Perspectives of Biotechnology

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In this article the developments of new biotechnology are assessed by putting the high expectations of the early eighties in perspective and elaborating on the prospects of the nineties.

The dreams of the Early Eighties

New biotechnology started in the late seventies when the discoveries of genetic engineering and cell fusion evolved from tools of research to industrial product development and manufacturing. The application of genetic engineering not only on microorganisms but on plants and animals as well, gave the impetus to an unprecedented excitement about a biological revolution of nearly unlimited dimensions. In retrospect three events are characteristic for the optimism about new biotechnology in the early eighties, (i) the DNA gold rush to found New Biotechnological Firms (NBF's), (ii) the projected markets for new products and (iii) the concept of a biological society.

DNA gold rush

The boom of venture capital investments in NBF's over the decade (Fig. 1) reflects the dreams of investors on quick returns by exploitation of unique research ideas from academic enterpreneurs to develop products and that NBF's would emerge as fully integrated and profitable pharmaceutical industries.

Projected markets

The investors' dreams were fueled by optimistic market projections (Fig. 2) indicating that biotech products would reach the market quickly in three successive waves of 7 to 8 years, penetrating major commercial markets of pharmaceuticals, agro-food products and basic chemicals.

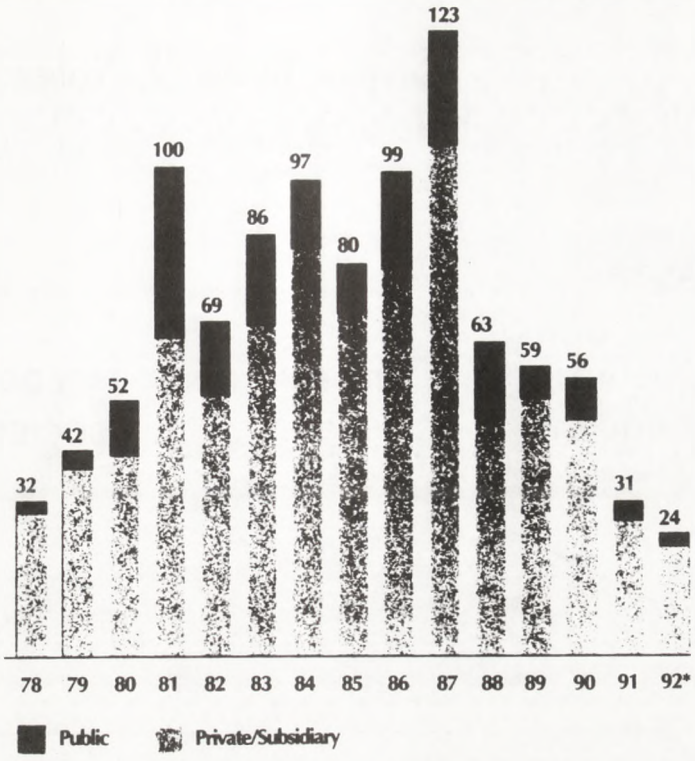

Fig. 1. DNA gold rush: founding of new biotech firms.

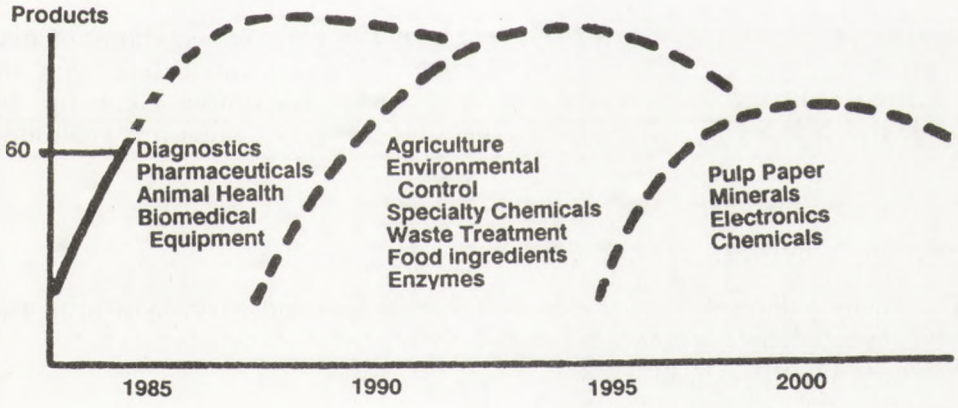

Fig. 2. Projected new biotech markets (A.D. Little, early 1980-s).

Biosociety concept

The concept of a Biological Society was postulated in 1983 by the FAST team of the European Commission (1). It assumed that the pervasive effects of new biotechnology could give rise to a transition of our information society to a biosociety after the turn of the century as visualized in Fig. 3.

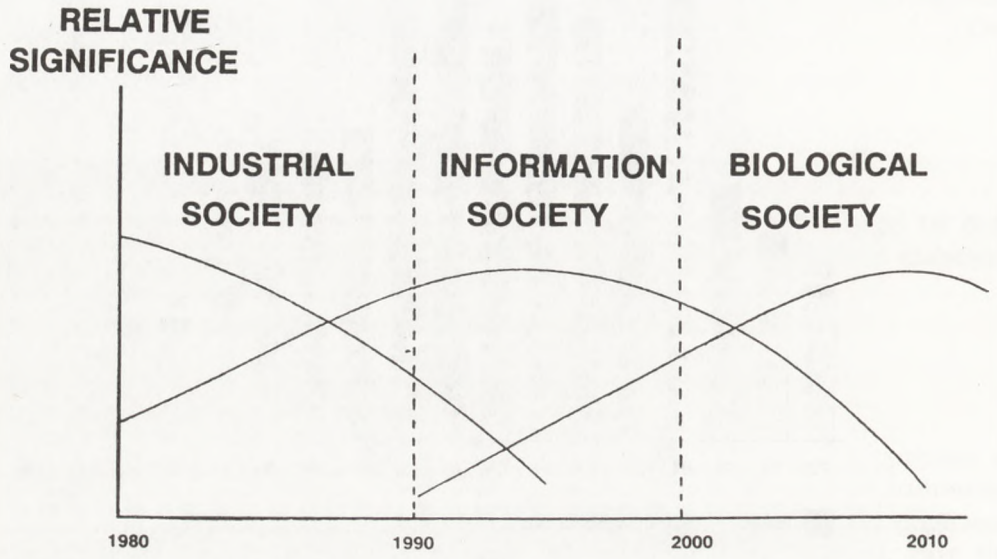

Fig. 3. Biosociety concept (1983).

The balance of the Roaring Eighties

During the eighties it became evident that the early expectations of new biotechnology were unrealistic in most cases. However, much has been accomplished although at a slower pace and new opportunities came up. By striking the balance of these roaring eighties, several issues are evaluated below.

New biotechnology industry (NBF's)

The formidable growth of the "new biotechnology industry" (NBF's) in the USA is reflected by the following data (1992):

*number of NBF's: over 1250
*employment: over 80.000 people
*R&D expenditure: $ 5 billion (1992)
*investment: $ 40 billion

*number of profitable NBF's: 4 to 5
*total loss all NBF's: $ 3.5 (1992).

The estimated number of NBF's in Europe is between 150 and 200 which is modest compared to the USA; no published information about the overall situation of the European NBF's is available as yet. Polastro (2) from A.D. Little recently reviewed the performance of the US biotech industry and concludes: "...while the success stories of NBF's such as Amgen and Genentech are widely published, they represent the exception rather then the rule. The failures greatly outnumber the successes and most probably, on a consolidated basis, biotechnology investments have yet to deliver a positive return". This criticism is in line with an earlier quotation from the "Wallstreet Journal" (1989): "Never has so much attention paid to so many companies that have lost so much money".

New biotechnological products

The first to market new biotech products are depicted in Fig. 4 which shows about equal numbers originating from the USA and Europe. However, all US products are biopharmaceuticals originating from NBF's and about 50% are new chemical entities. The majority of European products are enzymes made by rec. microorganisms and developed by established industries.

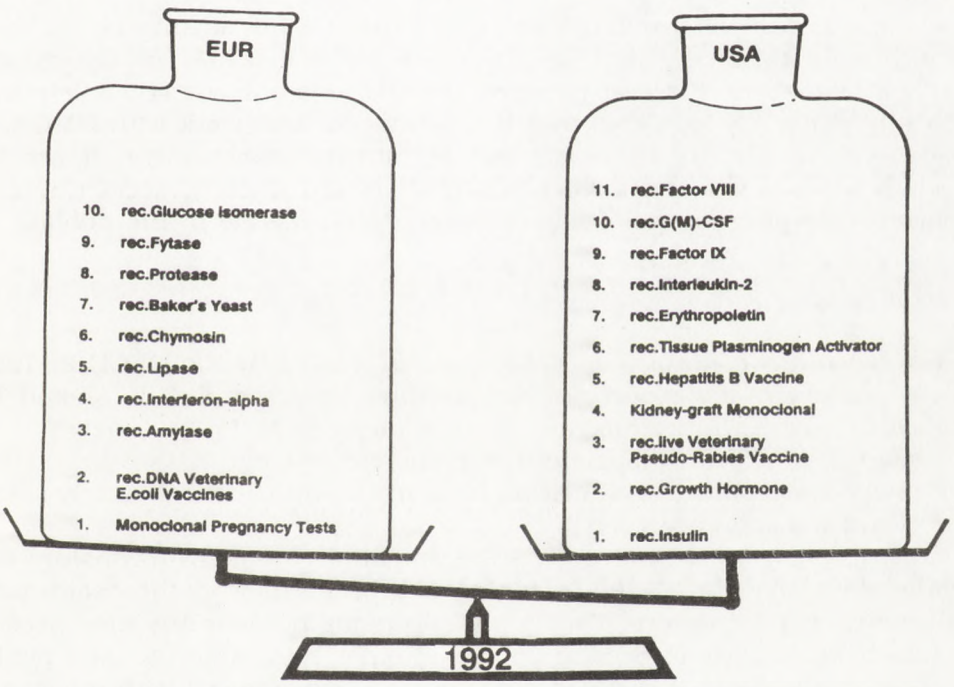

Fig. 4. First to market introductions of new biotech products.

World-wide sales in 1992 of biopharmaceuticals from US, European and Japanese companies account for $ 4.7 billion (4% of the total pharmaceutical market) and two products are selling over $1.0 billion each (human insulin, erythropoietin). It is interesting to compare the situation of today and the early market projections (Fig. 2). The expected first wave of new pharmaceuticals corresponds roughly with the actual number of about 20 biopharmaceuticals and several hundered monoclonal diagnostics. However, the projected second wave was far too optimistic mainly because of delays on market introductions of new agro-food products and environmental applications.

New technologies

In the eighties quite a number of important new technologies based on genetic engineering emerged, such as the polymerase chain reaction (PCR), protein engineering, antibody engineering, transgenesis of monocotyl plants and animals. These are the technology push for new products and processes in the nineties.

Safety

From the early days of the "Berg letter" (1973) and the mortorium on genetic engineering after the Asilomar Conference (1975), no subject has been more heavily debated than the (hypothetical) biohazards of Genetically Modified Organisms (GMO's) for man and the environment (4). Safety has been internationally regulated over the eighties for safe work with GMO's in closed systems and for deliberate release into the environment. It can be concluded that new biotechnology has a safe record since no accidents have occurred. The problem still exists to convey this message to the public.

New biotech, a new megatech?

The biosociety concept (Fig. 3) has been evaluated by the OECD in 1989 (3). In summary, the report states that three basic conditions should be fulfilled to become a mega-technology with major impacts on society:

- Pervasive effects throughout the economic system
- Public acceptance as a driving force in the transition of society
- Environmental acceptability

Although new biotechnology has the potential of a mega-technology the eighties have shown only the beginning of a penetration in the health care and fine chemicals sectors. This is not surprising because the time needed for new biotechnology to become applied in other sectors and to gain public acceptance will take a few decades as has been experienced with other new technologies.

Legislation

During the eighties patents and "Novel Foods" regulation are the prime issues in the field of legislation. The more than 10,000 patent applications causes such work load at the international patent offices, in Europe (EPO), the USA (UPO) and Japan that delays of 6-8 years are expected. Hiring of new and competent staff has the highest priority. To close the gap between patents and plant variety rights (PVR) has been a long lasting process which resulted in 1991 in a revised convention of the International Union for the Protection of New Varieties of Plants which no longer prohibits the availability of both a patent and a PVR (6). However, ratification by the member states is still pending. Patents on transgenic animals have been issued, first in the USA and later also in Europe. This is now under formal opposition by European anti-vivisection and animal rights groups (6).

The regulation of "Novel Foods" is pending for several years in the USA and the EC and successive concepts are still heavily debated.

Public perception

Three issues on public perception of new biotechnology which evolved during the eighties are of prime importance: public understanding, the image and the reliability of information sources. Public understanding of biotechnology is still low as shown by various interviews (4). The image of classical and industrial biotechnology as "green and safe" has changed for new biotechnology to "fearful and threatening" by the negative connotation of genetic engineering. According to surveys in Europe (Eurobarometer, 4) and the USA about the most reliable information sources concerning new biotechnology, consumer and environmental organisations scored highest (over 50%) with religious organisations, industry, trade unions and political organisations scoring very low (below 10%). It should be added that biotech antagonists in various countries are strongly opposing biotechnological applications even before they reach the market. This is illustrated by some examples. In the USA a notable activist is Jeremy Rifkin of the Foundation on Economic Trends who first of all persuaded a number of the largest supermarkets to boycot milk from cows if they would be treated with BST. Then he launched his Pure Food Campaign anticipating the approval of Novel Foods. He managed to get some chains of fashionable restaurants to put stickers on their door, announcing "We don't sell genetically engineered food", before there is any such food to sell. Recently, he opened the fire on the expected market approval of Calgene's "FlavrSavr" tomato with an extended shelf life by blaming these tomatoes as "Frankenstein food". In the meantime Campbell Soup Cy, who financed a great deal of the Calgene tomato project, announced not to use this tomato to avoid the risk of a buyers boycot. In Germany, the Gene Law (1990) was an initiative of the Green Party and is a hurdle for development and investment activities in new biotechnology. Several major companies have moved their R&D and production to the USA.

The Animal Rights movement in The Netherlands is principally opposed to animal transgenesis and launched an aggressive public campaign, including schools, under the title "biotechnology is swindle".

In the public debate, ethical issues are much in vogue. However, people uninitiated in new biotechnology tend to mix up ethical and other aspects such as safety and ending up in an unstructured ethical discussion. As an amateur in public information I have developed a model (Fig. 5) to explain how different societal aspects can be schematically separated from one another. This has proven in practice a useful instrument to show that there is no uncontrolled growth and that ethical concerns relate only to a small minority of applications of genetic modification.

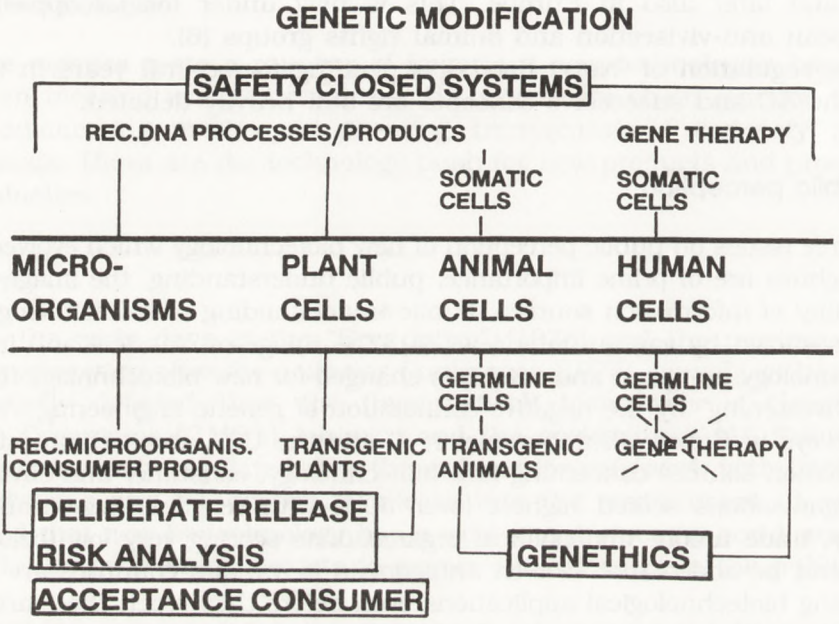

Fig. 5. Societal aspects of genetic modification.

The model in Fig. 5 presents the four types of cells used for genetic modification. The three main societal aspects are shown in frames and relate to:

— *Safety in closed systems*

This work with GMO's in laboratories and (pilot) plants is regulated according to an appropriate risk class and has a safe record. The products (mainly biopharmaceuticals and enzymes) do not contain GMO's and are generally accepted.

— *Deliberate release*

The products contain GMO's (mainly "Novel Foods", transgenic plants and fruits) and case by case analyses of risks for the environment and the con-

sumer are mandatory by international regulations. After approval on objective criteria the subjective acceptance of the consumer is at stake.

— *Genethics*

This term has been borrowed from Suzuki and Knudtson (5). In this model genethics is related to the limited area of transgenic animals; genetic modification of human germ line cells is internationally banned.

The model illustrates that for the majority of new biotechnological developments the safety aspects are of prime importance and these have been regulated world-wide. Ethical issues regard primarily the relatively small field of transgenic animals and ethical criteria are beginning to emerge (e.g. The Dutch law on Health and Welfare of Animals). The main problem area for industry and government is the regulation of "Novel Foods" and the uncertainties about public acceptance of consumer products made by new biotechnology.

Perspectives of the Nineties

The momentum of the eighties is slowing down and biotechnology is back to reality, facing longer but more realistic development time-lines than expected for biopharmaceuticals, transgenic plants and "Novel Foods". The main hurdles for the food industry, traditionally the largest segment of biotechnology, are the absence of international regulations for "Novel Foods" and uncertainties about consumer acceptance. The pharmaceutical industry is confronted by world-wide health care reforms focussing on lower drug prices along with clinical failures of biopharmaceuticals (Centoxin and Myocard from Centocor, Antril from Synergen, Xomen-E5 from Xoma, TNF receptor from Immunex) resulting in a 25% value decrease of NBF's and stiffening of public and private financing in the USA. In the field of environmental biotechnology the perspectives for the use of GMO's are a big question mark mainly because of ecological restrictions. In the chemical industry, biotechnology offers opportunities for fine chemicals only but not for bulk chemical as long as oil prices are low and world-wide production capacity is structurally exceeding the demand. Therefore, pessimists are expecting a malaise for biotechnology in the nineties. However, the future is not all that bleak, there are also rays of hope.

Biopharmaceuticals

Biopharmaceuticals is the fastest growing segment of the pharmaceutical market but they will not displace chemical drugs. With about 150 biopharmaceutical products in clinical trials or in the pipeline of FDA approval among which 11 biotech filings awaiting a final word, market approvals will exceed the one to three per year during the 1980-s. The more so if the efforts of Regulatory Agencies to speed up approval times are coming into effect. A new

perspective is the production of biopharmaceuticals by transgenic animals when this is ethically accepted and proven cost effective. Ethical concerns have become a political issue in The Netherlands in connection with the pilot project of transferrin production in transgenic cattle by Gene Pharming Europe. Transgenesis of animals has recently been regulated by the Dutch law on Health and Welfare of Animals. This law is based on the "no, unless" principle which means that transgenesis experiments are prohibited unless a number of criteria can be met such as no impairment of animal welfare and that the biopharmaceutical product can not be produced by another GMO. It is expected that the EC will develop a similar Directive which will limit this production method to exceptional cases in Europe.

The nineties will see new and more specific synthetic drugs with less or no side effects as a result of the ongoing world-wide research efforts on rational drug design based on recombinant cell receptor models and protein engineering. The market of these drugs will exceed the value of biopharmaceuticals.

Fine chemicals

The fine chemical industry will be further innovated by making available novel enzymes ("synzymes"), designed by protein engineering for specific use as detergents — being thermostable, oxidation resistant etc. — and for robust industrial applications.

Novel Foods

The most important issue for new biotechnology in the nineties is the introduction of transgenic plants and fruits and "Novel Foods", given the enormous market potential of the agro-food sector. The technology push involves some hundreds of products in the pipeline of development although progress is much slower than anticipated in the roaring eighties. The main reasons are the stringent requirements for ecological safety and the still pending criteria of international "Novel Foods" regulations which is partly due to the critical attitudes of consumer and environmental and organisations.

Given this situation, Unilever in The Netherlands has taken a remarkable initiative in 1991 to start a dialogue with representatives of bonafide consumer organisations in an attempt to prevent a clash such as in the case of food irradiation. Because of the credibility of the consumer organisations in the eyes of the consumer, they deserve to get first-hand inside information from industry about "Novel Foods" during the pre-marketing stage. The discussions started on long term biotechnological developments and their consequences for food products which are of vital strategic importance for the continuity of the food industry. Such dialogue based on "sharing dilemma's" resulted in an atmosphere of increased mutual trust. Then issues of product

safety and labelling were extensively discussed resulting in a collaborative market research effort. A "Novel Food" product was presented to consumer panels accompanied by articles from the consumer organisations which contained different levels of criticism on biotechnology. The results showed that the formulations used are extremely important for public acceptance. The discussions are now broadened to a "Dutch Informal Platform Novel Consumer Products" by inclusion of other interest groups such as environmental organisations, some six consumer goods industries (a.o. Gist-brocades, Sarah Lee/Douwe Egberts, Nutricia, dairy and agricultural cooperations) and supermarket leader Albert Hein. In the mean time Unilever is extending the positive experiences of this dialogue model to other European countries as well. Progress in the regulatory arena is the provisional "Novel Foods" regulation of July 1993 in The Netherlands, anticipating the long expected EC Directive. The Dutch regulation requires safety and nutritional criteria per product regardless the production method and voluntary labelling to be negotiated between industry and consumer organisations. The largest consumer organisation voiced already in the press a label proposal for "Novel Foods" in terms as "made by modern (or new) biotechnology".

The eyes of the world are now focussed on how consumers will accept the first transgenic product which is expected on the US market soon, the "FavrSavr" tomato from Calgenene.

Towards a structured ethical discussion

In a recent study commissioned by the Dutch Ministry of Agriculture (7) a framework has been developed for a more structured ethical discussion on new biotechnology. The analysis is based on concepts from the environmental philosophy (8) and refers to attitudes of man in relation to Nature, in a spectrum between the extremes of antropocentrism and ecocentrism.

Four basic attitudes are discerned, the "Ruler", the "Steward", the "Partner" and the "Participant". These are depicted schematically in Fig. 6 and shortly characterised below.

The *Ruler* reigns over Nature and strives to control and to exploit Nature as a supplier of raw materials for human needs. This is the extreme of the antropocentric technocrat whose attitude has been dominant for long in Western culture.

The *Steward* manages Nature on behalf of the "owner" to whom he feels responsible (God or humanity). The "capital" is the natural resources, the "interest" of which may only be utilized. Human interests prevail over vital interests of animals and plants but on the other hand vital interests exceed mere economic benefits.

The *Partner* respects Nature as an ensemble of life forms in a balanced interaction. Nature's own values and interests are of equal importance to those of man.

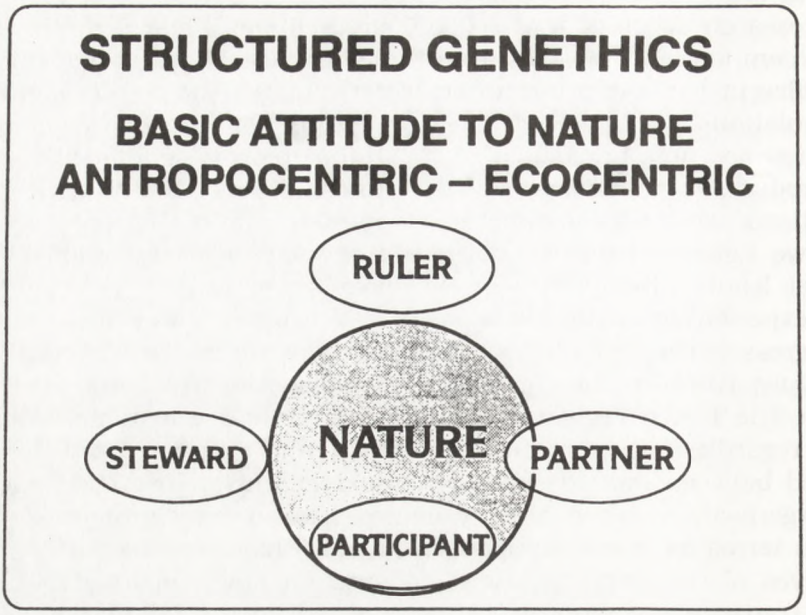

Fig. 6. Basic attitudes to Nature.

The *Participant* is the extreme of the spectrum on the ecocentric side and he views Nature as a totality to which he belongs on the basis of solidarity in a holistic and spiritual sense.

STRUCTURED GENETHICS

GENETIC MODIFICATION	BASIC ATTITUDE TO NATURE			
	RULER	STEWARD	PARTNER	PARTICIPANT
TRANSGENIC ANIMALS	YES	YES, PROVIDED	NO, UNLESS	NO
TRANSGENIC PLANTS				
. DISEASE RESISTENT	YES	YES	YES, PROVIDED	NO, UNLESS
. HERBICID RESISTENT	YES	YES	NO, UNLESS	NO

Fig. 7. Examples of preliminary ethical evaluations on critical issues of new biotechnology.

In the report some attempts have been made to evaluate ethical consequences of a number of new biotechnology applications towards the view points of the four basic attitudes. Three examples are presented in Fig. 7.

The meaning of the terms "yes, provided" and "no, unless" as used in Fig. 7 needs further explanation because this terminology has a legal background. "Yes, provided" stands for an ethically accepted procedure provided opponents do not bring up new convincing arguments against. The burden of proof rests with the opponent. "No, unless" concerns procedures which have been rejected on ethical criteria unless the proponent can get exemption by proving that his proposal does not violate the criteria. In such case, the burden of proof rests with the proponent.

The final report does not give an opinion on the ethical value of the different basic attitudes. However, a preliminary conclusion is that political consensus in W. Europe vis-a-vis ecological and new biotechnology options has moved away from a "ruler" position to one of stewardship if not to a partnership attitude. The fundamental approach of this study to structure ethical discussions on new biotechnology has been an eye-opener to me. I hope that colleagues who are involved in better understanding of public perception on their professional activities, will be inspired as well.

Conclusion

The prospects of new biotechnology in the nineties depend for a great deal on the market pull of "Novel Foods", transgenic plants and fruits, implying public acceptance. The role of the biotechnological profession is to gain public accountability for which an effective model has been developed in Denmark, already in the late eighties (9).

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Perspektywy biotechnologii

Streszczenie

Autor przedstawia problematykę dotyczącą rozwoju nowoczesnej biotechnologii w perspektywie do roku 2000.

Wiele miejsca poświęca analizie rynku zbytu produktów biotechnologicznych w aspektach: wartości finansowych, prawnych, bezpieczeństwa oraz odbioru społecznego.

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biotechnology, industry, market, perspectives.

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