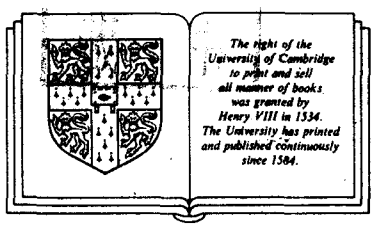
The biotechnological challenge

S. JACOBSSON
Research Policy Institute, University of Lund
A. JAMISON
Research Policy Institute, University of Lund
H. ROTHMAN
Centre for Research in Industry
Business and Administration, University of Warwick



CAMBRIDGE UNIVERSITY PRESS
Cambridge
London New York New Rochelle
Melbourne Sydney

Published by the Press Syndicate of the University of Cambridge
The Pitt Building, Trumpington Street, Cambridge CB2 1RP
32 East 57th Street, New York, NY 10022, USA
10 Stamford Road, Oakleigh, Melbourne 3166, Australia

First published 1986

Printed in Great Britain at the University Press, Cambridge

British Library cataloguing in publication data

The Biotechnological challenge.
1. Biotechnology
I. Jacobsson, Staffan II. Jamison, A. III. Rothman, Harry
660'.6 TP248.2

Library of Congress cataloguing-in-publication data

Main entry under title:
The Biotechnological challenge.

Bibliography: p.
1. Biotechnology – Social aspects – Developing countries.
I. Jacobsson, Staffan. II. Jamison, Andrew. III. Rothman, Harry.
TP248.2.B38 1986 338.4'76606'091724 85–21303

ISBN 0 521 30775 9

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Contributors

Ralph Crott
Institut de Recherches Economiques (IRES)
Université Catholique de Louvain
Place Montesquieu, 3
Bte 4
B-1348 Louvain-la-Neuve, Belgium

G.H. Fairtlough
Celltech Ltd
244-250 Bath Road
Slough SL1 4DY
Berkshire, UK

Rod Greenshields
Biotechnology Centre
University of Wales
Swansea SA2 8PP, UK

Staffan Jacobsson/Andrew Jamison
Research Policy Institute
Box 2017
S-220 02 Lund
Sweden

Harry Rothman
Bristol Polytechnic
Coldharbour Lane, Frenchay
Bristol BS16 1QY

Patrik Rousseau
Cabinet ow ministre a l'innovation (region wallonne)
19h avdes Arts
Brussels 1040, Belgium

Francisco C. Sercovich
Echeverria 2164, 6–26
1428 Buenos Aires
Argentina

Zbigniew Towalski
The Open University
Walton Hall
Milton Keynes MK7 6AA, UK

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Introduction

S. JACOBSSON, A. JAMISON AND H. ROTHMAN

What do developing countries need to know in order to devise appropriate policies for establishing their own indigenous industrial capability in the field of biotechnology? Three years have passed since we first set out to provide answers to that question; and even though a great deal has happened since then, both in the general area of biotechnology as well as in the relations between the industrialised and the developing countries, the essays in this volume still represent one of the first systematic attempts to monitor the potential impact of biotechnologies on Third World development.

When the United Nations held a conference on science and technology for development in Vienna in the summer of 1979, biotechnology was missing from the discussions;[1] today it would be impossible to consider science and technology policies in any country without paying close attention to the role of biotechnologies. In nearly all policy deliberations biotechnologies have come to occupy a crucial role, both from the perspective of basic research, where experimentation with genetic manipulation and enzymatic processes are some of the hottest items on any agenda, as well as from the perspective of economic competition, where biotechnology is considered one of the key growth industries in the international marketplace. Few, however, have sought to examine the biotechnological challenge from the particular perspective of the industrial capacities of developing countries.

It is not our purpose here in this brief introduction to summarise what has by now become a voluminous and rapidly growing literature. Learned volumes have been written on the history of the scientific discoveries leading to the biotechnological breakthroughs of the 1970s, on the ethical and philosophical implications of these discoveries, on the economic

viability of certain applications, and, not least, on the specific techniques of biotechnological research. New journals have been created, government commissions and international fora have evaluated the relevant material, university departments and educational programmes have been established and redesigned, and a host of new small industrial firms have been created, often with a strong involvement from previously 'basic' researchers.

Indeed, one may well ask, on the basis of all this activity, how much the supposed revolutionary impact of biotechnology is a result of media and government attention, and of a desire to sell magazines and lead faltering economies out of crisis. There can, however, be little doubt that investment capital has flowed into the field in a way that is reminiscent of the recent microelectronics boom. But even more so than in the electronics industry, biotechnology has been an area where the results of fundamental scientific research have been of almost immediate commercial interest, and where the relations between universities and industry are in a state of flux, if not disarray. In this volume, we have attempted to select from all the possible points of entry, a few that can be considered most relevant to the concerns of developing countries.

For the purposes of this volume, biotechnology can be defined as the 'scientification' of biotechnical production. It is the infusion of scientific knowledge into the manufacturing process by which marketable products are made out of biological phenomena that represents both the challenge and the enormous potential of biotechnology. In particular, the recent discoveries within microbial genetics have opened up a new world of possible applications. The most dramatic discoveries have been those of genetic engineering, involving the capacity to manipulate, or recombine, genetic material in the cells of bacteria. These techniques are the result of four decades of intensive scientific investigation into the structure of genes and the mechanisms by which genetic information is transferred from generation to generation. This research has, in its turn, required the development of special laboratory equipment and technical apparatus, and directed attention to particular kinds of genetic information, especially that information having to do with disease resistance. It is therefore not surprising that the first applications of the new technology have come in the general area of medicine and have been based on techniques primarily derived for experimental purposes. But the potential of the new technologies ranges far more widely. The technology of genetic engineering, as one of its historians has put it, has transformed life into a productive force. The scientification of biotechnology has been characterised by a widespread privatisation of knowledge. Institutions such as universities,

normally recognised as repositories of public knowledge, have entered into commercial relationships with industrial enterprises at an unusually early stage in the development of the technology. This may yet pose major problems of access.[2]

Genetic manipulation, or recombinant DNA technology, has also involved the development of a goal-directed and systematic understanding of enzymatic processes, in particular the capacity to stabilise or immobilise enzymes, and utilise them in the manipulation of genetic material. Here again, as the article on enzyme technology in this volume points out, the potential benefits of this new scientific understanding have hardly been grasped. What has been developed is a limited application of this scientific understanding, primarily the production of synthetic insulin, growth hormone, and interferon. Even though the commercial production of enzymes has been viable for several decades, a synthetic – and potentially mass – production was only made possible by the new scientific understanding that emerged in the 1970s. The potential effect of synthetic enzyme production on agriculture and industry could be highly significant. The possibility of replacing natural products in a wide range of areas, from textiles to medicines to food and drink, has come one step closer to realisation because of recent scientific achievements. A major resource of the Third World is its stock of plant genetic material. It has been observed that most of the world's germplasm for major crops is found in the Third World, whereas the scientific, technical and organisational skills needed to exploit this material in novel ways are found in the First World. There is a great danger that the developing countries will find themselves in the unenviable position of buying back at a high price new crop varieties for which they provided the genetic raw materials. There is also the danger, made clear by experiences with the Green Revolution, that traditional varieties will be eliminated by new ones. This so-called genetic erosion will lead to an irrevocable loss of valuable germplasm unless well-organised gene banks, easily accessible to developing countries, are created. Mooney has cogently argued that '... germplasm poses for the South a political problem (germplasm exchange and control): an environmental crisis (genetic erosion): and an economic opportunity (increased breeding and work in new technologies)'.[3]

As the chapter on fermentation well illustrates, however, the taming of biological processes for commercial use is no easy task, and the requirements for advanced scientific understanding are by no means the same for every process. Fermentation techniques have been known and understood for centuries, and utilised in the brewing of beer and the

baking of bread. The contribution of scientific research is, in the case of fermentation, not so much a matter of opening up new possibilities, as of testing and finding ways of controlling new applications. Here it seems more appropriate to speak of a goal-directed technological research into the nature of fermentation techniques, rather than of an increased scientific understanding of microbiological processes.

What has been sought, and largely achieved in the case of the Brazilian alcohol programme, is a capacity to *control* natural processes rather than to create new 'natural' phenomena. The breakthroughs have come in control engineering, in scaling-up and mass-producing, rather than in learning to manipulate structural properties of life. Even here, however, the recent scientific achievements can have an effect on the technological development. The possibility of combining genetic manipulation with fermentation techniques – in the production, for example, of specially designed types of maize for biogas – go far beyond the current range of commercial application. For example, the capacity that the Brazilian industry has already achieved provides an excellent starting-point for further development; it also provides, however, a lesson to other developing countries anxious to follow the example. The headstart, as we learn in Chapter 7, has been won at an enormous cost; the commercial utilisation of biomass for alcohol production rules out other – agricultural – possibilities, it has accentuated the economic hardships of large segments of the Brazilian population, and it has led Brazil into a research-intensive technological race that, to put it mildly, involves a large amount of risk-taking.

In referring to biotechnology, we are thus referring to a heterogeneous body of knowledge; but in each of the three general areas that are discussed in this book, namely genetic engineering, enzyme technology, and fermentation, the influence of scientific research has been significant (even though interest in fermentation has been inspired more by the 'oil crisis' than by a 'science push').

As an innovation, or set of innovations, biotechnologies can be seen as having two distinct kinds of development paths. On the one hand, there is the trajectory of the innovation chain itself, the path from basic science or fundamental invention through systematic application and early development to more specific engineering and advanced development. What characterises the biotechnologies – as indeed all advanced technologies in the 1980s – is the compression of this internal innovation chain; the time from basic discovery to advanced development has grown

shorter and shorter during the postwar period, especially during the past decade. On the other hand, there is the diffusion process, by which innovations are spread into the economy. Biotechnology seems to be an example of a new attempt to integrate these processes.

One important reason why the internal innovation chain has grown so short is that the market has pulled science in general, and biology in particular, to provide new products. Science has been called upon, as never before, to provide solutions to economic and, more broadly, social problems. There has been pressure on scientists to respond to that pull – and, as we are witnessing today, there is investment capital ready to be poured into potentially promising areas of science-based technology.

Thus, even though biotechnology resembles the 'radical technologies' of the past in the way in which it infuses science into the production process, it is more directly socio-economic in its implications at an early stage. Organic chemistry took many years to 'mature' internally before it began to produce commercial products; electrical technology also experienced a certain phase of internal development before the market began to pull. With twentieth century technologies, however – nuclear, electronic, and now microbial technologies – the time allowed for internal maturation has grown progressively shorter. The internal and external processes of direction and control merge into one another. It seems appropriate to refer to a socio-economic innovation chain where the process of diffusing innovations, of spreading them into the economy and assessing their social impact, is integrated with the analysis of the internal technical development. At least, such is the perspective of this volume; our interest is focused on the socio-economic significance of biotechnological development, where both the internal technical – and scientific – aspects are integrated with the diffusion and commercial aspects. It is such a perspective that best answers, we feel, the needs of developing countries to monitor the potential impact of 'new' technologies on development strategies and priorities.

For the developing countries, which, on the whole, are users rather than producers of new technology, it is of central importance to ascertain the time perspective involved in the application of the various biotechniques, as this will largely determine the horizon in which technological and industrial policies must have an effect. In other words, is the race already over or what time period do the developing countries have at their disposal to adjust to this technology? As experience tells us, industrial and technological policies may have a long gestation period

and one may need to wait a decade before significant effects can be seen. In innovation literature, the diffusion of new technologies is often analysed in terms of the product life cycle. The introductory stage involves the first commercial applications of the technology. The technology, in this stage, is largely unproven, and is associated with high risks for users. It is often not standardised, implying that the user needs to supply substantial applied engineering effort for the technology to perform well. The firms that are the first to use a new technology are therefore often very large ones, frequently multinational corporations.

In the growth phase, the technology is diffused rapidly as a consequence of improvements in performance and reliability, as well as in changes in awareness and knowledge of the technology among users. Changing factor prices also influence the adoption rate. In the maturity phase, the technology has reached its full potential in the economy. Often, a decline phase is also included, where the technology loses out in competition with new emerging technologies.

The length of the product life cycle of course varies tremendously between different products; a particular garment can have a cycle of one year, whereas a machine, such as a numerically controlled machine tool, can take 20 years to approach its maturity phase. Alterations in factor prices, for example, can also extend the maturity phase over and above its normal length. In what phase of its life cycle is biotechnology? Since biotechnology, as we have previously noted, encompasses a number of distinct technologies, we need to discuss each technology separately.

Let us begin with genetic engineering. In 1981 there was still no commercial application of a genetically engineered process. Thus, as late as 1981, genetically engineered processes had hardly begun to be marketed. Hence, taking the scheme discussed above, genetic engineering had not yet reached a point which allowed it to be analyzed in these terms. By 1983, an exclusive circle of firms used recombinant-DNA technology on an industrial scale. Often, these applications were in the medical and pharmaceutical field. Whilst the development in the basic technologies is fast, system design and commercial application is slower. The time horizon for the diffusion of genetic engineering processes is thus a long one and, at this point, very difficult to specify.

Enzyme technology has a longer history than genetic engineering. As discussed in Chapter 3, the history of identifying enzymes is over 100 years old, while that of using purified enzymes commercially is over 50 years old. Altogether, there are over 2000 enzymes identified, but only

150 of these are in commercial use. The small share of commercially used enzymes of the total number of enzymes identified suggests that the technology as a whole is still in its infancy, although certain applications are undergoing a period of rapid growth. Thus, out of a total market in the United States for enzymes of some $138 million in 1980 (excluding 77 million dollars for medical and diagnostic applications), around 36% was for enzymes used in the production of high-fructose corn syrup, or isoglucose. Apart from the isoglucose process, the other major use of enzymes in bulk is the use of alkaline protease in detergents. As a whole, therefore, enzyme technology appears to be in the early phases of the life cycle, apart from a limited number of application areas, such as detergents and brewing, and of course isoglucose, whose impact on the world sugar market is analysed in Chapter 5.

Finally, fermentation technology is, as is often pointed out, a very old technology, and, in many of its applications, a mature technology. As we have previously mentioned, the recent interest in fermentation technology is less the consequence of scientific breakthroughs and more the result of changing relative prices. In particular, the rising price of oil has made some products produced by fermentation more competitive. The prime example of such a renewed interest is the ethanol program in Brazil, which is analysed in Chapter 7. Fermentation technology is thus a relatively proven technology that seems more amenable to immediate application in developing countries than the other, more science-based, biotechnologies.

In terms of life cycle terminology, we can say that genetic engineering has barely entered into its first stage of commercialisation; enzyme technology has done so on a large scale only in a limited number of cases; and fermentation technology is in a stage of maturity, although its *relevance* is greatly dependent on relative price changes. As Rousseau points out in Chapter 6, problems associated with diffusion of already proven technologies are far more important, with regard to fermentation, than developing new science-based technical applications. On the whole, the time horizon in which the industrial and technological policies of developing countries must have an effect if they are not to be overrun by the nature of events would seem to be longer than one would expect from all the talk of a revolutionary new technology.

What then are the important issues in respect to industrial and technological policies for enhancing the use of biotechnologies in developing countries? Of primary interest are the resource requirements for

producing or applying the technologies to industrial or agricultural use. Various skill levels of importance in this application process can be identified, such as:

R&D and development of new organisms and enzymes,
system engineering, including scaling-up experience,
capital goods production,
utilisation of the new production process, and
collection and preparation of raw materials.

It is, of course, conceivable that a developing country could master all these levels for a particular application of biotechnology. In a sense, this is what Brazilian industry has managed to accomplish in the ethanol program described in Chapter 7. However, the normal case involves a choice: at which level of skills should a country's industry aim? The choice is partly a matter of comparative costs, but, it is a much more complicated choice than merely deciding whether to produce (parts of) the technology or 'only' to use it.

There may be important links among the different skill levels. In particular, it may not be so easy to distinguish between capabilities to produce the technology and capabilities to use it. The Brazilian case demonstrates how a developing country with a favourable natural resource base can attain a strong competitive position. But it also indicates that a long development of capabilities in the capital goods sector, both in plant production and in seemingly unrelated mechanical areas, was a prerequisite for Brazil to be able to change its comparative advantage as an energy producer. In general, it may well be the case that, given the large number of raw materials to be used in the fermentation of energy products, a local production of capital goods may be a crucial factor in the rapid diffusion of fermentation technology – if not an absolute prerequisite. Of central importance in the capital goods sector is the fact that the design of the fermenter and the downstream engineering functions must be based on the particular raw materials at hand – a standardised fermenter of ethanol, using many types of raw materials, simply does not exist. This is well elaborated on in Chapter 4.

This critical role of the capital goods sector can also be seen in the effective diffusion of enzyme production. In Chapter 3, Towalski and Rothman make the point that the reactor for enzymatic processes needs to be custom designed to suit each particular enzyme and the particular substrate (raw material) used. They write that 'considerable use will need to be made of empirical and experimental data during the design and scaling-up phase.'

This implies not only that reactor procurement has to be on a tailor-made basis, but also that the flow of information between the user and the reactor (capital goods) producer will be of great importance.[4]

For a developing country, with a large potential home market for enzymes, the implication would be that to rely on importing foreign reactors – i.e. buying a whole package – would not only be very expensive but would also risk impeding the flow of information, because of geographical distance and cultural differences.

The role of the capital goods sector in enhancing the rate of diffusion of both fermentation and enzyme technology is further heightened because the main technical problems lie in system design, in particular in the downstream processes, for example in separation.

The choice of skill level is also a function of the accessibility of the various components of the technology. In the case of genetic engineering, Fairtlough discusses the present and probable future structure of the industry in Chapter 2. A number of larger firms in the oil and chemical industries, as well as in the pharmaceutical industry, are integrating backwards to genetic engineering, but there are also a number of specialist companies that work on a contract basis. Fairtlough suggests that a forward integration into some specific applications can be expected from some of these newer firms. To the extent that such an integration does take place, it can be assumed that certain technical information will not reach the market, that is, that the accessibility of the technology will be restricted to developing countries. On the whole, however, a diversified industrial structure is likely to continue to exist; it would thus be possible to approach a specialist firm and ask for a particular application to be developed. An interesting case is the Swedish firm Kabi Vitrum which approached the US genetic engineering firm Genentech and assigned them to produce a human growth hormone. Kabi Vitrum now has 70% of the world production of growth hormones although Genentech has the exclusive sales right in the US and Canada. Indeed, according to Fairtlough, it can be expected that specialised genetic engineering firms will evolve in much the same way as specialised electronics firms have evolved for some application areas, for example numerical controls of machine tools or computerised airline ticket systems. It is of interest here that the entry barrier to genetic engineering appears to be modest. Only £12 million was invested in the UK firm Celltech even though the skill content of the staff is extremely high and diversified.

In the case of enzyme technology, we can be a bit more certain about industrial structure, since the industry has a longer history, and has

progressed further in its product life cycle. As is described in Chapter 3, the two leading countries in the world production of industrial enzymes are Denmark and the Netherlands. In 1979, 80% of all production took place in EEC countries, and 60% of that production was accounted for by two companies. Hence, the concentration in the industry is already high, which in turn is reflected in high barriers to entry. Novo, in Denmark, has 3000 employees, 600 of which are engaged in research and development. According to sources within the firm, it is already too late for an advanced country like Sweden to compete successfully in the industrial production of enzymes. A gestation period of 15 years was suggested for the necessary acquisition of skills and experience.

There seems, however, to be little forward integration; and bulk enzymes are already available on the international market. Furthermore, the leading firm also sells enzymes – immobilised enzymes, for application to a specific raw material, on a contract basis. In terms of the costs of production, the enzymes proper seem to constitute a very small share. For example, in the production of HFCS, the actual enzymes account for between 5 and 10% of the total production costs while the raw material accounts for some 50%. Hence, while the industry is already concentrated and exhibits high barriers to entry, the availability of products seems to be high.

We would therefore argue that, although the questions taken up in this volume need more research before they can be answered conclusively, there is a case for developing countries to emphasise the application side of biotechnology. This seems to be critical for rapid diffusion. The new, science-pushed elements of biotechnology, in particular genetic engineering but also enzymes, seem to be available on the world market from specialised companies. The application of biotechnology involves, however, a large number of skills. These include specialised engineering skills, and also biological and chemical skills. Indeed, it is suggested in Chapter 3 that the successful application of enzyme technology requires a greater amount of chemical engineering than basic science. In general, the application of biotechnology involves mastering system design skills, combining various specialised disciplines in both natural science and engineering. It is these combination capabilities that ought to be fostered in developing countries. Some of these skills do, of course, already exist in a number of developing countries which have built up process industries, and a potentially useful strategy might be for these firms to diversify into biotechnological applications, along the lines of the Brazilian case. It should not be forgotten that biotechnology poses quite unique safety

questions and developing countries will need to establish appropriate legislation, regulations and training. Otherwise, it seems valuable for developing countries to continue to follow the actual progress of biotechnology within the industrialised countries. We hope that the articles in this volume can provide a first glimpse that can – and should – be followed by more intimate acquaintance.

Notes

1 Morehouse W., (ed) (1984). *Third World Panacea or Global Boondoggle. The UN Conference on Science & Technology for Development Revisited.* Research Policy Institute, Lund, Sweden.

2 Yoxen, E. (1981), Life as a Productive Force: Capitalising the Science and Technology of Molecular Biology. In *Science, Technology and the Labour Process*, ed. C. Levidow & B. Young CSE Books, London. See also E. Yoxen, E. (1983) *The Gene Business*, Pan Books, London.

3 Mooney, P. R. (1983). The law of the seed: another development and plant genetic resources, *Development Dialogue*, 1–2 pp 1–173.

4 There is also, according to Novo, an important feedback of information from basic design development and pilot plant production to R&D in the enzyme proper.

2

Genetic engineering – problems and opportunities

G. H. FAIRTLOUGH

Genetic engineering is a subject of great interest but also of some misunderstanding. This chapter tries to explain briefly the technical background, to explore its worldwide industrial impact and to suggest some responses by developing countries to the problems and opportunities which this new technology will bring.

Technical background

Genes and genomes

All life on Earth depends on the information contained in the genetic material which each living organism receives from its progenitors and which each cell in a multicellular organism receives by the process of cell division. This information is in nearly every case contained in molecules of deoxyribonucleic acid (DNA), which are long chains built up from four rather similar sub-units best referred to as bases. The order in which the linear sequence of bases is arranged is the information within the genetic material, in much the same way as the linear sequence of the letters of the alphabet provides the information in a piece of writing. The four bases of DNA are used in a similar way to the 26 letters of the English alphabet or to the two symbols of the binary code in computers.

The information in DNA is read by first transcribing it onto another linear molecule called ribonucleic acid (RNA), which is translated to give yet another linear molecule, a peptide. Unlike DNA and RNA which each use their sequence of four different bases to convey information, the peptide molecules are chains built up from 20 different amino acids. Peptides are usually shorter chains than the DNA chains. Another difference is that the peptides are not primarily information-conveying

molecules, but rather are molecules with a variety of biological functions. When the peptide chain is formed with its sequence of amino acids specified (indirectly) by the sequence of bases in DNA, if it is of sufficient size it then usually folds up into a three-dimensional structure which is a protein molecule. So proteins are larger sized peptides,

Proteins can be of various kinds and they are normally capable of doing some biologically important task. Perhaps the most important of the proteins are enzymes. All enzymes are proteins and all are catalysts which make possible a huge variety of chemical reactions: the reactions which break down or build up the tissue of living organisms and which provide living organisms with their energy. Enzymes also provide the machinery for the transfer of information from DNA to RNA, and the build-up of peptide molecules but, although they do the work, they always need the information derived from DNA or RNA to build the linear molecules in the correct sequence. So DNA can be thought of as being similar to an architect, and enzymes as building workers, the difference being that DNA provides the plans on which building workers are made as well as the plans for the buildings. (However, without enzymes DNA would be useless, just like architects without building workers.)

As we have seen, proteins such as enzymes are built up from chains of amino acids, the sequence of which is specified by a sequence of bases in the DNA. The sequence of bases corresponding to, and coding for, a particular protein is called a gene, and the whole set of genes of an organism, its total genetic content, is called its genome. The genome of an organism is thus made up of one or more very long chains of DNA.

Genetic variation

The information in the genome of a living species makes that species what it is and, not surprisingly, nature has found ways of protecting that information from being lost or being damaged. But, as it is a physical entity, i.e. a set of DNA molecules, the genome must be subject to change, and change in their genomes is the means by which organisms evolve and adapt themselves to new environments. In nature changes in the DNA of the genome can be of two kinds: mutation, which is a chemical deletion or addition of one or more of the bases in the strand of DNA, and interchange of genetic information between organisms, particularly in sexual reproduction.

Of course, the variety within a species to which mutation and interchange of genetic information gives rise is what allows natural selection to operate. Ever since the domestication of animals and plants,