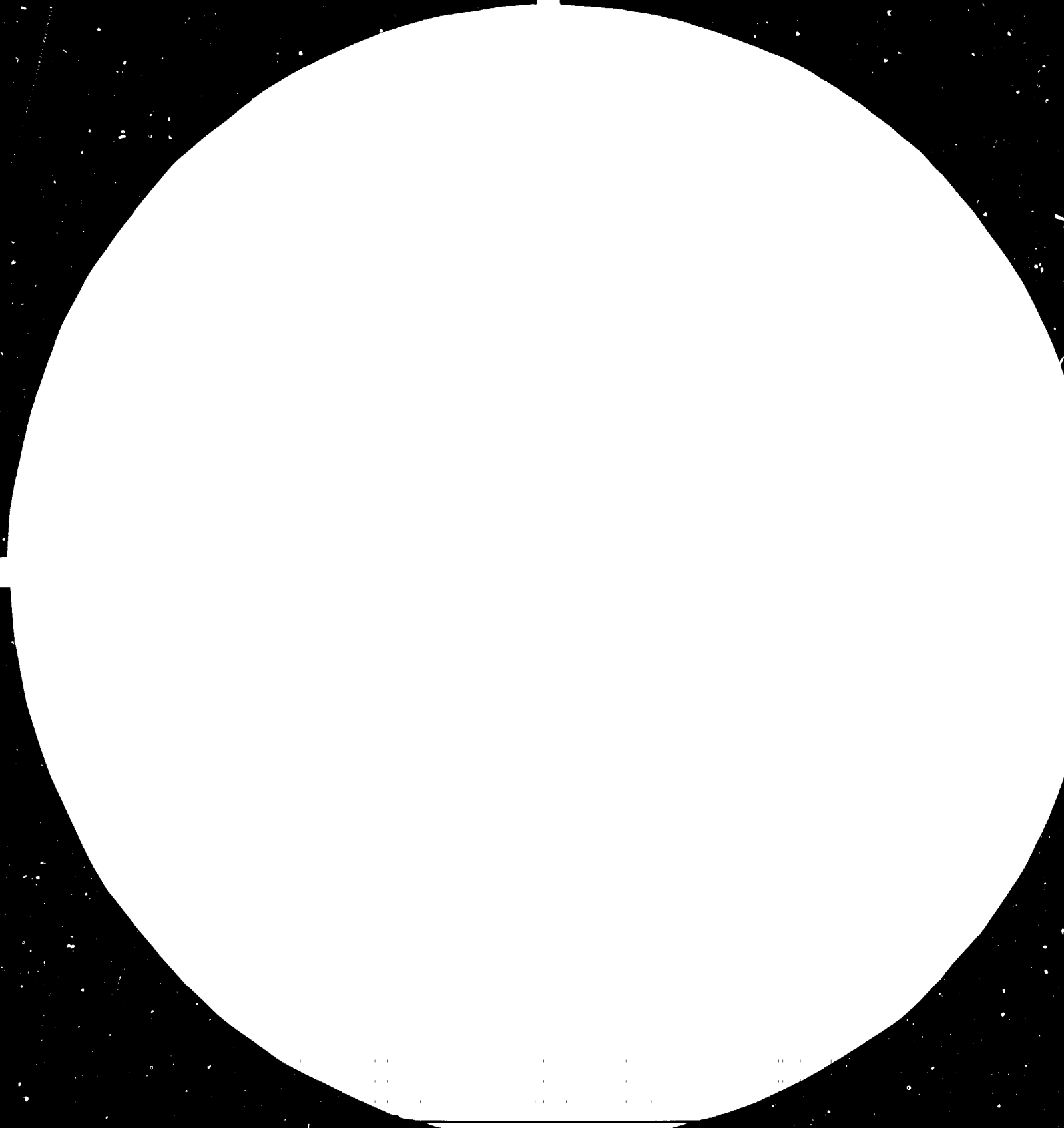

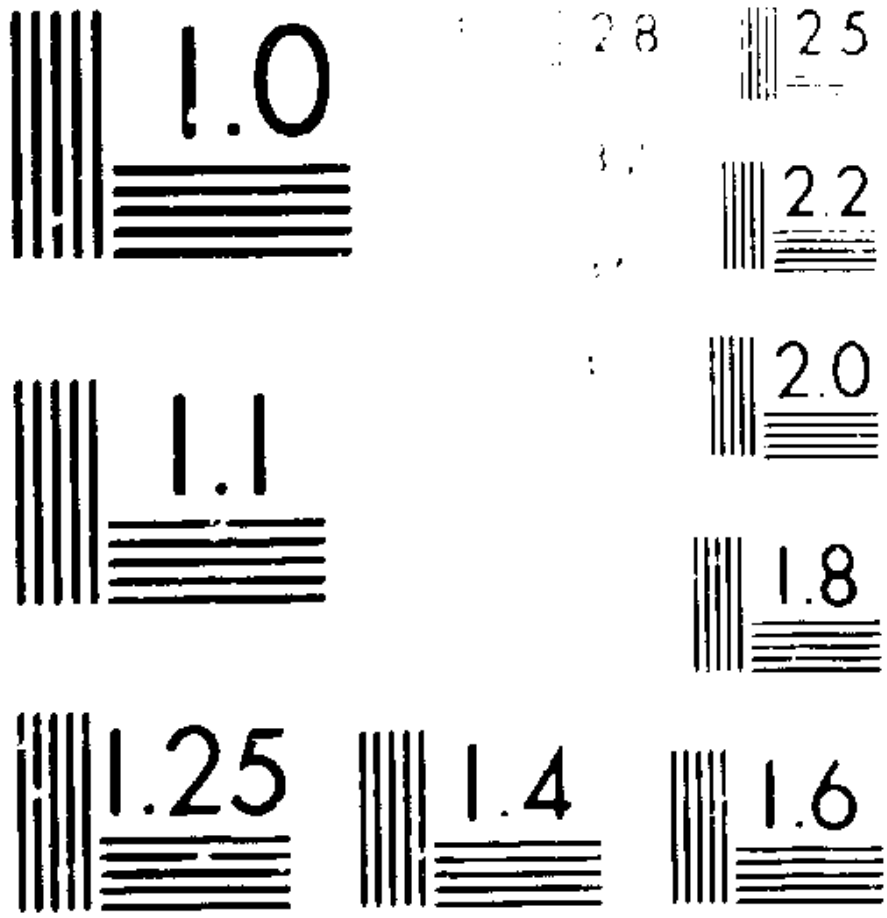
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PRACTICAL CONSIDERATIONS OF THE OPERATION AND WORK PROGRAMME OF THE INTERNATIONAL CENTRE FOR GENETIC ENGINEERING AND BIOTECHNOLOGY * ICGEB.

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INTRODUCTION

1. The concept of the International Centre for Genetic Engineering and Biotechnology (ICGEB) has undergone considerable evolution since the idea was first put forth more than two years ago. Preliminary documents were presented at the High-Level meeting held in Belgrade, 13-17 December, 1982, which discussed the possible organization, budget and work programme of the ICGEB. As the establishment of the Centre moves closer to reality, it now becomes important to address in more detail the organization and operation of the ICGEB, how it would actually function to achieve its goal of promoting biotechnology in developing nations, and how it would relate to other international, regional, national and other public and private institutions also engaged in research, industrial development and training relevant to the activities of the Centre. In addition, possible components of the work programme need to be carefully evaluated.

2. To be sure, biotechnology and genetic engineering are already firmly established in the world of 1983, building heavily on the spectacular advances in molecular and cell biology that have taken place over the past decade. The amount of new knowledge having practical implications that is being gained every year, particularly through independent basic research in universities and research institutions, ensures that biotechnology - the practical applications of biology - will continue to advance rapidly.

3. An industry has already arisen to offer biotechnological solutions to practical problems in medicine and pharmaceuticals, chemistry, agriculture and ecology. Existing private and state owned industrial organizations are turning more and more of their attention to biotechnology. More than two hundred smaller independent biotechnology companies have been formed, some of which concentrate in rather narrow areas of application. A number of national governments, including those of both developed and developing countries, have formulated specific policies and have taken steps to foster the development of domestic biotechnology industries. Many universities and research institutions are also engaged in programmes to develop particular areas of biotechnology,

both from public and private resources. Some have begun training programmes for bioengineers to ensure a supply of skilled manpower needed to sustain this growing industry.

4. In spite of these efforts, however, there is still considerable unevenness in the extent to which biotechnology is being applied to real problems around the world. This discrepancy is no more than a reflection of the existing differences in the distribution of wealth, natural resources and economic development among the nations and regions of the world and is not unique to biotechnology. As would be expected, the most advanced research and development, and nearly all of the existing biotechnology industry, is confined to the most economically developed and technologically advanced countries.

5. There is necessarily a skewing of the programmes of the privately owned corporations toward products which are believed to bring the greatest financial returns to their investors. While some fields, such as the development of human therapeutic agents, are receiving much attention from the commercial industry, many promising uses of biotechnology are not being developed adequately because the economics are not considered favourable. These include many of the needs of developing countries, such as the control of tropical diseases, improved food production and energy. For state owned industry, the object is still to focus on the production of goods for home use, or at least to add to the national treasury. In economically developed countries, then, the objects of industrial activity are rather similar, regardless of the economic structure which supports that industry; these will generally be different than the industrial goals of developing countries. In fact, it is in large part because of the dichotomy between the areas of activity of existing industry and human needs in many parts of the world that a raison d'être for the ICGEB exists.

6. The ICGEB represents a new type of structure, whose primary object is to foster biotechnology in developing countries. It is to be a free standing, intergovernmental, international organization, independent of the United Nations or any national government. Countries can become members in the Centre, contributing to its operation and

gaining the considerable benefits which membership bestows, including direct access to technology developed at the Centre, the training of their own technical people at the Centre, and assistance with the establishment of national research, development and industrial projects in these member countries. The Centre would provide advisory services to the countries with regard to the establishment of domestic biotechnology industries in appropriate areas of application.

7. Although the emphasis of the Centre's activities is to be on the problems of developing countries, the underlying technology is potentially applicable to a great breadth of problems, including those of interest to countries which are already industrially developed. It is expected, therefore, that many developed nations will also elect to become members in the ICGEB, to expand their access to high quality science and technology and to a wealth of information relevant to their own particular objectives. Their participation will, in turn, enhance the effectiveness of the ICGEB.

8. In order for the ICGEB to meet its objectives, a number of criteria must be satisfied:

(a) The ICGEB must be of a size and level of resources to be able to engage in an appropriate breadth of research and development activities, to be able to conduct extensive training programmes, and to provide a wide variety of information services.

(b) It must have an efficient organizational structure and adequate depth of support services appropriate to the size and programmes of the organization.

(c) Its relationship to existing international, regional and national research and development organizations, universities and other research and training institutions, and the existing biotechnology industry must be well defined with effective liaison established with these entities as appropriate.

(d) The work programme must be realistic, designed to achieve practical benefits in some areas in a relatively short period of time, emphasizing the areas of greatest human need.

(e) The work programme should not duplicate specific industrial activities in biotechnology already being conducted in other institutions.

9. This document examines the above requirements in somewhat more detail than those previously issued by UNIDO. Part I is concerned with the internal organization and function of the ICGEB, and its relationship to other institutions. Part II evaluates a number of possible elements of the Centre's research and development programme with respect to both the overall and specific objectives of the ICGEB.

I. ORGANIZATION AND OPERATION OF THE INTERNATIONAL CENTRE FOR GENETIC ENGINEERING AND BIOTECHNOLOGY (ICGEB)

10. In order that the intended practical benefits will result from the Centre's activities, it must have a well integrated internal structure, designed to function efficiently. The scientists and bioengineers who will comprise the professional staff must be free to pursue their research, development and production activities as well as to play the major role in the training of scientists and technologists. Thus there must be not only adequate technical support, but appropriate administrative and information services as well.

11. The effectiveness of the ICGEB will depend not only on its internal organization and function, but its relationship to other activities in biotechnology around the world. The Centre cannot operate in isolation from the other institutions at all levels which promote or have an interest in biotechnology as a practical solution to the real human and economic problems of the world. Appropriate liaison between the Centre and these organizations must be clearly defined. Part I examines the operation of the ICGEB in terms of its effectiveness in meeting the goals that have been set for it.

A. Internal Functions

12. An essential feature of the ICGEB is to be the co-operative interaction among the Centre's several components. These include administrative, training, research and development, information exchange functions, and support services for all of the divisions. It would be difficult to display the organization and function of the ICGEB in the way large organizations are usually described, that is, with rows of labelled boxes and lines connecting the appropriate layers of bureaucracy. If one attempted this exercise with the ICGEB, there would have to be lines connecting each box with virtually every other box. This "matrix" model does not imply a lack of order or direction, but rather a recognition that biotechnology is an enterprise encompassing a great many things: many branches of science, engineering and manufacturing. When one adds the training function and the requirement to foster a new technology in many parts of the globe, then the interaction functions become complex.

Administration

13. The primary responsibility for the organization, direction, and content of programmes of the ICGEB would rest with the Director. The Board of Governors, which would include representatives of member nations, would set overall policy, and a Council of Scientific Advisers would serve in an advisory role to the Director concerning the scientific aspects of the work programme. It may be advisable to expand the scope of this advisory council to include specialists in bioengineering and industrial production, as well as distinguished individuals from the fields of education, law and economics. This would reflect the purpose of the ICGEB to foster self-sustaining industries using biotechnology throughout the world, a goal which entails much more than excellence in science.

14. In addition to the Director's Office, the administration of the ICGEB must include a number of essential support services. Provision must be made to handle the financial and legal affairs of the Centre, the hiring and relocation of personnel, laboratory safety, security, building maintenance, the purchasing and servicing of equipment and supplies, and a variety of scientific and technical support services (including an animal facility, media preparation, and glassware cleaning). It is essential that these support services be sufficient to meet the needs of an organization with a minimum of fifty permanent scientists and technologists, as well as a substantial number of trainees. It is important that the professional staff of the ICGEB should not have to handle administrative details or engage in activities that do not make the best use of their time.

Science and Technology

15. Most of the personnel and trainees at the ICGEB would be directly involved in scientific and technological activities. The scientific and technical sections must include departments pursuing general methods in genetic engineering and biotechnology (e.g. an expression vector laboratory, a microbial screening laboratory), technical services (such as base sequence determination of gene segments, polynucleotide synthesis,

restriction enzyme isolation), a set of more focused targeted programmes [1/] which utilize these general methods, and perhaps some basic research at the frontiers of knowledge (e.g. molecular engineering). While it is not always practical in university laboratories to organize research in this way, usually because scientific departments tend to be small and diverse, it is far more efficient to separate the true research functions from the routine work that accompanies all research, if the size and focus of the institution permits. This is especially true in genetic engineering, which involves an enormous amount of analytical work and routine synthetic work. The ICGEB is planned to be large enough to separate these research support services from the conduct of the more creative programmes. In this way the senior, and most of the junior scientists and bioengineers, would not need to spend unnecessary time on routine technical work, which could instead be carried out by skilled technicians in efficient central laboratory facilities.

16. Since the scientists' time would also include training functions, both through formal courses and as individual research project mentors, the proposed structure of the Centre would allow time for this important role by freeing the scientists from routine technical or administrative work. Of course, an important part of the training would include a thorough grounding in such analytical methods as nucleotide sequence determination, and genetic engineering methods such as plasmid construction. The service laboratories would, therefore, provide the ideal training situations in which to provide the most efficient instruction in these techniques.

17. From a disciplinary point of view, it is also obvious that there would have to be considerable co-operation between the major scientific research departments, which could, for example, be organized along the disciplines of molecular biology, microbiology, immunology and infectious diseases, and plant genetics and cell biology, although these distinctions are, obviously, somewhat arbitrary. All of these areas share many of the tools and methods of genetic engineering and all would have need to use the scientific service laboratories. Nor is it anticipated that the process development and pilot plant activities would operate in isolation from

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1/ The work of the Centre thus includes activities in the general methodology which underlies genetic engineering and biotechnology (and which will form an important part of the ICGEB's training function), and projects in specific areas representing a breadth of technologies appropriate to the needs of developing nations. These focused elements of the work programme will be determined after the Centre's establishment by the Centre's Director and the Board of Governors. An evaluation of some possible programme components is provided in Part II of this document.

these research departments. Collaborative projects are essential. For example, the design of a process utilizing an immobilized enzyme modified in a way to prevent denaturation would entail possible theoretical calculations by a molecular engineering group of the modifications to be made, the isolation and modification of the gene for the redesigned enzyme, the cloning and expression of the enzyme, and the production of a large quantity of material. This would clearly involve many of the scientific and technical capabilities of the Centre.

Process Development and Manufacturing

18. Some of the earlier documents on the proposed ICGEB give the impression that there is too much emphasis on science, in fact high quality basic science, rather than on building useful technologies that would be directly applicable to the problems of developing nations. Indeed,some have expressed the fear that the Centre could become "just another graduate school", relatively out of touch with how research findings would be translated into practical technology, let alone the problems and needs of developing countries. This concern is a legitimate one, in that great care must be exercised in building a balanced institution, with all of its components meeting standards of excellence. Biotechnology is a science driven technology, and contains many elements scarcely separable in practice from basic research. The need for high quality science is, therefore, obvious. But science alone is not enough.

19. The bringing of the results of the research laboratories to practical fruition is not a trivial process. In fact, the experiences of existing enterprises which use biotechnology teach us that the research component of a programme is generally a relatively small part, in comparison with the development of an effective and cost-efficient process for the manufacture of a new substance, the testing for safety and efficacy that is required by law in most countries, especially for pharmaceuticals or other substances or human consumption, and the construction and operation of a manufacturing plant. These latter requirements are far more costly, and require much more time and manpower than the research needed to obtain the product in the first place. But they are necessary in order to bring the benefits of advanced biotechnology to the consumer.

20. It is not the purpose of the ICGEB to become primarily a manufacturing plant for selected needed materials. However, it must be able to demonstrate

the practical utility of research findings. For this reason, the Process Development Department and the Pilot Plant must comprise a significant fraction of the Research and Development activities of the Centre, and, accordingly, its budget. Also included must be the means for quality control of substances produced by large-scale processes, and testing of the products for efficacy and safety. The testing function is the key to several of the programmes suggested for the ICGEB. Vaccines, for example, require a rather long period of testing before one can be certain that they are both antigenically competent to confer immunity against the target disease, and that they are free of unwanted side reactions. Even though vaccines produced by recombinant DNA methods should be free of any infectious activity, they must still receive very careful scrutiny before being judged safe and effective for human use. Most countries have extensive regulations governing the purity, safety and efficacy of all drugs and biologicals for human or animal use, but these are not uniform among the nations of the world. Many countries also have laws pertaining to the quality of food and food products. The situation becomes more complex for such goods which are imported or exported. For these reasons, the Centre will require expertise in the laws and regulations governing the testing and use of such products, both to guide the Centre in its own activities and to advise member countries of the requirements that will have to be met for products used within the country and those exported.

21. For other programmes, the manufacture and testing of products will be of a different nature than large-scale fermentation and microbial harvesting, that which is usually thought of as being the principal means to produce genetically engineered products. Agricultural projects will require extensive land areas, green house and phytotron facilities. The production of genetically engineered seeds, for example, will require extensive facilities of this nature, even if only on a pilot or demonstration scale.

22. In order to make the most effective use of the ICGEB, it is clear that full scale manufacture will have to be confined to very few products. Nevertheless, if to serve the training functions proposed, demonstration programmes for several different kinds of manufacturing must be in place. It is envisioned, however, that, for similar types of production technology, the manufacturing facilities for most would be established in a regional

or national Centre, or, where resources are available, to start a new industry in a member country.

23. For some (but not all) types of biotechnology developed at the Centre, the Biological Resource Development Teams operating out of the ICGEB would be able to assist in establishing operating technologies, particularly fermentation technology, in some of the least developed areas. Other BIORED units may be specifically established for extending agricultural biotechnology methods to developing nations - that is by teaching plant cell culture methods and propagation techniques in the field.

24. Over all, however, the demands on the ICGEB for direct "technology transfer" are expected to be far greater than the capacity or resources of the Centre to meet these demands, without at the same time developing a network of affiliated regional and national centres. These peripheral institutions would be primarily devoted to the application of biotechnology to specific problems and perform a training function as well, but with far more emphasis on bioengineering than on sophisticated basic research.

Information Services

25. One of the most important functions of the ICGEB is to provide a variety of information services. This component of the Centre would have the responsibility for collecting information from outside the Centre as well as within, and making it available in a useful form to the member countries as well as the Centre's staff and trainees. The ICGEB eventually might also publish a newsletter or journal covering the scientific and technical proceedings of the Centre as well as information of value to the member countries. It will generally be the scientists' and bioengineers' responsibility to inform the Information Services of the activities within their departments. However, technical information specialists employed by the Centre would have to monitor continually developments in the relevant technical areas from all available sources around the world, not only in published literature, but from patents which have been issued, and directly from individuals. The Centre would have to co-ordinate such data in a way that was convenient to the user.

26. The Centre's library would provide a valuable resource in methods, knowledge of the state-of-the-art in all areas in which projects are conducted both within the Centre and by institutions in member countries, as well as others of interest. It must be remembered that the library is

a resource to serve not only the staff of the Centre, but the much broader network of member countries and affiliated research and development centres.

27. A particularly important function of the Centre's information service would be the maintenance of a data bank of nucleotide sequences for all known gene, plasmid and other useful DNA fragments, and where they can be obtained. Also useful would be a library of protein sequences and, where known, of three dimensional conformation data for proteins.

Training

28. The training of technical personnel at all levels is to be a principal function of the ICGEB, and probably the most important means by which the member countries will benefit from their affiliation with the ICGEB. The present proposal (see ID/WG.382/3) includes 26 science and engineering post-doctoral fellows to be working along with the permanent staff of 50 scientists and bioengineers. These would be continuing their training in applied research and development as well as learning production methods. In addition, however, many other models of training are to be carried out by the Centre. Senior scientists and technologists could visit the Centre for varying periods of time to learn a specific technique to be applied to projects in their own countries. Other more junior trainees may come to the Centre for apprenticeships in DNA cloning and expression, for example, or to study large-scale fermentation processes. The Centre would also be well suited to offer short courses, either by visiting faculty or resident scientists and engineers, similar to courses now sponsored by international bodies like European Molecular Biology Organization (EMBO) and by individual laboratories, such as the Cold Spring Harbor Laboratory in the United States.

29. The Training Division of the Centre would require a small staff simply to design and co-ordinate all of the Centre's training activities. The actual instruction, either through participation in an ongoing laboratory situation or through formal courses or seminars, would be carried out by the Centre's technical personnel and, occasionally, visiting instructors. It would be expected that all permanent doctoral level research and development personnel of the Centre would devote a certain amount of their time to training.

30. The concept of Biological Resource Development Teams, mobile units to carry out instruction and the demonstration of methods, even at a village level, is one which could be a valuable component of the Centre's training programme. While co-ordinated through the ICGEB, it is expected that these units would be staffed and equipped by the countries which used them.

B. External Functions

Relationship of the ICGEB to National, Regional and Other International Institutions

31. The ICGEB obviously requires the close alliance and co-ordination of its activities with other organizations which either conduct relevant research and development or provide research support. This includes national governments and the organizations they support, supra-national research organizations, the United Nations, universities and research institutions, and the biotechnology industry, including both commercial and state owned organizations.

United Nations Organizations

32. Several United Nations organizations are directly involved in extending the capabilities of what could generally be termed biotechnology to developing nations. The idea of the ICGEB originated in the United Nations Industrial Development Organization (UNIDO), which has been providing the organizational framework and staff support for the establishment of the Centre. While the ICGEB is to be an independent organization and not operated by UNIDO, this organization does anticipate a continuing involvement in the Centre after it is firmly established, especially with respect to UNIDO's primary mission of promoting the establishment of domestic industry.

33. The World Health Organization (WHO) has sponsored a number of research projects on tropical diseases, one of which concerned the development of a vaccine for malaria produced by gene splicing methods. WHO is also involved in health education and other public health programmes in developing countries. Other United Nations agencies, such as the World Bank, have been concerned with improving agricultural practices in developing nations. A number of other United Nations agencies are also involved in some way with health, food, nutrition, education, energy, natural resources, or the extension of new technology in developing countries, all of which touch upon the

broad range of activities which may be affected by modern biotechnology.

34. Since the ICGEB's activities overlap to a degree with all of these efforts, a close liaison with the relevant United Nations organizations is essential. Co-operative programmes in which, for example, WHO might take on the distribution and field testing of a vaccine developed at the ICGEB, could be envisioned. The possibility of United Nations organizations funding specific research and development projects at the Centre should also be considered.

Regional and National Affiliated Centres

35. As discussed above, the ICGEB's effectiveness will require the establishment of a network of regional and national centres, devoted to bringing specific aspects of biotechnology to developing nations as appropriate, and training scientists, engineers, and technicians to build domestic industries.

36. There are already in existence research and development centres in a number of countries which could qualify, perhaps with relatively minor changes, as affiliated centres. Many more will need to be established, however. Presumably, each of the affiliated centres would employ some individuals who had received training at the ICGEB and who could help bring current developments and skills to their home countries. The affiliated centres could build process and manufacturing plants based on pilot technology developed at the ICGEB, or perhaps even develop processes for producing materials obtained in the ICGEB's research laboratories, but for which production procedures have not been worked out. That is, the first priority of the affiliated centres must be to bring the practical technology to the people of the member countries as quickly as possible. This does not mean that both basic and applied research should be excluded. Depending upon the availability of skilled scientists and engineers, research functions, if not already present, could and should be included. Again, however, the balance of research and practical technology must be given careful attention, not only within each institution, but with respect to the relationship of each affiliated centre with the ICGEB. It must be kept in mind that the ICGEB will only be able to undertake full scale manufacturing in very few areas, serving a pilot and demonstration function for most programmes.

37. Research and development centres in developed countries would also be expected to become affiliated with the ICGEB. These institutions would generally be of a much different nature than those in developing countries, carrying out advanced research and development in perhaps several specialized areas of biotechnology. The work programme of the ICGEB is expected to complement rather than duplicate the activities of these affiliated centres. Accordingly, some of these affiliated centres in technologically advanced countries could provide training in areas not covered directly by the ICGEB. In effect, the network of affiliated centres, in both developed and developing countries, would expand the scope of biotechnology resources available to the ICGEB and its member nations.

Other National and International Organizations

38. There are many existing national institutions around the globe with an interest in and, in some areas, with ongoing programmes in bringing biotechnology to developing nations. For example, the United States National Research Council has the Board on Science and Technology for International Development (BOSTID) which has sponsored meetings and workshops on this subject. A division of the U.S. State Department, the Agency for International Development (AID) and the Swedish Agency for Research in Developing Countries (SAREC) have sponsored biotechnology programmes in developing countries. The Fogarty International Centre of the National Institutes of Health (NIH), has active programmes for training scientists from many countries in the NIH laboratories. Moreover, the NIH conducts and supports a number of programmes which have direct and indi relevance to the proposed agenda of the ICGEB.

39. Most developed nations have both an academy of sciences, and an agency of the government which supports research. While these organizations are, of course, primarily interested in fostering domestic science, many of their activities are relevant to the Centre. Other associations, such as the European Molecular Biology Organization (EMBO) have been effective in furthering the development of genetic engineering methods, especially through training courses and workshops. International Agricultural Research Centres(such as the International Rice Research Institute in the Philippines) have been developing high-yield strains of rice and other staple foods. Agricultural research and development institutes exist in most countries.

40. There are several types of relationships with these institutions which are important to the ICGEB's functions. The first is simply information exchange. The second might be reciprocal visiting research and training fellowships. A third would very likely be the direct sponsorship of research and development programmes at the ICGEB and possibly at affiliated centres. The NIH, for example, now funds several million dollars of research outside the United States. Scientists at the ICGEB should be in a good competitive position to obtain grants from this and similar research funding institutions.

Universities and Research Institutions

41. By far the greatest source of new knowledge,upon which modern biotechnology rests, is the world's research universities and research institutes. It is only through uninhibited and undirected scientific inquiry that this knowledge base will continue to increase, often in unpredictable ways. Universities are also engaged in applied science, and are generally increasing their activities in biotechnology and in the training of bioengineers.

42. It is, of course, a principal function of the ICGEB to collect and disseminate to member nations and affiliated centres all scientific and technical information relevant to its activities. This far from trivial undertaking would be the responsibility of the ICGEB's information services. However, the most current information tends to be exchanged around the world in a rapid, effective and very informal manner. The world community of scientists and engineers, a large proportion of whom work in the world's universities and research institutions, is one which knows no walls or geographical boundaries. In that the fifty permanent scientists and bioengineers and the substantial number of visiting trainees will be a part of that community, a close but informal liaison would be automatically established between the ICGEB and the leading research and development, and teaching institutions. The coherence of this collegial association is maintained through participation on conferences and workshops, visiting one another's laboratories, exchanging strains and research materials, often complex lineages of mentors and their students, and informal communication, rather than by a formally defined "network" or process. Inasmuch as the ICGEB

should be as much on the"mainstream" as any leading university, it is essential that it encourages among its staff the kind of activities conducive to the open exchange of ideas with other scientists and technologists around the world. As a practical matter, and in view of the international character of the Centre, this would entail a significant amount of travel by the professional staff, as well as an active technical seminar programme at the ICGEB in which the leading people in their fields were invited to visit the Centre and discuss their work.

43. Universities and research institutes are also principal sources of scientific and technical experts, who would be expected to be called upon by the ICGEB as consultants on particular projects or to teach courses. The Centre may wish to maintain a roster of such individuals who would provide their services to the Centre on a regular basis.

The Biotechnology Industry

44. There are at present over two hundred independent companies around the world devoted exclusively to some aspect of biotechnology plus many large industrial organizations that are actively pursuing research and development in many areas of biotechnology. These existing industrial activities encompass, at least in a general way, most of the research and development agenda proposed for the ICGEB. Many of the programmes of these organizations have gone well past research and development, with a number of products resulting from genetic engineering or other advanced methods in biotechnology now being manufactured and tested. Several products are now available to the consumer, including human insulin, animal vaccines, and diagnostic reagents for human diseases. Genetically engineered organisms and the enzymes they produce are now being tested in certain industrial processes. Most of the industrial activities involving advanced biotechnology are in developed nations, particularly the United States, Western Europe and Japan. Of these, most are privately owned corporations, although some are partially or entirely state owned.

45. Because of concerns in these countries over the past few years about the competitive position of each nation's biotechnology industry relative to that in other countries, pressure has been brought to bear

on national governments to follow policies which would promote the domestic industry, including, for example, adequate government support of the basic research upon which technology is built. Several countries, including Japan, Great Britain, France and Sweden, have active programmes to promote the development of an advanced biotechnology industry.

46. The programmes of ongoing industry in developed countries are generally directed toward the economic needs and consumer demands of those countries. The specific goals of research and development in biotechnology in these nations - such as cancer therapeutics, diagnostic tests for the disease prevalent in these countries, the improvement of industrial processes for the production of sweeteners and ethanol, and enhancement of the yields of the staple crop varieties in those countries - are generally not those areas of high priority to developing countries. The reason for this is primarily economic, but also reflects the fact that people from different parts of the world and different climates have different diseases and eat different foods.

47. The commercial biotechnology industry, which must set its priorities according to the most lucrative real or projected markets, will concentrate on producing those goods which people demand and can pay for, and for which development costs will be lowest. Thus there has been much attention paid to pharmaceuticals and biologicals relevant to the diseases of the affluent countries, especially cancer. However, the time and expense required for the testing and meeting regulatory requirements of any substance for human use can be considerable. Periods of five to ten years following the production of a substance are common. Therefore, animal vaccines have received much more attention than human vaccines, even for serious diseases which affect many people who can afford to pay for them. For diseases that affect primarily those in developing countries who cannot afford to pay for vaccines, there is no commercial incentive to invest the time and resources in their development. This is why the extraordinary potential of genetic engineering methods in the construction of safe vaccines has not been exploited for the control of most of the very serious and widespread tropical diseases. It is such dilemmas that make the need for the directed application of biotechnology to developing countries' problems acute.

48. At the same time, it must be recognized that the incentive which

has driven the commercial biotechnology industry has resulted in the investment of many hundreds of millions of dollars (U.S.) into some very productive research and development in many areas. The availability of these resources has attracted the world's foremost scientists and bioengineers, who have, in a short period of time, developed a remarkable variety of advanced methods which are highly relevant to the proposed work programme of the ICGEB and to the solution of the specific problems of developing countries. Some of the technology developed by existing industry could,with very minor specific adjustments, be of direct use by the nascent biotechnology industry in the developing world. It is, therefore, important that all industrial activities relevant to each area of the ICGEB's proposed agenda be taken into account when making final programme choices. It would be wasteful to pursue the development of techniques or products where the problem has already been solved.

49. For these reasons, liaison between the ICGEB and industries using biotechnology is essential. The merits of different types of co-operative relationships with industry should be thoroughly assessed by the ICGEB after its establishment.

50. There are also important lessons to be learned from the experience of existing biotechnology industry. The process of establishing and operating the research, development and manufacturing organizations devoted to biotechnology which are currently in place is in many ways comparable to the establishment of the ICGEB. The size, the mix between research and development, the efficiency and cost effectiveness of scale-up, and the manufacturing, testing and quality control of products are problems which all industrial organizations using biotechnology have had to address and which the ICGEB and the industry it is promoting will have to face.

C. Commercialization and Patents

51. It is not the intended objective of the ICGEB to become a commercial institution or to compete in the world of international commerce. However, it must be recognized that most biotechnology activities, as is the case in all other industries, are made available to the people of the world through international and domestic commerce. This is true regardless of the political and economic models followed by any particular nation.

Patents

52. The ICGEB must have ongoing legal counsel, particularly after it is operational and patentable inventions are forthcoming. Whatever moral view one takes of patents and proprietary rights, it is a fact that most countries of the world issue patents to protect an inventor's exclusive right to exploit his creation. It is defended as the means for making new discoveries available to the greatest number of people in the shortest possible time. It is feared that without patents, inventions would not be disclosed to the public and technology would be veiled in secrecy and fraught with conflict.

53. It is very important that the ICGEB seek patents on the fruits of its research, just as most universities, research institutions and corporations now do. International Patent Law, especially in biotechnology, is rather murky. The courts will spend many years trying to clarify the obscurities unless an international patent convention can do it more effectively. Until then, the ICGEB has no choice but to protect its proprietory rights in the same way that all other research and development organizations must now do.

Commercialization: Problems and Options

54. In order to obtain effective world-wide patent protection, it can cost the inventor from US$ 5,000 to 20,000 per patent. This is clearly an expensive proposition for any organization which produces many patentable discoveries in a year. Thus, both commercial organizations and universities must formulate a patent policy and a strategy which gives them the optimum protection of their inventions at the lowest cost. Obviously, no one can afford to patent everything. The ICGEB will, there-

fore, have to formulate a patent policy, and be sure that resources are available to implement it. What this policy might be, however, depends upon the course chosen with regard to commercialization of the Centre's inventions.

55. One option would be for the ICGEB to compete in the world market in a small number of areas. For example, the Centre, in the course of one or more of its specific projects, might develop a product for which an adequate commercial supply might be made easily in the Centre's 5,000 litre pilot plant. This could be true, for example, of a vaccine produced by a viral antigen, synthesized in a genetically engineered bacterium. In the course of carrying the project to completion, what would the Centre do with this product, which many people needed and was unavailable elsewhere? One option is to market it. In this way, the ICGEB could control the price, especially to the poorer developing countries, while selling it to wealthier countries as a source of revenue for the Centre. This would also serve to train individuals in marketing and distribution.

56. Another alternative would be for the Centre to sell products to the United Nations, a government, or a commercial organization, which would then sell and distribute it. In this way, the Centre would gain operating capital without having to engage in commercial practices per se. The Centre could impose pricing conditions as part of the sale contract. Or the ICGEB could retain patent rights but license the manufacture of its products to governments or industrial enterprises. The ICGEB could write in any conditions into the licensing agreements that it saw fit to ensure the availability of the product. At the same time, the ICGEB could receive royalty income.

57. All of the above options would retain for the ICGEB the control of how its inventions and, presumably, the useful products resulting from such innovation, would be made available to consumers, especially those in developing countries. Whatever policy on commercialization is ultimately formulated, it is a matter that must be given careful consideration by the ICGEB in order to ensure that the primary purpose of the Centre is fulfilled - the availability of the fruits of a promising new technology to the peoples of the world who need it most.

II. AN EVALUATION OF POSSIBLE ELEMENTS OF THE WORK PROGRAMME FOR THE INTERNATIONAL CENTRE FOR GENETIC ENGINEERING AND BIOTECHNOLOGY (ICGEB)

58. The purpose of this section is to consider the breadth and nature of possible elements of the research and development programme of the ICGEB in somewhat more detail than was discussed in earlier documents. Six suggested areas were discussed in the addenda to the proposed Five-Year Work Programme of the ICGEB (ID/WG.382/2). Most of these dealt with rather general areas of research and development. One (Bio-Informatics) dealt with the information function of the ICGEB rather than a research and development programme. The collection and dissemination of biotechnological data and information is considered to be an essential function, to be incorporated into the internal organization of the Centre.

59. With regard to the content of the research and development programmes most appropriate to the Centre, several criteria must be applied. First, it is preferred that projects be pursued initially which represent those technologies most appropriate to the needs of developing countries, including large-scale fermentation for the conversion of readily available organic resources to energy or food substances, the treatment and prevention of infectious diseases, especially certain tropical diseases, and the improvement of food production. Second, one of the principal functions of the Centre is to train scientists and bioengineers so that they will be able to apply the techniques of genetic engineering and biotechnology to a broad spectrum of problems. Thus, the Centre's programmes must serve as a training ground in the various general methodologies upon which biotechnology is based, including gene splicing, the analysis and synthesis of polynucleotides and proteins, large-scale fermentation, monoclonal antibodies, the design of vaccines, and plant cell culture, in addition to training in specific areas of application. Third, the specific projects undertaken should not duplicate work being done elsewhere. And fourth, the projects should represent a balance between those for which the technology is known and can be brought to fruition for the solution of specific problems in a relatively short time (for example, the large-scale production of a vaccine through genetically engineered bacteria), and longer term projects for which the technology must still be developed (such as a species-specific biological insecticide).

60. It is clear, then, that there are general programmes which should be undertaken regardless of the specifics of the work programme. These would include the development of microbial expression vectors, the heart of genetic engineering. Also necessary are technical service departments to perform analysis and synthesis of nucleic acids and proteins required for the various projects, a gene and plasmid bank, and a microbial culture collection.

61. It is often not appreciated that biotechnology is not scientific research per se. It is applied research, taking the findings of the scientists doing basic research and translating them into tangible and useful products, organisms or services which can solve real world problems. The ICGEB is not intended to engage primarily in basic research in molecular biology, microbiology and plant genetics. Rather it is to assemble a group of highly talented applied scientists and bioengineers,who can help to bring to developing countries the actual benefits of this new technology as quickly as possible.

62. Accordingly, one should not assume that the professional staff is to consist entirely of scientists. It must also include those skilled at fermentation and process engineering, purification and testing of products on an industrial scale, and manufacturing and quality control experts. That is, every step of the process of taking a research result from the laboratory to the consumer must be thoroughly covered by the ICGEB in order to meet its objectives. Again, then, regardless of the specific projects chosen, the Centre must include, at least at a pilot plant or demonstration level, a bioengineering and manufacturing component, which should be one of the principal concerns of the Centre.

63. As for the specific projects to be selected within each general area, it should be remembered that the Centre can engage in only a limited number of specific projects. These, therefore, must be chosen with great care, in order to best fulfill the stated purposes at the Centre, including providing demonstration projects for the training of individuals. The Centre should also consider very carefully any decision to embark upon completely new projects on which very little basic information exists. Recognizing that an appropriate mix of short and longer term projects is important, the feasibility of all projects to be undertaken should be carefully evaluated.

64. Included herein is a brief discussion of the criteria described above as applied to each prospective project considered. Obviously, it is not possible to anticipate every possible area of endeavour in which the Centre may some day engage. The selection of topics discussed here is based upon available data, previous UNIDO documents and the areas which have been receiving the most discussion as germane to the interests of developing nations. No doubt, much more relevant information will be available at the time these decisions will have to be made than exists at the time of writing.

Comparative Evaluation of Specific Projects

65. The following summary is intended to provide data to aid in the selection of specific projects from among the large number that would be appropriate in any given category. It is representative, rather than exhaustive, looking at the prevalence and seriousness of the problem to be solved, other research and development activity that is already taking place, the feasibility of a solution and other relevant problems. When the management of the ICGEB finally determines the details of the work programme, it will require far more data than are presented here, and updated accordingly. At present, however, this analysis should help to bring into focus the kind of work programme that would be both appropriate and feasible for the ICGEB to undertake.

Infectious and Parasitic Diseases

66. Biotechnology offers novel solutions for the diagnosis, treatment and prevention of all infectious diseases. Because of the prevalence of many serious human and animal diseases, affecting both the quality of human life and the economies of many developing countries, work in this important area should receive a high priority in the work programme of the Centre. It is expected that the ICGEB will maintain laboratories exploring the methodology of genetic engineering and providing services appropriate to all projects using genetic engineering. Accordingly, diagnostic procedures based upon the size distribution of DNA fragments resulting from restriction enzyme digestion provide a sensitive means of detecting not only the presence of an invading disease organism, but in many instances can determine whether or not an individual is susceptible to a given disease.

67. Safe and effective vaccines can be produced by the cloning and expression of suitable disease specific antigens, such as a part of a viral coat protein, a bacterial cell surface protein, or, in the case of a parasitic disease, an antigen specific for perhaps a spore, or other essential organelle which would be sensitive to antibody or T-cell inactivation (although the immunology of parasitic diseases remains a difficult area). Such vaccines could be produced in large quantity through large-scale fermentation procedures. An advanced large-scale fermentation facility (pilot plant) is planned for the Centre.

68. The development of specific antibodies (monoclonal) now offers another important tool for the diagnosis and treatment of infectious diseases. Monoclonal antibodies may also be produced in bacteria by large-scale fermentation methods. This discussion is confined to some of the most serious human and animal diseases [2/].

Malaria

69. Malaria is a serious cause of disability and death, especially in tropical climates, afflicting approximately 200 million people, or about 10 times the prevalence of cancer. There is no vaccine currently available, although work was begun at New York University under funding from the World Health Organization. Genentech Inc. had arranged to develop, manufacture and market the vaccine, but withdrew from the project when it seemed that it would not have exclusive commercial rights to the vaccine. Because of the importance of this disease as a world-wide health problem and the lack of activity at present, the development of a malaria vaccine should receive a high priority.

Schistosomiasis

70. This severe parasitic disease of the tropics is in need of a novel means of control. Because of the parasitic nature of the disease, the development of an effective vaccine is a very difficult problem. Therefore, means should be explored to interrupt the bilharzia worm's life cycle at

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2/ A summary of progress in vaccine development for all of the major human and animal infectious diseases may be found in "Priorities in Biotechnology Research for International Development," National Academy Press, Washington, 1982, pp.67-86.

a critical stage, or to create an infectious agent (e.g. a virus) specific for the worm. The snail, in which the parasite undergoes part of its life cycle may be an appropriate site at which to control the disease.

Dengue Fever

71. There is no vaccine for this disease, nor a commercial incentive to develop one. This is a less than straightforward problem because of the four antigenically different types of virus.

Other Human Diseases

72. There are obviously many other appropriate candidates for research programmes, including Japanese encephalitis and leishaniasis. Current research is being undertaken in commercial laboratories to develop vaccines against hepatitis, rabies, chlamydia trachomatis, and herpes simplex, which remain serious diseases at present in many areas.

Animal Diseases

73. In large part, because the approval procedures of most governments for animal vaccines are much shorter and simpler than for human agents, there has been somewhat more commercial interest in the development and production of animal vaccines than in vaccines against human diseases. There are already severe vaccines against scours (diarrheal diseases in new born pigs and calves), which is now being sold, and a vaccine for foot and mouth disease is undergoing tests. There are others for which efforts are needed, such as African swine fever, the animal hemotropic diseases (babesiosis and anaplasmosis) and tuberculosis. The United States Department of Defense is now funding a project to develop a vaccine against Rift Valley Fever, which affects both humans and animals.

Agriculture

74. The development and improvement of general methods for plant genetic engineering is an appropriate subject area for the Centre. This subject is, of course, receiving much attention in both public and private research institutions and from the biotechnology industry. However, the technology is fundamental to the improvement of plant species. It is appropriate, therefore, that the Centre establish an active effort

in this area, not only to develop the general methods for the possible specific applications discussed below, but as an important training ground for scientists and biotechnologists from developing countries, who will ultimately use these techniques to improve food production in a variety of species. Several possible problem areas are discussed below.

Nitrogen Fixation

75. The problem of enhancing the productivity of plants through either microbial or intrinsic nitrogen fixation has received a great deal of attention from the commercial industry. The direct addition of nitrogen fixation genes to plants is generally considered to be too complex at this time, so that most efforts are being directed towards the improvement of rhizobium. In view of the intense activity in this area, it could be viewed as redundant to undertake such a project at the Centre. However, the possibility of engineering nitrogen fixing soil bacteria, more appropriate to the unique soils of specific developing nations, should be considered.

Pest Resistance

76. While there is much general interest in engineering useful plants to be unpalatable or even toxic to their chief insect and perhaps other predators, this is generally viewed as a technically difficult problem which would have to be solved on a case-by-case basis. There is concern that adding the genes for the production of an alkyloid toxic to certain insects may also render the edible portion of the plant at least partially toxic to human consumers, or spoil the taste. The first toxin gene suggested for insertion directly into plants is that from Bacillus thuringiensis, now used as a commercial biological pesticide. This is being explored, but its possible effectiveness is not known. Of course, for plants used primarily for fibre (e.g. cotton), the problem could be easier. There has been little progress thus far in this area, since it has been only very recently that the successful expression of foreign genes in plants has been achieved. Because any solution of this sort is likely to involve several genes, one may not expect advances to be forthcoming from commercial organizations for some years to come. On the other hand, the technical difficulty of the problem and the prospects for

only a long term pay off may make it a low priority item for the Centre's agenda as well.

Biological Pesticides

77. The prospect of producing either specific microbes which attack certain species of insect pests, or of a species-specific toxoid by genetic engineering methods has excited several of the large producers of agricultural chemicals. Research arrangements to develop such products are now being negotiated with biotechnology firms. Several approaches are being explored, including the insertion of Bacillus thuringiensis (B.t.) of toxin genes into various bacteria. This toxin might be made more specific for a target insect by finding a specific insect parasite and adding the B.t. toxin genes. Other approaches are based upon linking a potent toxin molecule to a species-specific monoclonal antibody. However, none of the suggested approaches has proved very successful thus far. In insects, the problem of delivery of a highly toxic molecule in very low concentrations to a site of vulnerability within the organism has not been solved.

78. Methods employing pheromones (sex attractants) in insect traps have been partially successful. A trapping mechanism to concentrate the population of insect could be an important adjunct to any approach to pesticide development.

79. The concept of insect contraception or sterilization may prove to be more successful than the traditional methods of the broadcast of an environmental poison, whether or not it is species-specific. In any case, there is a great deal of room for creativity in this area, the effects of which on agricultural productivity could be enormous.

80. It is important to keep in mind here that the development of biological pesticides (or any other) should still be a part of an integrated pest management approach for agriculture. The judicious selection of crop varieties, the condition of the surrounding environment, and the use of natural predators should be considered an integral part of pest management. The Centre's information services would be expected to provide such advice whenever pest control information is requested.

Engineering of Soil Bacteria

81. The condition of the soil and its ecology is known to have a very important affect on the agricultural productivity of land. The prospect of enhancing the properties of certain soil bacteria to stimulate plant growth is receiving increasing attention in commercial biotechnology organizations. Of interest are not only nitrogen fixation, but the production of growth factors which, for example, can stimulate the proliferation of roots. Other microbes are necessary for making minerals available to the plant. Because the quality of soils is so intimately connected to agricultural productivity, it is appropriate that the Centre would maintain efforts in this area. Much of the work would have to be specific for the area, climate, soil composition and crops of interest. For this reason, the work being carried out in this area at present, particularly in the United States, is only of general relevance to the specific problems of developing countries. Thus, such a programme at the Centre would complement, rather than compete with other such activities.

Stress Tolerance

82. In large parts of the world, the land is unsuitable for agriculture because of either a lack of water or a high concentration of soluble minerals. A few plant varieties have adapted to these conditions but these are generally not suitable as food sources, nor for fibre or as a construction material. An important challenge to plant genetic engineers then is to develop economically important varieties which can thrive under these highly stressed conditions. At present, there is interest in this problem in only a few of the commercial biotechnology companies, and no suitable technology has yet been developed.

83. It should be remembered that in many cases, the present poor condition of the soil is the result of man's intervention, that is, watersheds have been destroyed and incorrect irrigation and fertilizer application practices have added excessive minerals to the soil. Education in proper maintenance of agricultural soils, methods such as drip irrigation which are effective in arid climates, and in long range land management are perhaps more important than the development

of a quick technological "fix". In this area then, as in most, the development of technology and its establishment in areas of need must be coupled with an integrated educational programme.

Microbial Engineering

Microbial Selection Methods

84. A general programme to develop methods as well as to examine specific problems which can be solved by suitable microbes is essential for the Centre. Not only have microbial screening and selection methods been used to isolate virtually all at the strains now used for bulk fermentation for food and chemical production, but provide the starting point for genetic engineering to be used to enhance the desired properties of a microorganism. The methods of elective culture and selection are well known and perhaps represent the "low-tech" end of biotechnology. On the other hand, such techniques are likely to be of the greatest immediate use to developing nations, particularly for the design of fermentation processes utilizing abundant local materials for a variety of purposes (e.g. alcohol or sugar from high cellulose biomass).

Energy Production from Biomass

85. At present, there is little economic incentive in most of the world to produce ethanol from starch or cellulose for a fuel, in view of the world price and supply of petroleum, although in some parts of the world (e.g. Brazil) extensive programmes exist. Because the economics of petroleum, and ultimately its supply, are unpredictable, it is very likely that fuels derived from plant material may one day be important in much of the world. At present, the economic conditions which prevail in some developing countries, especially those without petroleum resources, may permit the cost of effective biological production of fuels.

86. There are clearly cost advantages to be obtained through the selection or genetic engineering of more efficient organisms producing more of needed enzymes or more active forms of these enzymes. At present, most commercial establishments are not attempting such improvements because the economic incentives are not great enough.

87. It should be mentioned, however, that cellulose has received a great deal of attention from both publicly and commercially supported research. The organism receiving the most attention is Trichoderma reesi. Several laboratories have developed strains which produce 50 - 100 fold increases in the enzyme. These are now proprietary and not generally available.

88. There has also been much work on the series of enzymes which degrade starch from the naturally occurring branched chains into glucose. In most processes, the first object is to obtain glucose. It may then be fermented to ethanol, or converted to fructose with glucose isomerase. The principal commercial interest in these enzymes and/or the organisms which produce them is the manufacture of 55 per cent fructose/glucose syrup as a sweetener, which is cheaper to produce than sucrose. In the United States, no substance derived from wood may be used legally as a food. For that reason, glucose, fructose or ethanol derived from wood cellulose cannot be used for human consumption. This is not true in many other countries, however.

89. The cloning and expression of the genes for all of these enzymes is being attempted and has been accomplished for most of them. There is still interest in developing a super yeast, which secretes cellulose and can thus carry out the direct conversion of wood to ethanol in a single process. In view of the degree of activity in this area, it would be unwise for the Centre to undertake a programme to repeat what is being done commercially. A biomass project may still, however, be in order if some of the appropriate technology could be licensed from its developers. There may also be cloning vehicles other than yeast (e.g. Zymomonas mobils) which are preferable to yeast in some applications. Before a decision is made to proceed with these applications, however, the current status of knowledge must be thoroughly evaluated.

90. A second approach to energy production may also be the production of fuels other than ethanol, such as methane or perhaps other hydrocarbons. This would mean studying and exploiting classes of microbes for which much less is known than yeast. However, the available substrates in some areas may be much more suitable for this approach. If the Centre undertakes a protein engineering programme, this might well be applied to the design of novel enzymes specifically for fuel production.

Degradation of Pollutants

91. Microbial ecology has not proceeded as rapidly as our ability to fool Mother Nature with chemicals she has never seen before. As a result, many chemicals, particuarly pesticides, have accumulated in the environment. These are not only disruptive of the ecology generally but appear at toxic levels in the food chain. These include DDT, PCB's 2,4,5-T and its notorious contaminant dioxin. Strains of microbes have been found which degrade some of these compounds (e.g. PCB's, 2,4,5-T). These are not, however, necessarily able to survive in the natural environment where they can effectively remove such residues. Thus, much practical work needs to be done. Moreover, there is a specific need for a microbe capable of degrading dioxin, which is now causing serious health problems in several parts of the world. At present, toxic chemicals pollute large areas, making them unfit for human living or the growing or harvestry of foods. This could become an important activity of the Centre.

Hydrocarbon Microbiology

92. One of the addenda to the work programme presented in Belgrade (ID/WG.382/2/Add.3) was devoted to hydrocarbon microbiology with special reference to tertiary oil recovery. At present, there are a small number of research and development projects underway, dealing with various aspects of microbial physiology and biochemistry as it relates to the components of crude petroleum. Efforts to pursue tertiary oil recovery are being organized, at least one of them (in England) on a grand scale.

93. There are a number of criteria which must be evaluated before the ICGEB decides to engage in a programme specifically devoted to the microbial conversion of the constituents of petroleum, and, if so, how large this programme should be and on which points it should focus. First, relatively few of the developing nations have significant petroleum resources nor are they engaged in oil refining, although a small number of them are major producers of oil. Possibly for this reason alone, the activities of the ICGEB should be confined to rather basic microbiology with an affiliated centre devoted to hydrocarbon microbiology established in an oil

producing country. However, there are a number of peripheral problems, all involving hydrocarbon microbiology, which would be of interest to a greater number of countries. These include the refinement of petroleum, either for fuels or as a starting material for the production of other chemical products, and the degradation of oil spills and perhaps other hydrocarbon-based environmental pollutants. The development of bacteria which could function in an environment high in hydrocarbons, or possibly enzymes designed to catalyze reactions involving hydrocarbons and function in a non-polar solvent (this could be a challenging topic for a molecular engineering programme), could revolutionize the energy intensive and polluting methods of oil refining and hydrocarbon chemistry now in use. Some efforts in these areas may be suitable projects for the ICGEB.

94. Tertiary oil recovery per se is generally considered a very difficult, long term problem, which may require a different solution for each individual source. While perhaps appropriate for an affiliated centre in an area with hard-to-get oil reserves, the ICGEB must take into account the feasibility of meeting the programme objectives and the economics of the project in relation to the Centre's other prospective programmes before embarking on tertiary oil recovery as one of the Centre's major programmes.

Molecular Biology and Biochemistry

95. The development of recombinant DNA methods grew out of efforts to understand the basic mechanisms of gene structure, regulation and expression. To tne degree that the ICGEB will pursue basic research (as opposed to applied research), most will be carried out with the objective of ultimately developing methods to facilitate the manipulation of genes and biological molecules.

Development of Cloning and Expression Vectors

96. In order to produce large quantitites of biological materials, especially useful proteins, it is important to design plasmids, bacteriophange, or modified viruses which allow the efficient expression of any gene one chooses. In addition, it is also desirable to develop hosts

which not only manufacture large quantities of a selected gene product but secrete it outside the cell, thus greatly facilitating isolation of the substance (e.g. Bacillus subtilis). While this area is receiving a great deal of attention in both the commercial and non-profit laboratories, it is an area which is in constant need of innovation. Because it is so fundamental to all microbial genetic engineering, it is essential to include such a programme at the Centre. It will be especially important for the training of scientists and technologists in genetic engineering methods.

Molecular Engineering

97. An area on the frontier of biotechnology which is bound to be of great importance in five or ten years is that of protein engineering. That is, the enzymes and other proteins which occur in nature do not necessarily represent the optimal solutions to the problems of mankind. For example, if one wishes to construct a catalyst to convert long chain fatty acids into low molecular weight hydrocarbons for fuel, it would have to be able to function in a highly non-polar environment, where most enzymes are not even soluble. By designing a molecule with a lipophilic active portion and a hydrophilic portion which could work at the oil-water interface of emulsions, one could solve the problem.

98. The means to construct a gene to synthesize a protein of any desired amino acid sequence are now available. The ICGEB would presumably have both the analytical and synthetic capabilities to make genes to order. The problem is in knowing what one should make in order for it to have the desired physical and catalytic properties. To do this, much more basic work is needed on the theoretical analysis of why proteins fold the way they do. An interdisciplinary effort involving both experimental and theoretical scientists is needed to develop the methods needed to design the cloned protein for a given function or conformation. Extensive computational facilities, as well as advanced computer graphics would be needed. Thus, the ICGEB's computational facility should be built with the size and speed to handle what can

be formidable calculations. A programme of this sort was mentioned briefly in the "Bio-Informatics"[3/] paper, but is properly included as a programme in fundamental molecular biology.

99. There is limited interest in investing in this type of project in the commercial sector, although two companies have undertaken such projects. There is, however, a great deal of academic interest in what is one of the most challenging current problems in biophysics and which scientists recognize to be of tremendous value in the future of biotechnology. Commercial interests are avoiding support of molecular engineering programmes because of no clearly defined pay-off. Independent scientists are hampered by lack of funding, adequate computational facilities and a highly able interdisciplinary team assembled in one place. The structure of the ICGEB would be ideally suited to undertake this programme. However, its initial value must again be weighed against the other suggested programmes in view of available resources. This would be a relatively expensive programme, and practical results would not be expected to follow for many years. This is, however, the type of long-term project which might be added when the Centre is well established, and has some of its short-term programmes well under way.

3/ See ID/WG.382/2/Add.6.