Basic Life Sciences and Human Society

Proceedings of the 10th DISCOVERIES Symposium 1991

Alexander von Humboldt Foundation

Basic Life Sciences and Human Society

Basic Life Sciences and Human Society

Proceedings of the 10th DISCOVERIES Symposium 1991

Alexander von Humboldt Foundation

This book is based on papers
given at a Symposium organized in
Bonn in June 1991 by the Alexander
von Humboldt Foundation in the DISCOVERIES
series sponsored by the Honda Foundation.

Jean-Paul-Str. 12
D-5300 Bonn 2

Editors: Heinrich Pfeiffer, Thomas Schmidt-Dörr

Layout: Papyrus – Schreib- und Büroservice, Bonn
Printed by Druckpartner Moser GmbH, 5308 Rheinbach

FOREWORD

10th International DISCOVERIES Symposium of the Honda Foundation June 1991

The Tenth International DISCOVERIES Symposium of the Honda Foundation, Tokyo, was held in June 1991 in cooperation with the Alexander von Humboldt Foundation in Bonn, Germany. Fifty scientists from different disciplines (molecular biology, genetics, biochemistry, medicine, philosophy, law) as well as representatives from industrial, chemical and pharmaceutical laboratories from 12 nations reported on their new findings and experiences. This interdisciplinary and international approach of scientists brought new insights and new questions, thereby showing trends for the ongoing development in the biosciences.

The outstanding success of the life sciences at the end of this century was clearly demonstrated by the interchange of many disciplines, where mathematicians, physicists, chemists, engineers together contributed to the success of life sciences.

Always, when progress in science is recorded – and certainly the life sciences contribute to the well-being of mankind and nature – expectations on the one and fears on the other side are expressed by scholars and the public. All of us have to be aware of those developments as well as obstacles, but best qualified scientists know from history that this experience is as old as mankind.

It is safe to say that the achievements to be expected of life sciences in the years to come may deliver more findings as a base to diminish sickness for mankind and disturbing and destroying developments in nature. There is, however, still a long way to go, and any support for research in this field on an international scale should be given high priority.

The publication of the 10th International DISCOVERIES Symposium held jointly in Bonn by the Honda Foundation, Tokyo, and the Alexander von Humboldt Foundation, Bonn, is now at our hand. The statements made by the Prime Minister of Japan, Toshiki Kaifu, and the Chancellor of the Federal Republic of Germany, Dr. Helmut Kohl, are included at the beginning of the proceedings. Thereafter most of the lectures held at the symposium follow.

The organizers of the conference consciously did not record the very fruitful and stimulation discussions following these lectures.

It has been a great pleasure for the Alexander von Humboldt Foundation to organize the present symposium upon request and with financial support of the Honda Foundation. The participants of the symposium had the honour to meet one of the two founders, the 84 years old Soichiro Honda at this conference, a most impressing personality, who after World War II founded the Honda Motor

Company and thereafter established, together with his brother Benjiro Honda, the Honda Foundation in 1977. Unfortunately, Soichiro Honda will not be receiving the present proceedings since he passed away only a few weeks after the symposium, closing a successful life as an inventor, industrialist and maecenas of the sciences and culture.

The Honda Foundation was established in 1977 in Tokyo. The main task of the foundation is to promote science and technology for the well-being of the human society, improvement of its environment and nature. To reach this goal, the Honda Foundation sponsors research and conferences in the broad field of eco-technology on an international, interdisciplinary scale:

- by organizing the international DISCOVERIES Symposia of scholars and specialists from all over the world for realization of eco-technology;
- by awarding a Honda Prize annually since 1980 to a personality or an organization (open for all nationalities) for outstanding contributions in the field of eco-technology; and,
- by sponsoring international seminars and thereby propagating and promoting the understanding of culture and technology as well as their interdependence.

The word "DISCOVERIES" is, besides being the plural of the word "Discovery", an AKRONYM for "Definition and Identification Studies on Conveyance of Values, Effects and Risks Inherent in Environmental Synthesis".

On behalf of the participants of this "DISCOVERIES Symposium", on behalf of the Alexander von Humboldt Foundation and on behalf of the science community I would like to thank the Honda Foundation for the initiative taken and for the implementation of this symposium.

Professor Dr. Reimar Lüst August 1992

CONTENTS

OPENING SESSION

Chairman: Benno Hess

Address by the President of the Honda Foundation, Tokyo, Takeso Shimoda, to the Participants in the 10th DISCOVERIES Symposium

It has been our firm belief that the greatest desire of mankind at the present time should be the creation of a civilization in which utmost respect is paid to the human beings themselves. We believe also that this goal can only be achieved through inter-disciplinary cooperation of the many intellectuals belonging to various fields, especially those engaged in the field of science and technology. Based on this concept, the Honda Foundation has sponsored the "Discoveries International Symposia" and this symposium has gathered since 1976 the world's leading intellectuals, first in Tokyo, next in Rome, then in Paris, Stockholm, Columbus, Ohio, London, Melbourne, Brussels, and Vienna. This year we are very pleased to be able to attend the first Discoveries Symposium to be ever held here in Bonn, capital of this newly re-united Germany.

I am also very much pleased to notice here again the presence of distinguished leaders of past Discoveries Symposia including among others Prof. Eduardo Caianiello, Prof. Jean-Claude Simon, Prof. Hess, and Prof. H. J. J. Nijkamp. We are also very pleased to welcome for the first time in the history of Discoveries International Symposia the participation of a leading Soviet scholar, Dr. Juri Gleba of Kiev.

Ladies and gentlemen, it is true that the modern society has achieved greater prosperity than ever thanks to sustained high economic growth, which has been made possible through a rush of technological innovations in the field of production and other areas of human activities.

This achievement made at a very fast pace, has had also negative effects on human life, such as environmental destructions and other hazards plus a number of other deeply rooted complex issues.

In the past Discoveries Symposia, we have thus far attempted to deepen our awareness of the potential catastrophe lying within our civilization and have addressed ourselves to the comprehensive study of information and communication. Past symposia have taken up such themes as a social impact of advanced technology, Columbus; social and cultural technology, London; the use of resources and technology in the interest of mankind, Melbourne; roles of nature and human conduct, Brussels; complexities of the human environment, Vienna. The participants of the present symposium are to discuss the issue of "basic life sciences and human society", a very interesting theme, which in the same time is very important for the future of mankind.

Let me promise that, based on those visions and conclusions of the discussion to be given at this symposium, the Honda Foundation intends to further the idea of the creation of civilization which contributes really towards promotion of human happiness and welfare.

We are very grateful, Prof. Reimar Lüst, Honorary Chairman of the Organizing Committee and President of Alexander von Humboldt Foundation and Dr. Heinrich Pfeiffer, Organizing Secretary of the Committee and Managing Member of the Board of Trustees of the Alexander von Humboldt Foundation, who together with other members of the Foundation have taken their leading initiative in the preparation and convening of this important symposium.

Address by the Prime Minister of Japan, Toshiki Kaifu, to the Participants in the 10th DISCOVERIES Symposium

I would like to express my best wishes for the "Discoveries International Symposium 1991".

To my knowledge, this is the tenth "Discoveries International Symposium" that takes place. In the past, numerous leading experts and decision makers from many countries participated in the symposium and discussed intensely, from a global point of view, the "organisation of a philosophy in a technological culture".

This time leading experts from science and technology have come together here in the unified Germany in order to discuss the very important topic of "Basic Life Sciences and Human Society". I am convinced that you will elaborate valuable guidelines in an open and frank discussion that may be of considerable use on our way into the 21st century regarding the organisation of a culture of dignity of man.

I wish the "Discoveries International Symposium 1991" much success and hope that the "Discovery"-activities will make further progress in future.

Tokyo, June 24, 1991

Toshiki Kaifu
Prime Minister of Japan

Address by the Federal Chancellor of Germany, Helmut Kohl, to the Participants in the 10th DISCOVERIES Symposium

I would like to extend a cordial welcome to the participants in the 10th Discoveries Symposium "Basic Life Sciences and Human Society". I am pleased that Germany has been chosen to host the 10th in this series of symposiums, which have gained high international recognition.

I also wish to pay tribute to the Honda Foundation, which is providing generous support for this event, as well as to the German organizers of this symposium, the Alexander von Humboldt Foundation. By virtue of its mandate, it is particularly committed to promoting international scientific exchange. At the same time, it can look back on a tradition of almost 100 years in its relations with Japan.

Just like all previous Discoveries Symposiums, the event which commences today is characterized by its interdisciplinary nature and international orientation. The disciplines represented here range from the arts and natural sciences to engineering and social sciences, as well as medicine.

The theme of the Symposium — modern life sciences and their impact on human society — concerns not only scientists engaged in this field. Understandably, it is also of great interest to the general public. Research and technology are affecting our lives in an unprecedented fashion. Progress made in the basic life sciences, in particular, touches the very foundations of human existence. It is not only a question of what we are capable of achieving, but also of what we may do from an ethical point of view.

We must courageously strive for progress in order to safeguard humanity's basis for existence and do everything in our power to overcome poverty and disease. However, we must also learn to accept limits. It is not enough to merely base our actions on the respective laws and regulations. What we need is a broad ethical consensus. With this in mind, I wish the Symposium every success.

Bonn, June 24, 1991

Helmut Kohl
Federal Chancellor of the Federal Republic of Germany

Basic Life Sciences and Human Society — Fundamental Considerations

Mutsuo Michael Yanase, Life Science Institute,
Sophia University, Tokyo, Japan

"I am very honoured to be able to participate in this very important symposium on basic life sciences and human society and make a speech at the beginning of this symposium.

I would like to make some observations on this theme of the symposium from a more fundamental point of view.

First, I would like to use the word 'ecological' in a wider sense. That is, not only from global but also extended to cosmological as well as microscopic dimensions.

Second, I would like to express some opinions, not only on a scientific level, but also on a meta scientific or philosophical level.

The personal reason why I would like to have this stand-point is the following: I am not a professional life scientist but I was trained first as a physicist, then as a philosopher and also as a theologian. I have always been interested in the fundamental problems of natural science in general, but during the last ten years in biological or life sciences in particular.

Hence, if I could make a speech, the proper thing for me to do would be to talk as a generalist with this background rather than as a specialist.

With this viewpoint in mind, I would like to consider the following three points:

First: the object of the life sciences, which is 'life'.

Second: the methodology of the life sciences.

Third: the teleology of life sciences.

The Object of the Life Sciences, which is 'Life'

The word 'life' is used in our daily conversations with a common understanding. This is evident if we consider that if someone is talking, using the word 'life', then it is understood by others in daily conversations what it means. We do not need to interpret or define more exactly the meaning of this word.

However, as St. Augustine wrote about a conception of time some 1,500 years ago, when we do not reflect on the meaning of 'time', we think that we understand the meaning of time, but if we are asked, what is time?, then we notice that we do not know the meaning of it.

Likewise, if we do not reflect on the meaning of the word 'life', we think that we know what life means. But if we want to make an exact definition of life for the scientific study of the phenomenon of life, then it is not so simple to do it.

For example, in the Japanese language, we have at least three different words corresponding to the English word 'life', or *vita* in Latin, even in daily life.

The first is *seikatsu*, which means daily life.

The second word is *seimei*, which means the phenomena of living systems or actions or functions of living systems in general.

The third word *inochi* is also used for a wider and more essential sense of life.

Of course, in this symposium, the meaning of 'life' is not the same as that of *seikatsu*, namely daily life, but *seimei*, namely phenomena of living systems including their functions, constructions and all their actions.

However, it should also be used in the sense of *inochi*, so that we can have a more fundamental and wider horizon of the concept 'life'.

With this understanding in mind, I will move on to the second point of my talk, namely on the methodology of life sciences.

The Methodology of the Life Sciences

It is also a common understanding of academic society that when we do life sciences, we make a distinction between living systems and non-living systems. Of course, this statement is tautological because we are using the word 'living' and 'non-living' as verbal progressives of the word 'life', if we stick to the second meaning of the word 'life' in the sense of *seimei* in Japanese. However, in the context of this symposium, as mentioned before, we use the word 'life' in the sense of Japanese *inochi*, which has a wider and deeper sense than the second one, so that we can avoid the complication of a tautological use of this word.

Now I would like to make some points on this distinction between living and non-living systems.

First, every material entity in the universe follows laws of physics without exception, including living systems. This is a rather firmly established statement of science in general and of physics in particular.

When we do physics, we use a more or less established methodology of induction and deduction as well as proper use of mathematics. As a result of tremendous intellectual efforts of many physicists using this methodology we have found rather unified, well ordered picture of the universe.

Starting from elementary particles, extending to the end of the universe of 15 billion light years in space dimensions and 13 to 15 billion years of time dimension, we do not think there is any exception or deviation from the physical laws which govern this whole universe and control every single material entity in this universe.

All the phenomena of living systems can also be described by physical laws, because all the living systems are part of the entire universe and every part of the living systems is composed of elementary particles and follows physical laws, without exception. One important point in this context is that phenomena of living systems are found, so far, in an extremely limited area of the whole universe, namely only on our planet, the earth.

However, it is not possible to identify various characteristics of living systems by the laws of physics only.

In our daily conversations, we have some common understanding of various phenomena of living systems which we recognize as defects or deviations from the proper functions or states of living systems such as 'disease', 'sudden death', 'deformity'.

On the other hand, we know that all these phenomena of living systems follow physical laws, precisely because they are all composed of elementary particles. As long as we describe these phenomena or states by physical laws, there is no defect nor deviation from the physical laws. Still, we cannot deny that these phenomena or states 'are' defects of deviations from these systems, if we consider these systems as 'living' ones.

Moreover, there exists a special field of science, or art, from ancient times, called medical science or art, to 'cure' these defects or deviations. It means what medical doctors are doing is to try to correct the functions or states from defects or deviations.

These are the most significant features of the living systems, which are not found in non-living, natural systems.

Now we can ask the reason for this difference between these two kinds of systems. Again we have a common understanding among ourselves that the reason can be found in two specific characters of living systems, namely the holistic character and teleology of living systems.

It is rather well known that already in ancient Greece there were philosophical discussions on this problem. To clarify the point, Aristotle, for example, argued for artificial, mechanical systems which have similar characteristics to living systems.

Take a watch, for example. It clearly has a holistic character, i.e. it has a specific function of a system as a whole, and parts of a watch only have meaning as long as they are incorporated to the total system as a part. A watch has an evident purpose to tell the time, which is clearly a teleological function.

Still it is a mechanical, non-living system. The decisive difference is that according to their discussion, apart from the lack of characteristic functions like self-reproduction, the teleology is put artificially from outside, from a human being, in order to know the time. This kind of teleology is called external teleology. We can specify, in a generic way, who is responsible for the input of this teleology, namely, a human being.

Then, what about the teleology or finality of living systems? It is almost evident that living systems have finality, but this teleology apparently is not put by a human being, but something else, or otherwise it is put internally. Again it

is a common understanding among biologists, it seems to me, that this internal teleology is expressed by the essential characteristics of living systems as conservation of the individual and conservation of a species as a whole. To avoid the use of the concept of internal teleology it is called 'instinct'.

The methodology of the life sciences, which corresponds to these characteristics of living systems, is and must be different from that of physics, which deals with non-living systems. From a physicist's point of view, this problem of methodology is extremely attractive and fascinating. As far as I understand, we have not yet found a proper methodology especially to cope with peculiar phenomena of living systems, but I expect that various approaches by excellent scholars will soon make a decisive breakthrough.

I would like to make one remark in this context. It is most useful and even necessary to use the concept of teleology or finality in living systems, if we want to deal with the problems of life sciences, not as an independent group of problems, but as those related to the human society.

Now, it is proper to go over to the third point of my talk, namely the teleology of life science.

The Teleology of the Life Sciences

The reason why we put the emphasis of this element of teleology or finality is the following. In order to discuss human welfare in a global dimension, it is natural to give a teleological consideration, not only for individuals but also for global human society, because it is almost evident that every human being has the freedom to behave with finality, aiming at his or her purposes.

This is the characteristic of human society and human individuals. Therefore, if we want to discuss the life sciences and human society, we cannot neglect the vital element of teleology in this problem complex.

Now, the concept of teleology evidently has an element of value. (Not just in the category of existence). Therefore, if we want to discuss sincerely the basic life sciences and human society, we should have a clear value system to cope with this problem complex.

Value systems cannot be discussed within the natural sciences only. Meta-scientific and philosophical considerations are evidently necessary. This is a point which I wanted to make at the beginning of this talk, although we do not need to go into the meta-scientific or philosophical level in so far as we discuss individual problems of life sciences. It is sufficient to discuss these problems within the lines of the pure scientific level. However, it is vitally important to have this horizon of teleology in the global dimension.

In order to carry out discussions on this level, namely between science and technology as well as the ecological structure of our globe, an eco-technological approach has been proposed and investigated by foregoing Discoveries Symposia in the last decade. This eco-technological discussion started more than ten years ago.

It was a time when the global environmental problems both from the ecological and technological point of view were not so much discussed.

I think this was a very farsighted scope of this Discoveries Symposium. It is the programme not only for scientists but for all human society to deal and discuss with deeper and fundamental considerations of a meta-scientific or philosophical, maybe also from a theological point of view. Because, otherwise, we will never arrive at a clear insight of this most important and urgent problem complex imposed on us all.

I will stop my talk at this point. Thank you for your attention."

Impact of Biology on Human Society — A Critical Analysis

Prof. Ernst-L. Winnacker, Centre of Gene Technology, University of Munich, Germany

"The impact of biology in general and of genetics in particular on human society has, of course, never been negligible. Let us look at some examples:

Canonical law has forbidden consanguineous marriages for centuries and still requires Diocesan dispensation as a prerequisite for marriages between first cousins. Charles Darwin himself, after having fathered ten children with his cousin Emma Wedgewood, was so worried about the prospect of an impending biological disaster that he tried — without success — to include a question concerning the effects of first cousin marriages on the 1871 census for Britain and Ireland.

Some hundred years earlier the Prussian king Frederick William I — the so-called 'soldier king' — was interested in establishing for himself and for Prussia a guard of tall soldiers. Realising that this might be accomplished in the same successful way as his farmers produced outstanding crops of sugar beets and rye, he decreed that tall young men had to marry women of corresponding height. The experiment did not work out very well, as one would assume and of course, understand today. Whether this failure was reason for the lack of support from the king for the Prussian Academy of Sciences, founded under the reign of his predecessor by G.W. Leibniz, remains unknown.

More significant would be a jump to the year 1904 when on August 12 of that year the long expected son and Tsarevitch Alexis was born after four daughters to Tsar Nicholaus II and his wife, the Empress Alexandra. Unfortunately, it took only several weeks for this young and cherished boy to develop mysterious bumps and hemorrhages under his skin and within his joints. Although no one was ready to accept the diagnosis he had, of course, succumbed to hemophilia, a genetic disorder inherited from his great-grandmother Queen Victoria, who had transferred this disease through her daughters to the royal families of Spain, Prussia and Russia. Since there was no remedy at the time for the 'royal disease' and since a factor VIII substitution therapy had not yet been developed, the family sought advice from many unusual sources including the Siberian 'monk' Gregory Rasputin. It is, in general, a vain effort in history to ask the question of 'what had happened if', but there is little doubt that the course of history of our century, and not only that of the house of Romanow, had been different if this disease could have been treated properly.

A final example leads us into the year 1969, when Arthur Jensen, Harvard Professor of Sociology, wrote his notorious article in the Harvard Educational

Review with the title 'How much can we boost IQ and scholastic achievement?' In this article he contended and maintained that black children are genetically inferior to white children as to a variety of cognitive parameters including intelligence and that there are thus genetic limitations to their achievements. This conclusion not only stirred up controversy within the scientific community, but led to serious social conflicts in addition to the tensions already created and sparked by the Vietnam war protests in the hot summer of 1968.

Apart from the scientific flaws and pitfalls within his findings and conclusions, it is interesting to note that Jensen got criticized for his statements most profoundly by the same conspiracy of theologians, legal scholars and social scientists that now, 23 years later, has come around 180° to attribute most of the serious problems in this world, from the vanishing rain forest to the cholera in Peru, to the power of the gene.

How did this turn in opinion come about? Why did it happen that biology in general and genetics in particular are suddenly at the centre of discussion and have become a focus of broad dissent, the object of serious and outright suspicion, when only 20 years earlier any reference to genetics in this field was equally unacceptable?

The answer in a certain sense is very simple: to paraphrase Charles Dickens 'Ours is at once the best of times and the worst of times' for biology. It is the best of times, because never before has biology experienced such a bonanza as today. Wherever or whenever one asks and digs, a strike is inevitable. Biology has finally achieved what physics and chemistry already managed to do in the early parts of the 18th century, namely to leave the somewhat dusty aura of a purely descriptive science in order to become synthetic. Thanks to the revolution brought about by our understanding of the nature of the genetic material and our possibilities of isolating and expressing it in any living organism, it is now laboratory practice to synthesize genes, to introduce any possible mutations into proteins and to create proteins with novel properties, properties adapted to almost any technical challenge and problem.

And it is only beginning. Who would have predicted only ten years ago that we can buy recombinant human insulin in any drugstore around the world and that a whole industry would be built on these observations. A serious economic forecast by Frost & Sullivan predicts sales of pharmaceutical products based on recombinant DNA technology to rise by 300% to 4.3 billion dollar between 1989 and 1994. Who would have dared to think that RNA molecules have enzymatic activities, that a complex virus such as the AIDS virus could be identified and characterized only four or five years after the discovery of the disease, that antibodies can be made to behave like enzymes, that genes have been and are being identified which are responsible for the most common forms of cancer, breast- and colon cancer and for a variety of genetic disorders; that cloning in living organisms just for the sake of amplification of a piece of DNA can be circumvented and replaced by *in vitro* methods, the PCR reaction, that the genetic information of an entire chromosome of a living organism, in this case

baker's yeast, would be known basepair by basepair. This enumeration could go on forever and will be discussed in detail during the forthcoming sessions.

On the other side, this tremendous progress is paid for and met by mounting criticism and uneasiness from the general public? It is not only that 'Greens are against genes' or that a colleague calls ours the 'age of scientists as murderers' or that laboratories working in the field are being physically attacked and have to build fences around their buildings to protect their experiments; more important, legislation regulating the field of biotechnology in many countries including the entire EC not only threatens the biotechnology industry, but the pursuit of science as well.

Why did it really happen? There are of course some easy, too easy answers to this question, relating to the fact that novel developments in science have always met with criticism. 'For in much wisdom', says the preacher, 'is much grief and he that increases knowledge increases sorrow!'

Henry-David Thoreau, the Guru of the flower-power movement of the late sixties, already suggested a solution in his 'Walden' when he wrote: 'Most of the luxuries, and many of the so-called comforts of life are not only not indispensable, but positive hindrances to the elevation of mankind' and withdrew into a life as a monk on the shores of Walden pond.

Not only is his advice difficult to follow today, as Henry Kissinger would have put it: 'I have been poor, I have been rich; rich is better'; his objections are much too broad, too unspecific and much too general, while the current controversy about the 'New Biology' suggests that there is something very special about it. As it were, I think, there is.

A growing body of people seems to think that the 'New Biology' is getting close or reaching towards the core of life itself, hereby intruding into their privacy and a variety of personal matters close to their heart. Here, at the core of life, biotechnology meets with ethics. Here it is, where moral conflicts can readily arise over scientific questions and where the endless and often deliberate confusion of recombinant DNA technologies with reproductive technologies finds its breeding grounds. The recent excitement concerning a gene for maleness is a good example. Even well-wishing people, who normally would not criticize our field, regarded this discovery as quite ominous. Although it dealt only with a short stretch on the Y-chromosome, whose activity can act as an early switch in human embryonic development, leading to a mere directional decision for a male or a female organism, this discovery was understood or perceived as something which can be achieved readily on grown-up people and is thus well in line with a reductionist view of life which appears much too simplistic and superficial. The experiment confirmed the worst suspicion for many, namely that man may soon meet the same fate as the giant mouse, transgenic for the human growth hormone gene, depicted not only on the covers of 'Nature' and 'Science', but also of many daily papers.

These and other experiences teach us that people have and must have highly prejudiced ideas about the progress of sciences which are quite understandable. There are many reasons for this. People, for example, for lack of experience

have lost their ability to deal with living organisms other than themselves. 'There was a time', to quote Teilhard de Chardin, 'when this planet appeared much bigger. But the human flood has covered everything; the earth is encircled irrevocably by the human mind'. Wherever he looks, man indeed sees only other men. Animals are left to the zoos, let alone microorganisms. Who knows and realises that there are more microorganisms within a human body than body cells, that 90% of all the weight of life on this earth is made up by microorganisms within the upper 50 cm of the soil, that bakers's yeast lives and divides well in every glass of beer we drink. Even the pathogenic microorganisms have been forgotten. How could we otherwise explain that even the most basic hygienic principles are constantly being disregarded when people deal with diseases like syphilis and AIDS.

Unfortunately some relics of an impending threat from rapidly expanding Andromeda strains seem to be left over in the heads of some of our more fundamental critics, just enough to envisage here the greatest possible accident of recombinant DNA technology, thereby ignoring the existence of the one species already spread in astronomical numbers around this globe, *homo sapiens* himself. Such scenarios leave enough to think and to ponder in even the well- and open minded. In addition to this, people have not forgotten the Bhopals, Basels, Sevesos and Chernobyls, and finally they have had their individual, their personal disappointments with the course of science, disappointments which arise out of a tendency of the scientific community to raise undue expectations in public, expectations which are only conjectural, which can never be met or which can only be met in a far too distant future. Thirty years ago, in the Nixon years, we initiated an all-out war against cancer, for not much avail. It is only now that we realize that we looked into the wrong direction and that we started this programme much too early, prior to even having developed the tools for genetic analysis which now are beginning to bear fruits in the field. The interferons are another example. Discovered in the late fifties, their cloning late in 1979 developed into a media and money event. Even sober scientific journals like 'Science' got carried away with headlines like 'Cloning gold rush turns basic biology into big business — cloning a gene can help you raise 50 million dollars'. Interferons were called *the* magic bullets in the fight against cancer, as the ultimate weapons which, of course, they never were. Now, that the dust has settled, they remain valuable drugs both in the cancer and the virus field.

We also have a tendency to use vocabulary which rates scientific endeavour too close to God or the Creator. However, it has to be made clear that the replacement of an amino acid in a protein, as it is a common procedure in 'protein engineering' or even the design of a novel enzyme catalyst, is not an act of creation and has nothing to do with a 'redesign of life'. Such misconceptions have been dangerous in the past. In his play 'Galileo', Bertolt Brecht lets Sagredo, Galileo's confessor and friend, ask the following question: Where is God in your system of the universe? A question to which Galileo answers: Within ourselves — or nowhere. Sagredo: Ten years ago a man was burned at the stakes for saying just that. Galileo replies: Giordano Bruno was an idiot, he

spoke too soon. He would never have been condemned if he had backed up what he said with proof. So, let us continue to speculate, but not to oversell.

The question remains, of course, how we should proceed from here? Can we actually and can we ever achieve some degree of public acceptance for our work, public confidence, without which financial support will eventually dry out and without which the enormous potential of the New Biology, as we see it, will never be realized?

An answer to this challenging and critical question may be the quest for an honest and open dialogue with the public, a dialogue which does not know 'masters and slaves', but equal partners within a complex modern society who recognize each others' interest and who realize that they are all dependent on each other. Such a dialogue will only be achieved if two prerequisites are met, a common and minimal basis of knowledge on one side and a certain sensitivity to public concerns, an open ear for broader aspects touched off by scientific matters, on the other side.

It may seem unrealistic on a first glance to ask and strive for more literacy in biology, not to speak about DNA literacy, in a time in which the gap between technological advances and public understanding is widening more rapidly than ever before. My optimism that nevertheless we may have a chance to stop if not to reverse this development stems from a number of experiences which I had in the recent past. We have, for example, initiated a DNA learning programme for high-school teachers at our Centre for recombinant DNA technology in Munich. We are doing less well than the 'DNA learning Center' in Huntington, N.Y., which evolved out of the Cold Spring Harbor Laboratory, but nevertheless have probably reached almost every biology teacher in Bavaria so far — and will continue to do so.

Between 1984 and 1987 I was a member of an Enquete Commission of the German Lower House which was established to analyse prospects and risks of recombinant DNA technology. The commission consisted of 17 members with only two molecular biologists among them. You may not be surprised to hear that in the beginning most of the other members, which included lawyers, social scientists, theologians and administrators, were deeply convinced that all the New Biology was something quite dangerous and immoral and should thus be severely restricted and controlled. The final outcome was quite different. With constant, patient and ever repeating explanations it was eventually possible to establish a mood of confidence and to convince almost everybody that sweeping and far-reaching judgements are not the correct approach towards this field. Rather it is necessary to judge the many different applications of recombinant DNA technology separately for their own merits. And this is what the commission eventually did, when it adopted almost 300 recommendations to the government, various government agencies and to Parliament itself, recommendations which, in general, are quite sympathetic to the cause of our field. One of these was a proposal for a special law regulating recombinant DNA technology. It has come into effect on July 1, 1990. I must admit that it was not easy to vote in favour of such a provision. It did not seem necessary and the first year of experience in

living with it has been a mixed blessing. The law contains some legal inconsistencies, the scientific influence in matters of classification of experiments has been reduced, accompanied by a concomitant influence of state and local politics. Much of this will level off as soon as more experience has been and will be gained, and most people already agree that the situation for L1 and L2 type experiments is quite tolerable. It may well be, however, that more novel and less routine applications like deliberate release experiments or human gene therapy may lead to insurmountable difficulties and that at least for these cases the umbrella may have been opened too early, thereby drawing rain unnecessarily. We have to do our outmost to prevent this from happening.

It is quite ominous, in this context, that a law took effect on January 1, 1991 in this country which makes research on human embryos a criminal offence, thereby denying pre-implantation genetic screening to most (not all) couples at risk for giving birth to children with genetic disease. Sure enough, the law still permits prenatal screening and testing at a later embryonic stage. Nevertheless passing of this law attests to a serious loss of confidence in the ability of the scientific community to address and to solve voluntarily the range and limits of scientific works with human embryos.

Be that as it may, in the matters of recombinant DNA legislation, there was little choice, since the dialogue of which I spoke requires the acceptance of certain boundaries in the pursuit and conduct of science which have to be respected. Only a Don Quixote recognizes 'no limits other than the sky' thereby becoming the embodiment of unrealistic dreams. There is no question in anyone's mind, scientist or other, that human dignity and the preservation of human health must always override freedom of research.

In this context, the times of abuse of genetics, such as were incurred in the formulation of the immigration laws of the US in the early nineteen twenties or, beyond comparison, during the quest of the Nazi government in Germany for racial purity in the nineteen thirties, have not been forgotten. The spectre of positive eugenics introduced in the middle of the last century by Francis Galton, Charles Darwin's equally brilliant and dazzling cousin, is looming above our field and, in particular, the Human Genome Project. I am an ardent advocate of this endeavour. On a long term basis, it will definitely lead to an understanding of the molecular basis of many human diseases; it will increase therapeutic options and will lead to therapies for some diseases that treat the cause rather than the symptoms of illness. At the same time DNA analysis will be pushing back the threshold of early disease detection not only for infectious diseases but also for many gene-linked complex disorders, like Alzheimers disease, arthritis, cancer, diabetes and many others. A battery of DNA tests thus will soon be part of a routine visit to a doctor's office. This raises legitimate concerns, ranging from the demand for a 'right-of-not-to-know' to the necessary protection of individual privacy rights which may have to be enforced by law.

As scientists we should play an early and active role in these discussions, instead of only appearing to respond and to react to public pressure in matters which most of us are ready to accept anyhow. Thus, I see no problem to hunt for

the Huntington gene while, at the same time, developing procedures to protect Huntington patients from undue pressure by their employers or their life-insurances!

In Germany, in this context we formulated a resolution or declaration last year, which laid out and stated the essential values and goals of our work. This declaration starts out with a definition of recombinant DNA technology by emphasizing its role in modern biomedical and biological research and by contrasting it with the reproductive technologies with which it is often and invariably confused. It goes on to describe the system of containment measures which has proven reliable and adequate to maintain high safety standards in our laboratories. In addition, the declaration pledges to guarantee individual privacy in DNA diagnostics, to abstain from genetic manipulations of human germ line cells, and from any efforts directed towards the developments of biological weapons, as well as to proceed with utmost care in the deliberate release of genetically manipulated organisms. The fact that almost 3,000 colleagues signed this declaration is widely regarded as a significant contribution from the scientific community towards raising public confidence and acceptance.

Another proposal addresses the management of biological safety. The record is impressive. Few, if any accidents can be attributed to recombinant DNA technology. The Pasteur incident is quoted occasionally in the press as is the notion that the AIDS virus is an artificial construct, which escaped from some tissue culture laboratory. These particular cases may be dispelled readily; however, we face the constant charge of potential long-term effects of our work, effects which may only become apparent within 15 to 20 years. In this context I consider it admirable that some of our US colleagues, Peter Howley, Arnold Levine, Frederick Li, David Livingston and Alan Rabson recently took up the cases of two molecular biologists who had worked extensively with a tumor virus, SV40, and had died of cancer at a comparably young age. They could not detect — even by using the most sensitive technology available — any sign of the viral sequences in the respective tumor samples and thus could conclude that SV40 played no part in causing these tumors. This effort should not be taken for granted and could not be more exemplary. We should continue to remain constantly on the alert in these matters by developing our own procedures and by taking these matters up on our own initiative to prevent others, like self-appointed experts, or the government to take the lead in such prospective matters.

Apart from these normative boundaries as exemplified both by the above mentioned declaration or by the recombinant DNA legislation, we should not forget to emphasize and to publicize the existence of some fundamental boundaries to the power of genetics itself. For the development of a higher organism the set of genes in an embryonic cell has to be regarded merely as a blueprint with potential to grow into an adult organism, a potential which requires interactions with the environment to be transformed into a living reality. This is particularly true for the nervous system and many of the cognitive parameters, among them behaviour and intelligence, through which man distinguishes himself from other living creatures. A human being thus has to be looked at as much

more than the sum of its genes. Since non-genetic parameters obviously cannot be manipulated by genetic means, the spectre of the Frankenstein monster must have its limitations. A 'Gene-above-everything' mentality clearly has no basis in the biology of higher organisms, in particular man, a conclusion which ironically is the result of modern genetic research. It is hard to rank the degree of discoveries in the 'New Biology' these days, but if one deserves a top position, it is the revelation that important mechanisms in biology, e.g. in signal transduction and growth control, are highly conserved throughout evolution. This results in the fact that we do not only share more than 99% of our genes with the chimpanzee — not exactly our relative, but at least regarded as the second most evolved organism in this world — but even more surprising, probably up to 20% with baker's yeast. There is thus no such thing as a 'human gene', a 'mouse' or a 'fly gene'. Rather the gene has to be regarded as a continuum of information the elucidation and understanding of which will vastly increase our knowledge about human identity to a novel, higher level, but will not answer *all* the questions as to our identity as human beings, not even the purely biological ones.

Finally I would like to make a plea for the role and significance of basic biological research. I certainly agree with Francis Bacon that it is one of the most honourable, if not the only task of science, to serve mankind and to improve the human condition. I have already indicated that it is dangerously back-firing, if not immoral, to raise undue expectations in the public. We rarely mention in public, however, that if anything, the new technologies surrounding the gene, so far contributed mainly to the progress of basic research in all of biology, from anthropology, botany, ethology to zoology. We have asked for an appreciation of science and for money to pursue it by emphasizing potential applications only, instead of also pointing to basic biological questions. We have promised a cure of cancer, instead of explaining that this may be a spin-off from studies on the mechanisms of cell division or the intricacies of the replication of esoteric and exotic virus. The Human Genome Project is sold exclusively as an instrument for curing complex genetic diseases — which it is — instead of also pointing to the more fundamental aspects of the project, too. The failures, which will inevitably ensue, as people will still die of cancer even after the establishment of the genetic map, will then be blamed sweepingly on all our endeavours and will not spare fundamental research. However, human society needs these efforts in order to secure — to speak with Winston Churchill — 'the empire of the future as the empire of the mind'."

FIRST SESSION

Future Perspectives of Basic Life Sciences

Chairman: Fotis C. Kafatos

Multiple Approaches are Existing to Comprehend Principles of Life

Kazuhiko Atsumi, Institute of Medical Electronics,
Tokyo University, Japan

The Era of Paradigm Shift

"The characteristics of modern age seems to be expressed as the era of paradigm shift.

In the various sciences of physics, chemistry, mathematics, philosophy, ecology, neuro-science, psychology, politics and also in the fields of art and religion, the paradigms have been shifting:

In the field of physics, from atomism to quantum theory, from mechanistic to holographic, from absolute to relative, from universal to complementary, and from definitive to non-definitive.

In the area of chemistry, from static to dynamic, from entropy increase to entropy decrease and from reduction to formation.

In the field of ecology, from ideal eco-stability to elasticity and from closed system to open system coexistence. In the area of neuro-science, from fragment of localized information to decentralized tuning system and from circle model to holographic metamorphosis.

The relationship between the shifting characteristics and the various sciences is interesting and some similar tendencies can be observed. Complexity, holography, uncertainty, relative causality, structure formation and perspectivity are listed up as the characteristics.

According to the paradigm shift, the quality conversion can be seen in the changes of human consideration, value and social structures, from simple to complicated and multiple, from hierarchical to heterarchical, from mechanical to holographic, from decided to undecided, from linear causality to non-linear causality, from congregated to formative and from objective to subjective.

These converting characteristics are considered to be the attributes of living body. In this meaning, the trend of future society is aiming to 'life'.

The Era of Biomation

Since human beings have appeared on earth, they formed groups during a long time and continued to survive by the living methods of hunting and farming.

In the early stage, the agriculture society was formed and the society was developed to the industrial society by the breakthrough of technology — the invention of steam engine. Then, as the development of post industrial society,

the information society is realizing in the developed countries. However, in the information society, some disadvantages are coming out and biomation society will be created as the new society of the next generation.

Human beings have developed the new technologies until now. The invention of steam engine could release man from labour and initiated the industrial revolution. Car provided transportation to carry man and baggages, telegraph and telephone contributed to communication, radio to broadcasting, xerographix to duplication, computer to calculation, ink-jet printer and audio-response and recognition instruments to writing, speaking, reading and hearing.

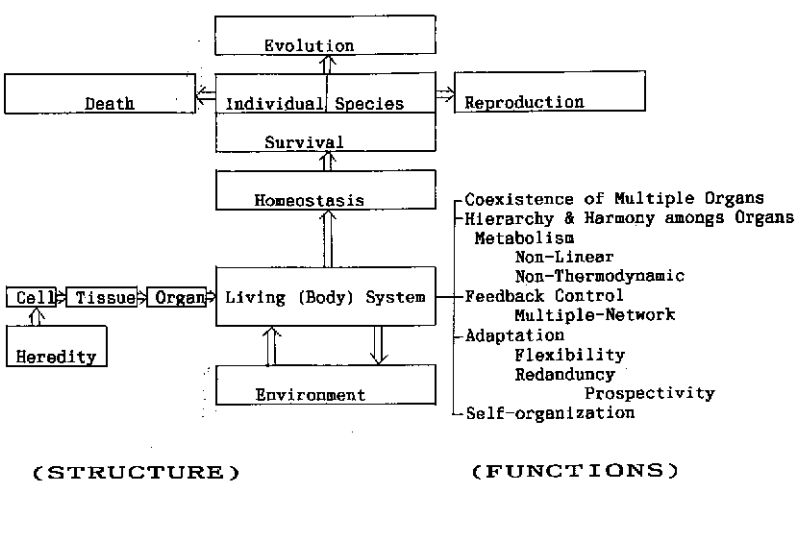
At the present state, the various data processing machines can replace human's higher activities such as learning and creative thinking. Namely, the history of the development of human technologies can be said to be the history of automation technologies.

The hybridization between automation — man-made technology — and bio-organism — natural realm —, is 'biomation'. By the 'biomation', the mechanical civilization can sublimate up to the human civilization.

In the state, the essential structure and functions of living body should be considered.

The biological individual has been forming from cell, tissue, organ and their congregated existence and it has been receiving impacts from both sides — heredity and environment.

Figure 1: Structure and functions of living body



Living body has been completely regulated by the network of the multiple feedback system, has maintained 'homoeostasis' and has survived and evolved.

The individuals die, however, the species can evolve through the individual's reproduction.

Living body has wonderful functions such as coexistence of multiple organs, hierarchy and harmony of organs, metabolism, feedback control, adaptation and self-organization. Flexibility, multiplicity, individuality, centralization and decentralization, holography, total system, and sub system etc. can be named as characteristics of the living body.

In shifting to the biomation era, the parts of the social structure have been converting, from hardware-oriented to software-oriented, from economy to life, from centralization to decentralization and from sub system to total system.

The value views are changing from rigid to flexible, from simple to multiple, from static to dynamic, from steady to metabolic, from inefficient to efficient, from bulky to compact, from rough to sensible and from partial to total.

Modern Trends of Science and Technology

In 1990, MITI reported the 'White Paper on Technology' and analyzed the modern trends of science and technologies.

The 1st trend is development of science and technology on molecular level. In the field of electronics, electronic parts were started by use of vacuum tube, then transistor, IC, LSI, Super LSI and now molecular elements are recently investigated. In the area of bio-medicine, the study was started on the research for organ, tissue, cell, virus and now the research on protein and DNA is proceeding with the topics of protein engineering and genetic engineering.

The 2nd trend is the resonance between science and technology. The invention of the super conductive material in science stimulates development of technology associated with energy, measurement etc. As the result, SQUID system is developed. By the SQUID system, magneto encephalograms are detected and the data processing mechanism in brain can be analyzed. The scientific knowledge can contribute to the new technology to construct a neuro-computer. As the result of the resonance between science and technology, the time gaps between scientific findings and technological production were shortened year by year.

The 3rd trend is development of interdisciplinary fields in science and technology. These fields are mechatronics, opto-electronics, photo biology, biomaterials etc. Molecular biology and bio-medical engineering are typical interdisciplinary ones. These new fields can make fusing each other and the new interdisciplinary regions will be created.

The 4th trend is development of super-technology. The super-conductive material, nuclear fusion by super-high pressure, super high speed laser analysis within pico second etc. belongs to the trend.

The 5th trend is development of modern science and technology associated with life and bio-organisms.

Bio-Medical Engineering and Bio-Technology

In the 20th century, medicine was extremely modernized by the contribution of the surrounding sciences and technologies. From the view points of medical technology, bio-medical engineering and bio-technology have played a great role to promote the progress of modern medicine.

The development of bio-medical engineering such as ECG, X-rays, ultrasonography, artificial organs, medical lasers, has been contributing to enable precise diagnosis and radical therapy.

The progress of life science and biotechnology has been bringing the revolutional technologies such as DNA recombination, cell culture, cell fusion and opened the door of genetic engineering.

The biomedical engineering is the interdisciplinary technology between medicine and engineering and includes the area of bio-monitoring, therapeutics, data processing, biomedical system. Artificial organ is one of the areas of biomedical engineering.

Artificial Organs

1. The Definition and Development of Artificial Organs

The definition of artificial organs is the devices and systems to replace the target organs' functions, without consideration of the shape, size and installed position. Namely, artificial organ is a simulation model of biological organ.

The process of development of artificial organ can be started to analyze the functions of the target organ, to construct the prototype model, to check the functions in vitro and vivo, then to apply it in the clinical use. The devices are miniaturized and finally incorporated in the human body.

2. The Classification of Artificial Organ

The artificial organs can be classified into four groups, according to the grade of the functions, duration time and incorporation into the body.

The 1st group includes artificial bone, joint, vessel, valve etc. which can be incorporated into the human body and replace the target organs' functions for 10 to 20 years.

The 2nd group comprises artificial kidney and heart which can replace the functions for several years, their size, however, is still large.

The 3rd group includes artificial liver which only can replace partial functions for several days and the size is bulky.

The 4th group comprises artificial uterus, of which functions were not clarified clearly and the research just has started.

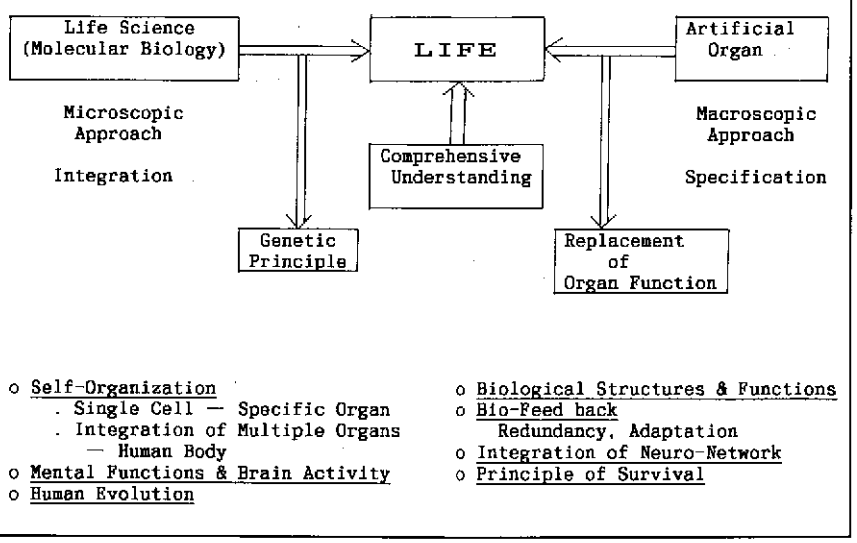
In Japan, the number of patients of chronic dialysis is estimated at almost 100,000 and the longest survival is 22 years long at the present time. The functions of the artificial kidney are not complete compared with those of

biological kidney, therefore, some complications such as disorders of bone and nerve were experienced. The reason considered is that the membranes of dialysis and filtration are not ideal compared with the biological ones.

3. Analysis of Organs Functions by the Research of Artificial Organs

In past, urea in blood is considered as the cause of uraemia. However, the uremic condition could not be improved after removal of urea from the blood. Therefore, the other substances such as creatinine and middle molecule substances have been approved to be original causes.

Figure 2: Comprehensive understanding of life through the research on life science and artificial organs



The purpose of R&D on artificial organs is not only to construct the device to cure the patients but also to analyze the organs pathophysiology and to understand the biological functions.

These technologies of dialysis, filtration and absorption developed the methodology of blood purification through the progress of plasma exchange.

The basic research on the substances to be dialyzed and filtrated could clarify the pathophysiology on liver and the complicated diseases.

The content of ammonia in blood was considered as the cause substance of hepatic comma, however, the many substances of hepatic comma have been identified by the research of artificial liver such as the various kinds of amino acid, fatty acid and protein-bounding substances.

4. Miniaturization of Artificial Organs

One of the purposes of R&D on artificial organs is miniaturization in size and incorporation into the human body.

In the development of artificial kidney, the movable, the wearable and the implantable devices have been constructed.

In 1985, the blood pump of total artificial heart was incorporated into the human thoracic cavity, and a patient could survive for 622 days. Recently, the R&D on implantable total artificial heart of which blood pump, driving unit and energy source are incorporated completely in human body have been continued in the USA. According to the NIHLB project, the hardware will be completed in 1991, the device will be incorporated in human in 1996 and the follow up study will follow in 1999.

5. Hybrid Artificial Organs

Liver has various and complicated functions such as synthesis, analysis, detoxication, metabolism, storage etc., and the artificial substitution is necessary to construct the huge factory. Therefore, at the present state, the complete construction of artificial liver is difficult. Therefore, the concept of hybrid artificial liver comes up.

In hybrid artificial liver system, the liver cells are cultivated outside of the membrane of hollow fibres and they can replace liver functions. When the blood of the patient of hepatic comma comes into the inside of the follow fibre, the toxic substances can reach and contact with the cultured liver cells through the wall membrane of the fibres and can be treated with the liver cells.

On the other hand, the antigens of the hepatic cells are blocked against the membrane. Therefore, if the heterogenic animals' liver cells are used, the antigen-antibody reaction can not be introduced.

The excellent ideas can be realized by the introduction of biotechnology.

Pancreas is the regulatory organ on blood sugar to release insulin according to the blood sugar level and is constituted from alpha cells and beta cells.

The alpha cells include storage for glucagon and pumps to insert glucagon and the beta cells include blood sugar sensor, storage for insulin, pumps to insert insulin, computers to calculate the insulin input, energy sources etc.

It is not easy to miniaturize these units, therefore, hybrid artificial pancreas was considered.

As the hybrid system, the following ideas are developed to culture beta cells outside of membrane, to incorporate beta cells inside the biomaterial gel or capsules.

Furthermore, hybrid artificial vessels, blood and skin are investigated. The hybrid artificial vessels, the inner surface of which is covered with the cultured endothelial cells, have been studied.

6. Molecular Design of Biomaterial

In 1960, the research on artificial blood — oxygen carrier — was done by the authors to develop the Wang's model and to construct poly-imidazol compound utilizing hem from the cow's hemoglobin.

In the condition of membrane, the capability of oxygen carrier function of the synthetic artificial blood was approved. However, the experiment was given up because of the difficulty to make molecular design and to synthesize the amino acid sequentially. After that, the research on artificial blood has been aiming to improve the function of fluorocarbon which can solve lot of oxygen. However, recently, the study of molecular design of artificial blood has been investigated.

In conjunction with molecular design of biomaterial and understanding of biological phenomena with molecular level, the new frontier of artificial organ has started.

As the topics of the researches, the following subjects have been studied.

1. Biocompatibility in the interface between cells and biomaterial surface.
2. Adhesivity of cells on the synthetic materials.
3. Protein absorbability in the interface of antithrombogenic materials.
4. Proliferation of hepitic cells on the surface of artificial materials.
5. Selective cell separation.
6. Elongation and contraction of biomaterial by chemical and electrical stimulation.
7. Research on DDS.
8. Research on intelligent materials.

The study of wonderful characteristics of concanavalin A was reported. In the situation of sugar, sugar can bind to concanavalin A and release insulin bound to concanavalin A. Utilizing the biochemical function, the miniaturized artificial pancreas can be made.

The functions of filtration, DDS and artificial muscle can be realized by elongation and contraction of synthetic material with the optical and electrical stimulation.

These advanced technologies of artificial organs can be listed up as follows:

1. Development of new biomaterial by molecular design of synthetic polymers
2. Ultra miniaturized devices by micromaching
3. Biotechnology (cell-fusion, DNA recombination)
4. Bio-energy
5. Bio-computer

Furthermore, biosensor is an indispensably useful technology for artificial organs and the various kinds of biosensors were developing.

8. The Future of Artificial Organs and Organ Transplantation

In the research of organ transplantation, the studies of 1) hetero transplantation 2) organ transplantation into the other organ in the human body — hepatic cells transplantation into spleen — 3) cultivation of organs ex-vivo, will be promoted

in future and the donors' problems will be solved. In the research of artificial organs with higher functions, intelligent and implantable artificial organs will be developed.

Table 1: Comparison of Artificial Organs and Organ Transplantation in Future

		Kidney Tx	Kidney A	Liver Tx	Liver A	Pancreas Tx	Pancreas A	Heart Tx	Heart A	Lung Tx	Lung A
Near Future	1,991—2,000	>	Wearable	>>	Hybrid	>>	Wearable	>>		?	
Middle Future	2,000—2,025	>		>>	Hybrid	>	Implantable	>	Implantable	>	Wearable
Far Future	2,025—2,050	=	Implantable	>	Wearable	=	Implantable	=	Implantable	=	Implantable
	After>2,050			?	Implantable						

Tx : Organ Transplantation
A : Artificial Organs
excellent>>, good>, equal=

At the present state, organ transplantation of kidney, liver, pancreas, lung and heart seems to be superior compared with artificial organs. However, 50 years later, the functions of artificial organs will be levelled up and be competed with those of organ transplantation.

9. Technology Assessment of Artificial Organ

The impacts of research and development of artificial organs are so deep and wide, multiple viewpoints of technology assessment will be necessary — not only from medical but also economical, ethical, religious, ecological viewpoints."

Some Remarks on the Study of Genomes

Prof. Peter Starlinger, Institute of Genetics, University of Cologne

"I will not try to speak about the politics of the genome project, because there are so many people here who know these things better than I do.

Let me instead try to make a few remarks on potential benefits from our understanding of evolution that may come from genome projects. I should like to address three questions:

1. Does genome research contribute to the completion of a natural system of living organisms? Will it help to construct complete and reliable pedigrees of existing and extinct species?
2. Will we be able to construct a similar system for the existing genes?
3. Will we learn something about evolutionary mechanisms?

The answer to the first question is positive in principle, if enough organisms are included into a large-scale mapping and sequencing project. As modern RFLP techniques and similar methods provide an unlimited number of genetic markers, pedigrees will be constructed with ever increasing accuracy. This would enable taxonomists and evolutionary biologists to resolve questions that were hard to answer with a limited and restricted number of morphological markers. If, however, the large-scale efforts are concentrated on the human genome or, at most, on a few other species, not very much will be learnt with regard to the first question.

While such answers will be important for scientists concerned with a particular question, I have no doubt that the general question, whether all organisms are related to each other by evolution, has been solved long ago. We must ask ourselves about the costs and the benefits of knowing pedigrees with ever increasing accuracy.

My second question concerns the origin of genes. How are they related to each other?

In some cases of genes encoding proteins of similar structure and function, such a relation has been known since a long time. In other cases, evolutionary relations were detected only after protein sequencing and, more recently, DNA-sequencing became available. Related sequences were grouped in families. In the last years, families could be grouped into larger structures, the super families. How far will this process continue?

If we state this question in extreme terms, we might ask whether all genes might descend from one original gene which arose first as a replicating structure, or whether there is an original set of genes that has been created independent of

each other. For this latter hypothesis, S. Ohno has formulated the elegant hypothesis that a gene can be created by a tandem amplification of relatively small oligonucleotides, followed by point mutation.

For the other extreme possibility that all existing genes go back to a first emerged replicating structure, we do not have any evidence now, and it may be doubted whether the study of present-day genes will be sufficient to bridge all the gaps between sequences that direct comparison does not show to have a relation to each other. While we cannot say yet whether this will be possible, I think that an answer to such questions may be an outcome of large-scale sequencing projects. I also think that the sequencing of the DNA of one organism will already substantially contribute to this question and that the sequence of a very large number of organisms may not have to be necessary for this problem. Therefore I think that the human sequence project, or maybe first the complete sequencing of the DNA of an organism with less DNA may yield answers to this interesting evolutionary question.

While we have some insight into the evolutionary relations of whole organisms and of single genes, our knowledge of evolutionary mechanisms is still rather incomplete.

On the one hand, evolutionary biologists contend that natural populations are highly polymorphic and that selection is, at any moment, capable to alter allelic frequencies in response to a changing environment. Geneticists, who were not studying natural populations but rather single genes in laboratory strains had difficulties with this concept. They were used to see a wild type gene with a certain function and recessive mutants, usually loss-of-function mutants which they believed to be weeded out quickly.

This did not explain the evolution to higher forms of life and good explanations for this have not really been brought forward.

Molecular genetics have, in my opinion, not altered this situation. Numerous polymorphisms have been found in the form of electrophoretic protein differences or of DNA RFLP's, but they are largely thought to be neutral and therefore not subject to selection.

Selectable mutations concern important protein structures, e.g. catalytic centres, and they are usually causing a loss of function and are subject to loss from the population. Neutral mutations may be located with sequences encoding regions without function in the protein. Both types of mutations do not explain the emergence of genes with radically new functions, let alone the evolution from relatively simple to much more complex life forms. More specifically, these lessons from molecular genetics do not tell us which polymorphisms persist in a population, and where both alleles do have a selectable function of their own.

The best examples that come to my mind are allelic sets that have been created by some kind of co-evolution. The relation between parasites and their hosts is an example. U. Henning's studies on the relation of the protein on a bacterial surface that serves as a bacteriophage receptor, and the bacteriophage protein binding this receptor, are a beautiful example. Another one are the studies of the allelic sets of a plant gene-determining resistance to a particular

fungus and the fungal gene-determining dominant avirulence. In both cases, it is understandable that a biological interaction allowing the host to escape from the attack of the parasite should be overcome by the latter via a mutation abolishing this interaction and that the host should regain the rescuing interaction by an appropriate mutation in the gene encoding the interacting structure. In both cases it is known that large series of both genes can coexist in the population.

Can this give us a hint, how evolution from simple life forms to the much more complicated later forms has occurred? Is it conceivable that co-evolution of genes occurs not only between those encoding proteins in different organisms but also between genes encoding proteins that have to react with each other within a given organism? Is it possible that these interactions are responsible for aspects of cell cycle, growth control and differentiation? In this case, present-day population may harbour functional polymorphisms of this kind, and we have not yet detected them. That fact that such polymorphisms have not been detected in the genes encoding enzymes may not be so surprising. Since the substrates of the enzymes are always the same, it is conceivable that the enzymes recognizing such substrates have evolved to a certain quality and need not evolve further. Such thoughts have been expressed in evolutionary texts quite often.

If, the ligand of a given protein is not an immutable substrate molecule but rather another protein possessing a domain whose only function is the recognition of the first one, a continuous co-evolution of the two genes encoding these proteins can be understood.

The question arises, whether our interest in understanding evolution should not be focused on protein- or DNA-binding rather than on those binding low-molecular weight compounds.

While at this moment hardly anything is known to substantiate such a speculation, it is also true that molecular genetics up to now has not yet provided an understanding of the polymorphisms that Darwinian theory postulates. I would hope that large-scale DNA-sequencing projects might either lend some support to the idea that the co-evolution of pairs of proteins might be important, or else reveal how the necessary population polymorphisms are brought about. However, such knowledge would only be gained, if many genes were sequenced more than once, allowing the chance of detecting polymorphisms. Whether this will be intended and whether it will even be possible with regard to the work and cost I cannot say. If, however, the idea should prevail that 'the human genome' is a unique structure rather than a population of alleles, and if consequently each sequence would be determined only once, we would not learn much regarding the question discussed here.

I should like to close by reminding ourselves that the most interesting and far-reaching discovery for evolution, the discovery of the enzymatic function of RNA, has come from the study of an economically and medically unimportant protozoan, namely Tetrahymena, and that it certainly did not come from a preconceived plan. Therefore, I should hope that the well-organized and planned projects in biological research, of which we are discussing the genome project here, will not lead to a monoculture and allow the continuation of much diverse

biological research that has proven in the past to be as important for discovery as biological diversity has proven important for biological evolution."

On the Analysis of Human Genome and the Human Genome Project

Kenichi Matsubara, Institute for Molecular and Cellular biology, Osaka University, Japan

"Ladies and gentlemen, it is a great honour for me to speak on the human genome project in this important occasion. I was pleased to hear Dr. Peter Starlinger's excellent introduction about genomes, and the relationship among living organisms on the earth. Among them, human, of course, is the most interesting and important target for study.

In the human genome project we ask how many genes our genome has, what these genes are, how they are arranged on chromosomes, and how their expression is controlled in the process of construction of our body and the maintenance of its health. Through pursuing these problems, we will eventually be able to understand the blueprints of human beings.

We now have about 1,000 human genes registered in the DNA data base, and about 1,500 genes of E. coli in the same data base. These numbers are increasing rapidly, since more and more people are working to decipher genetic codes, and better technologies are being developed. The rate of increase in the number of analyzed human genes is so significant that in ten years more than half of the genes will be deciphered through structural analyses of the genome and through the so-called cDNA projects that analyse expressing genes. Understanding large number of human genes and their regulation will no doubt open a new era for medical sciences that include diagnosis, developing pharmaceuticals and treatment of diseases. Without doubt, the ideas and technologies developed will be applied for improvement of other useful organisms.

In the human genome project, we are bound to construct a large data base that requires intensive international collaboration. In the project, global approach is being taken towards understanding the blue print that underlies and controls biological phenomena. This style of work has not hitherto been attempted in existing biology, such as embryology, immunology, or brain science which focuses on studies with mechanisms acting in individual biological phenomenon. Genome projects with the unique style of work are being organized with many other living organisms, including mouse, flies, nematodes, rice, arabidopsis, yeasts, and bacteria. The concerted efforts for understanding genomes of many organisms will, no doubt, change the future of biology, and will effect our understanding of the human species.

Today, I would like to focus my talk only on these problems in basic biology, since much has been talked about the formulation of the human genome project, its strategies, and its short-term goals.

Animals, plants, microorganisms, and all living things on earth use essentially the same genetic code. This finding strongly suggests that they are derived from one and the same ancestor, however they look different. The genome studies will unravel the unique feature of DNA that underlies this paradoxical situation, viz. uniformity and diversity of genetic systems, and will lead us to understand two important aspects of man: Firstly, it will provide us with better understanding on the relationship between man and other organisms. Secondly, it will unravel the course of our evolution, since the histories are recorded in the genomic DNA. Our culture, based upon understanding man, can not escape from the impact brought forward by unravelling these problems. There may be a "revolution in understanding man", for the second time since Darwin proposed the theory of evolution.

Dr. Ishihama at the Institute of Genetics at Mishima gathered all available information on the E. coli genome. He classified the genes into four categories: genes for energy production, (about 70 per cent of the total genes), genes for substrate production, (about 27 per cent), genes for cell envelope (about 26 per cent), and genes for core machineries which involve protein synthesis, DNA synthesis, and RNA synthesis. Among all of the genes so far studied, about half of them are acting in regulation of other genes.

It is highly likely that most of the genes found in E. coli will find counterparts in higher eukaryotes such as man, mouse, rice and insects. Thus, the E. coli genome project can have an important influence on other genome studies. It is being run in Japan as well as in Europe and the United States. Although the human genome is almost 1,000 times more complex than the E.coli genome, we will soon be able to discuss its genetic constitution at a similar level to that of E. coli, as analyses of the linear structure of the human genome (the so-called mapping efforts) and the studies with phenotypic expression of human genes in tissues (the so-called cDNA project) progress.

The Human genome project can also cast light on our biological history, because the DNA in the genome carries all records of evolution. Through analyses of global distribution of polymorphic markers among races and tribes, much will be learnt about their migration and massive changes in their populations. In addition to these short term historical records since man has appeared on the earth, we will learn much about our longer course of evolution. Genes in prokaryotes, such as E. coli and B. subtilis, are densely located along the genome, and possibly about 70 per cent of the genomic DNA is occupied by open reading frames. In contrast, only about 5 per cent of the human genomic DNA is assigned to open reading frames, leaving the function of the rest mostly unknown. It looks as though prokaryotes have come towards minimizing genomes, and that eukaryotes, such as man, have come towards expanding genomes. Many intriguing questions can be asked to connect such huge differences: How aerobic cells emerged from anaerobic ones? How they became eukaryotes, viz. cells carrying nuclei? How multiple cellular systems evolved? How such complex animals as vertebrates emerged, and how mammals have replaced dinosaurs in the past... As an optimist, I believe that some of these

questions may be answered through genome studies. Learning about our relationship to other organisms will give us a clue to think how we, the living creatures on the earth, should interact with one another.

Searching for records of events that have happened relatively recently in our genomes can provide us with interesting and rewarding findings. Human genome carries thousands of retroviral genome copies, some of which have been converted into control elements for human amylase gene expression. Similar cases will be discovered in other genes.

Let me come back again to the realistic part of human genome project. The project, of necessity, promotes development of very efficient and high speed DNA technologies. In addition, there will be a flood of genetic information that will lead to the fusion of biological sciences and informatic sciences. For this reason and for the expected revolution in biology, biotechnology, and medicine, many developed countries are participating in the genome project. However, this project is influenced by science policy makers who are mostly interested in technology developments and its applications. In the contemporary society where developments in basic science and application go almost simultaneously, I think that human genome project is providing interesting social experiments for considering the relationship between biology and its application.

The human genome projects run by different countries are different, as each project is strongly influenced by grantors under influence of national interests, and by personality of the scientific and political leaders. In some countries, leaders have put strong emphasis on the usefulness of the expected outcome from the project. To the usefulness, some of the prominent proponents in the human genome project have gone so far as to declare that talents in mathematics or music, for example, could be predicted in individuals, through developing the project. I do not, however, like to see such oversellings: It should be made clear that the human genome project at this stage is not to understand individual human genomes for useful information. It should be clearly declared that the current project is for understanding the human species."

Gene, Cell, Behaviour

Katsuhiko Mikoshiba, Institute for Protein Research,
Osaka University, Japan

"The signals outside our bodies are recognized by specific sensory organs prepared on our bodies. And the signals recognized are transmitted to the brain. After complex information processing, brain sends outputs in the form of behaviour. Not only it is the centre for behaviour, brain is the site for learning and memory.

Recent development of cell biology and molecular biology has now enabled us to correlate gene, cell and behaviour. Since there are not so many neural scientists here, I would like to show the present situation by presenting our data as materials to promote discussions. Since next speaker Professor Jean-Pierre Changeux is also a brain scientist, a great scientist, I will try not to overlap with him. Therefore I will focus on the correlation between gene, cell and behaviour.

Our brain is composed of two hemispheres. It is composed of numerous small lobes. We can easily distinguish the hippocampus which is the centre for our learning and memory. Brain is actually the centre for learning and memory, and also the centre for regulation of (motor)movement. The grey matter of the brain is the accumulated part of the neurons. And in the so-called white matter number of fibres is accumulated. Since it contains myelin to ensheath the axons, it contains a lot of lipids, therefore, it is white.

Our brain is composed of mainly two types of cells: one is neuron and the other is glia-cells. Neurons send out their axons to make synaptic contact with the next neuron, thus form a neuron network. This is the essential mechanism for the brain function. However, the number of glia-cells, which are located adjacent to the neuron, are ten times more than that of neurons. They are composed of astrocytes, oligodendrocytes and micro-glia-cells. Recently cell biology has revealed that not only neural cells but also glia-cells are important. For example, astrocytes or micro-glia-cells spread various kinds of cytokines which are essentially the same as cytokines in the immune system. So it is considered now that glia-cells are the link between the immune system and brain system.

The brain tissue is composed of various kinds of cells. Cells proliferate at a typical part of the brain, they migrate, and then finally they differentiate.

Recently, many mutants were described that have abnormalities at the various steps of development and differentiation. There are neuro-pathological mutants, which have an abnormality at the cell proliferation step, the cell migration step, or the final step of differentiation. There are mutants lacking a specific type of neuron, or abnormality in glia-cell development.

Analyzing these mutants and comparing then with each other has given us great information on the normal development of the nervous tissues.

First I will go to the study of glia mutants, and then I will show some of the examples of neuro-mutants.

Oligodentrocytes in the central nerve system, a type of glia-cells, send their processes to recognize axons of neurons. There is a neural-glia-recognition in this myelination step. And then it wraps to form a compact lamellar structure. The material for the myelin structure is believed to be synthesized at the cell body and then transferred through these processes to make the myelin structure. Inner surface of the oligodentrocyte cell membrane forms a major dense line here. An outer surface fuses to form intraperiod membrane. A major dense line corresponds to the deposition site for myelin basic protein. And PLP (myelin proteolipid protein) traverses the outer surface membrane forming intraperiod line. We have various kinds of mutants that have mutation in PLP-gene and also myelin base protein gene. Once there is an absence of myelin base protein here, there occurs an absence of electron dense major dense line causing the animal showing abnormal shivering and tremoring behaviour. So myelin is a very good place to correlate molecule, morphology and, at the whole animal level, behaviour.

Some mutants have abnormalities which correspond to defects of expression of myelin base protein. One mutant is called shiverer. I will not give a detailed story but I will just mention the name shiverer here. This is an antosomal recessive mutant. Usually when we stain by the antibody against MBP we can easily recognize the myelin. Namely, we can visualize a myelin molecule, especially a myelin base protein molecule by histochemistry. But in shiverer mutant myelin base protein is completely absent. And we have found that myelin basic protein was also absent in a peripheral myelin. But the problem is: is this the primary defect in oligodentrocyte or not. There is an example of Purkinje-cell degenerative mutant, called Gunn rat, there is a defect in enzyme of liver, so that some toxic factor is produced in the mutant, then it attacks Purkinje-cells in the cerebellum. In that case, the analysis of the cerebellum gives us no answer. So it is very necessary to determine that oligodentrocyte itself is abnormal. We have to analyze, if the primary defect lies in oligodentrocyte or not.

When we look into the nervous system, any positive myelin comes from the normal and negative myelin comes from shiverer. We can clearly see the patches of positive myelin and negative myelin, indicating that humal factor can be eliminated, either toxic or humal. Therefore, the mutation occurs intrinsic to the cells themselves: neural side is abnormal, or glia side is abnormal. We could observe MBP-positive myelin and negative myelin on the same axon. If the neural side is abnormal that causes this mutation, one exon should always have the same phenotype, MBP-positive or negative, so that all myelin forming cell itself is abnormal, so that we could deeply go into the gene analysis.

Myelin basic protein is composed of seven exons. It is 32 kilobases, a very long gene, but 20 kilobases were deleted, so this corresponds to the exons, and by alternative use of these exons proteins are synthesized. So deletion of this part

causes the absence of the production of this protein. But this mutant has given us a great information, further information that transgenic mice by introducing a whole gene rescued the animal, expressing the tissues and also the transgenic mice containing 1.3 kilobases promoter plus MBP cDNA also rescued the animal, expressing cell specific expression, indicating that this 1.3 kilobases promoter is so important. And recently we found the sequence by DNase I footprinting, where the enhancer binding protein attaches to the promoter. We finally succeeded to clone the nuclear factor one (NFI) from the brain cDNA library.

Another very interesting mutant which we call myelin deficiency shows very similar symptoms as shiverer. Surprisingly, although there is low level of expression at the tissue level and also the phenotype was very similar, there was a duplication of the gene. And finally the promoter region — this activity was exactly the same in both cases, and we found that the deleted parts are just inverted. The problem arises, why the gene expression is very low, it was only about 3 per cent of the control, why the expression is suppressed. We finally found the inverted gene produced antisense RNA that suppresses the RNA produced from the normal gene. That causes the very low amount of myelin base protein expression. This was the first case demonstrating antisense RNA that suppresses the normal gene in vertebrate.

Now I would like to talk about some interesting mutants that have abnormality in neurons. Cerebellum is one of the good materials to analyze. Neuronal network of the cerebellum is well understood. By morphological analysis we can easily identify each cell. The cerebellum receives only two inputs, input from mossy fibre input and climbing fibre input. Purkinje-cell receives granual cell in addition to climbing fibre. This is the main neural network. The advantage of using cerebellum is that we have various kinds of mutants which show abnormal cerebellan taxia. A mutant called weave for example lacks only exitatory neuron in the cerebellum, granual cell. "Nervous" and "PCD" are Purkinje-cell deficient mutants. The "staggerer" mutant is characterized by the absence of synaptic contact between Purkinje-cells and granual cells. In the "reeler" mutant, only a small number of Purkinje-cells are located in a normal position, but most of them are localized just below the granual cells. So there is an inversion of neural cells in the cerebellum. And cerebral cortex is also characterized by a disarrangement of cell position.

In a normal cerebellum a Purkinje-cell makes dendrites in molecular layer. The axons of Purkinje-cell are located in white matter. G-cells, granual cells, send their axons to make synaptic contacts with Purkinje cells. The number of granual cells is enormous in granular layer.

A weaver mutant lacks granual cells. This mutant has offered information that granual cell itself has glutamate as a neural transmitter.

In a reeler mutant only a limited number of Purkinje-cells exist. Most of the Purkinje-cells are located just beneath the granual cell. So we can say that this is a mutant in which the position of granual cell and Purkinje-cell is inverted.

In addition, the reeler mutant shows a typical abnormal morphogenesis. Whereas in a normal cerebellum we find a beautiful morphogenesis a reeler cerebellum does not form a lobule. So analysis of the reeler mutant comparing with that of the control animal will give us information how the brain forms gyrus or lobules. You may expect that the brain of the reeler mouse also lacks the lobule. But unfortunately the rodent cerebrum lacks the lobule even if it is normal.

Usually at very early stages in the embryonic stage, early formed cells stay in a very deep part, and the next formed cell migrates through the early formed cell so that each brain cortical cell layer is formed by inside-out-pattern, so that the outer part is occupied by the newly formed cells. But in reeler cerebral cortex, the position of neurons are just inverted. This is like the case in drosophila. This migration step may be acquired during the evolution when the animal becomes a vertebrate. So analysis of this mutant comparing with that of the wild type control animal will give us great information on how the cell migrates to reach a normal position.

In reeler neurons are randomly mixed. Analysis of this mutant provides us great information on how cerebral cortex is formed. If the animal is very young, it shows very strong abnormal behaviour, but when the animal gets old, the symptoms gradually disappear, but not completely.

It was found that there is a reorganization of neural network when the target of some neurons is absent. Mossy fibres should make a synaptic contact with granual cells here, but if the target cell, granule cell, is absent, mossy fibres make a synaptic contact with a genetically non-determined neuron and this form another neural network. Probably this is the cause for the recovery of the symptoms of abnormal behaviour. This can be said also in the case of weaver. Our brain in some sense really has plasticity with regard to neural network or in neuron-neuron recognition.

The most important neuron in the cerebellum is the Purkinje-cell. The image of a Purkinje-cell is very similar to a leaf of a tree. So when we look from the other direction it looks like a line. The morphology always correlates with the function of the cell. When we see a cell by optical microscopy, we can imagine it function, even though we do not examine the function of the cell. So function and morphology is closely related. I was highly interested in the molecule that determines this function.

The morphology of a cell is accomplished by a combination of genetic and epigenetic factors. What happens if the input into a Purkinje-cell is abolished? Usually a Purkinje-cell receives more than 20,000 inputs from outside the cell.

And the information processing is just like a computer. The Purkinje-cell without inputs shows very poor dendritic arborization. Again: Which are the humoral factors to maintain this normal morphology? It is always very difficult to analyze the humoral factors.

There was a genetic normal morphology mutant which is very convenient to analyze the molecular basis or morphogenesis. The staggerer mutant shows a genetically abnormal Purkinje-cell.

In the staggerer Purkinje-cell spines, which should be formed on the dendrites, are completely absent. There is an absence of synapse, so there is a disruption of the neural network.

These animals show typical cerebral ataxia.

We have analyzed the proteins by SDS-gel and found that high molecular protein called P400 was absent in the staggerer. This is the data about 15 years ago when I was in the lab of Jean-Pierre Changeux. And finally, it came out to be the very important protein, inositol trisphosphate receptor (IP3). We called it at that time P400.

We could localize by histochemical staining that P400 is highly enriched in Purkinje-cell neuron. If the Purkinje-cell is absent, this protein is greatly decreased. In the mutant which lacks this dendritic arborization, even though Purkinje-cells exist, the content of P400 was very low.

To make a long story short, after 15 years of research, we came to the conclusion that P400 protein was IP3 receptor, which plays a very important role as calcium channel located on the endomembrane, smooth endoplasmic reticulum. Usually it was believed that calcium channel is only localized on the plasma membrane, but this was a new type of calcium channel, which differs from their sequence and localization. When the signal comes from outside the cell, it is transmitted inside the cell producing IP3 and open the calcium channel, IP3 receptor. We could fortunately clone the whole cDNA and the size was about 10 Kilobases. At that time it was the second longest cDNA ever reported. The analysis of the mutant has finally brought us to the very important discovery that the calcium channel is located inside the cell.

I have been working on the mutant showing typical cerebellar ataxia or shivering behaviour. But by analyzing histochemically, we can see that some of the cells show typical abnormality, and that a certain cell is abnormal. At that time independently by biochemical methods we find that some proteins are missing, for example myelin base proteins or P400 protein, i.e. IP3 receptor, but we could not correlate that this abnormality correlates with the absence of these protein. Chimeric mice work has finally made a link between the protein missing with certain abnormal cells. We directly looked on the DNA level and finally we found that a certain gene is abnormal. In some cases, genes are duplicated or genes are deleted or genes are inverted to produce antisense RNA. By introducing these mouse mutants we obtained great information on the normal development from gene, cell and behaviour. We have the same phenomena in human being as hereditary disease. So these mutants can be used as animal model for human disease, and also these mutants can be used to develop new drugs to rescue the disease. Also by molecular analysis, for example, IP3 receptor, we can make a new drug by molecular design. Here I have just demonstrated some materials for discussion."

NEUROTRANSMITTER RECEPTORS, Synapse Epigenesis and Cognition

Jean-Pierre Changeux, Pasteur Institute, Paris, France

"Several families of membrane proteins contribute to the genesis and transmission of signals in the nervous system, still the further identification of their repertoire as the elucidation of the diverse mechanisms which regulate their efficacy, offer avenues for the understanding of communications in the brain and for the design of novel neuroactive pharmacological agents.

The recent progress of molecular embryology in invertebrates and vertebrates yields clues to analyze the genetic constraints of mammalian brain development, but analysis of the epigenetic regulation of developing neural networks by their state of activity gives new ways to understand the interaction between the brain and its social/cultural environment.

The development of techniques of brain imaging and of activity recording at the cellular and global level, as the elaboration of formal models of neural networks offer new opportunities to approach the neural bases of higher brain functions."

References

J.-P. Changeux (1983) Neuronal Man, Pantheon Books, New York.

J.-P. Changeux and S. Dehaene (1989) Neuronal models of cognitive functions. Cognition 33, 63-109.

J.-P. Changeux and A. Connes (1989) Matière à Pensée, Editions Odile Jacob, Paris.

Vision by Computer

Jean-Claude Simon, University Paris VI-CNRS, France

Computer Vision, a Province of Pattern Recognition

"Perception is an essential and marvellous quality of any living being. Philosophers and physiologists rightly put the understanding of perception as the central key of any theory of man. But introspection gives very little information on these phenomenons, which are out of reach of consciousness; and physiology has only shown the complexity of brain neural processes, without explaining them at the system level. Since the advent of logical machines, i.e. the computers, modeling perception has been an endeavour in the domains of speech and vision. Pattern Recognition is the usual term to designate these efforts. Up to recently, the competition between man and machine was so much in favour of man, that many considered pattern recognition as a science fiction tale. But the facilities offered by computer science (Informatique) are changing the picture. Not only the speed of computers has increased, their price decreasing; but the programming environment is facilitating also the experimental approach, which seems the only way to an understanding of these very complex and fascinating phenomena. Nevertheless, even though some success has been achieved, a lot of mystery remains; computers are not brain...

Information and Computers

Long before its present industrial realization, computers were understood as the most general logical machine, implementing the concept of algorithms or programmes. Being given an input data, a computer executes a programme to process the data and gives an output result, in a completely deterministic way.

An item of information, more simply an information, is a pair consisting of a physical representation and its interpretation(s). A representation is any real mean representing an object; for instance, the light waves radiated by an object are a representation of the object, the pressure waves delivered by a mouth are a representation of a speech. The input data of a computer are also representations, if they may be interpreted.

Computers can be viewed as interpretation machines: starting from a representation, the input data, the execution of a programme gives an interpretation, the output data. In turn, this result may be interpreted by an observer or maybe another representation which a new programme could interpret again.

The quantity of information in computer science is the amount of memory in bytes, or octets, requested to store a representation *(signifiant)* into a computer memory. It should not be mixed up with the term information, which implies an interpretation *(signifié)*.

Goals and Means of Pattern Recognition

Pattern Recognition (P.R.) tries to simulate the visual or auditive perceptions of human beings. Algorithms, implemented by programmes, are executed by the computer which operates as an interpretation machine. Starting from representations stored in his memory it delivers interpretations, mostly identification of objects.

Representations are stored in the computer memory as numerical values, the pixels, which are samples of 1-dimension signals of speech versus time, or of 2-dimension signals in space of an image. The sampling process, and particularly the number n of samples depends on the nature of the signal, essentially on the bandwidth in time or space. To give an idea of the order of magnitude, storing 10 seconds of speech requests a quantity of information of 100 K bytes, storing a printed character 500 bytes, an A4 sheet of paper 6 M bytes, a satellite image 200 M bytes. Sometimes a reduction of the quantity of information may be made by using binary (0,1) representations, instead of multi or grey level representations. One binary digit or bit is then enough to represent a pixel. Linear sensors such as microphones of TV camera do not deliver binary signal; it should be realized that the binarisation of a representation, obtained by a non-linear thresholding operation is a delicate operation.

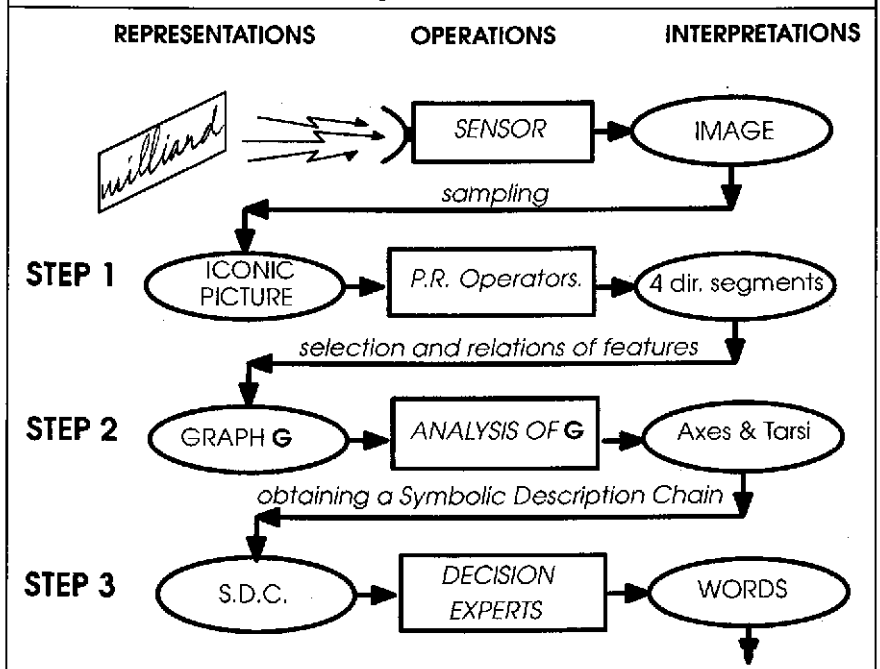
Figure 1 describes a typical chain of P.R. operations. The first step is already described. In Figure 1, a sensor interprets the outside world representation as an image. This image, scanned and sampled, gives way to a new representation, called an iconic picture, n pixels, stored in a computer memory. The P.R. operations, execution of P.R. algorithms or programmes, take place at successive levels. At each level, a representation is interpreted to give new representations which either are interpreted by the observer or by the next level of the logical machine.

A Basic Difficulty: Computing Complexity

Why is it not possible to jump directly from the iconic picture representation to the identification of object or to scene analysis? The reason is computing complexity.

Let us comment on this term. As other computer science processes, P.R. operations are constructive operations. Unlike mathematics, which deals with objects by their names and properties, computer science deals with representations and algorithms on these representations. The price to pay for constructivity is the limits imposed by computing complexity.

Figure 1: A schema of P.R. operations for the line image of a word



Computing complexity is defined as the order of magnitude O(n) of the number of elementary operations which an algorithm has to performed on n elementary data, here pixels, to obtain a result, here an interpretation. Sometimes the algorithm never stops, it is said undecidable. Sometimes the algorithm requests a number of steps polynomial with n, $O(n^p)$. If n is small then the algorithm is tractable (let us recall the size of n for an image, easily 10^6).

Algorithms such as template matching, which obviously would be useful for P.R. are exponential with n. Most of algorithms in computer science are in an intermediate class, the NP (non deterministic polynomial) class, which makes them intractable as soon as n is not small.

The only ways out are:

- to lower the dimension of n, i.e. of the data; in other words to operate on small partial pictures;
- to decompose the process in several decision levels, each starting with more abstract representations;
- to use polynomial operators of low degree, thus tractable; but the consequence is to allow errors; in a way computing complexity is then exchanged for uncertainty.

From Pixels to Features

Going back to Figure 1, let us comment the interpretation step of level 1, starting from the pixels of a picture and obtaining the first interpretations, i.e. the features. This step, which conditions the success of the final operation, is most difficult. It is in fact the birth of concepts. Pixels are undifferentiated objects; they have the uniform type of numerical values. Such a picture of n pixels may be seen as a point in a n-dimension space R^n. Of course such a space is immense and most of the points represent only noise image, like an out-of-order TV screen. Without interpretation, the possible points are all similar in type and infinite in number. On the contrary, features have different types, i.e. different interpretations: for an image, a texture, an edge, a liner; or for speech a vowel, a consonant. The step from pixels to features allows to progress in comprehension from an infinite world without meaning, the Chaos of the Greeks, to finite ensembles of features, already different from each other and having a meaning, a semantic.

On which properties can we rely to build up these P.R. operators?

- On properties of the representation space R^n, which is a topological space, having all sorts of good properties: continuity, metric, etc. ... Statistical P.R. is the name often given to the techniques which rely on these properties, i.e. projective techniques, linear transformations, Hough transforms, probability or fuzzy density decision functions, hyperplanes, nearest neighbours.
- On properties of the interpretations and of their corresponding operators; the most important being invariance to transformations of the object, such as translation, size, projection. In fact, experience shows that some features are more easy to find than others. They are characterized by the invariance to translation, in other words they are periodic.

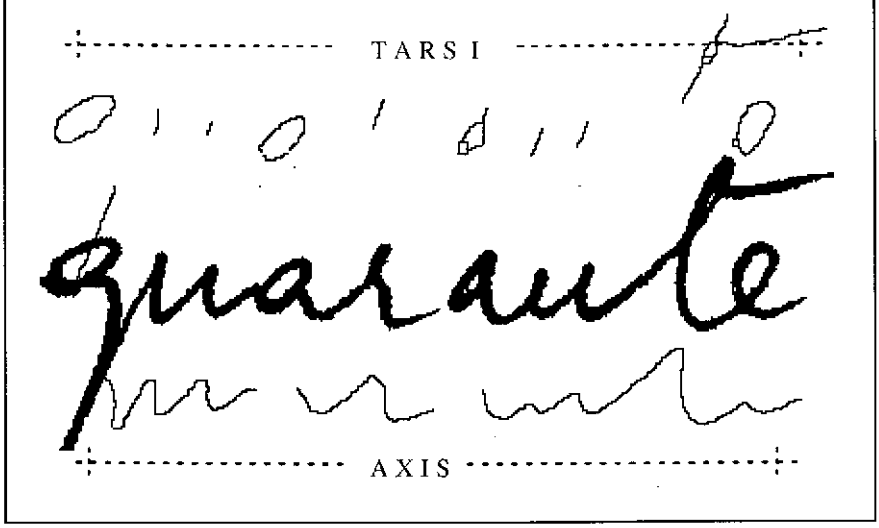
Examples are textures or line for images, vowels for speech.

A Complementarity Principle

We may classify features, and more generally representations in two classes: the regular class, defined by regularities such as periodicity, the singular class which are the accidents of the regular features or representations. The errors of identification of regular features are usually very small, of the order of 1% for vowels for instance. The singular features are found as the complements of regular features to the total signal.

Figure 2 shows an example of the application of these ideas to the graph G, representation of level 2 of Figure 1. In the middle of Figure 2 is the binary picture of the handwritten word 'quarante'. The features 'lines' are found, and the result is a graph G, representing the line image of the word. The regular part of G is the AXIS, in the lower half of Figure 2. The singular parts of G, here called TARSI, are obtained by subtracting the AXIS from G. These singular features represent the most important part of the information.

Figure 2: Below: AXIS. Middle: initial picture. Above: TARSI.



Higher Level of Interpretation

From level 2 and up several other interpretation levels may be found; each starting from a representation, obtained from the interpretation of the former level. These representations are more and more abstract or symbolic, embedding more and more 'knowledge' (comprehension). But conversely, the price to pay for this universality is a loss of numerical definition. Restoration of the original picture is less and less possible. As said Aristotle, 3,000 years ago, 'When comprehension increases, extension (precise definition) decreases'.

Such P.R. processes are particularly interesting for linguists, in the sense that they exemplify the birth of languages, which to our opinion were generated by the abstraction mechanisms refined in the ontogeny of neural mechanisms and brains, for the essential purpose of recognition of images and sounds. Each recognition level has its own types (words), syntactic and semantic rules, in short a micro-language, up to the final human languages as the last level of the chain.

Artificial Intelligence, A.I., starts with concepts of level 2 at least, and of course there is no real difference between A.I. and P.R. in higher levels, except maybe that A.I. philosophy and technique is more top-down and P.R. more bottom-up. On the other hand, the success of such recognition processes is based on the essential jump of level 1, from the continuous world of pixels to the discrete ensembles of features, comparable to the jump from classical to quantum physics. Many A.I. projects have failed by assuming as solved the lower levels steps of concept formation.

Future Research and Developments

The applications of P.R. are already impressive.

Concerning speech, 1,000 words for a few speakers or 50 words for most speakers, with a few percent errors. But continuous speech recognition is still an open problem. It seems clear that a lot of linguistic information (meta-knowledge) has to be used to segment a continuous speech. O.C.R., optical character recognition, is applied in reading postal documents, more generally in document analysis. Printed and even handwritten characters are already read with very little errors. But handwritten cursive script recognition is still at the research stage.

Remote sensing, radar, medical and robotic pictures are also processed in industrial or military applications of routine type; but P.R. does not compete in quality with man for difficult recognition problems. On the other hand, all these systems have the greatest difficulties in the acquisition of new knowledge, i.e. in learning. There seems to be an antinomy between programmability and learnability. Finally, the slightest error in a programme or in a component deteriorates completely the execution. It is quite surprising that such large programmes and complex machine may work at all. Brains are notoriously more robust and work well even with a lot of dead neurons or of errors...

All this makes conspicuous the differences between human brains and computer programmes. Criticising the differences, efforts are made to imitate neural nets, reviving the Perceptron endeavour of the 60s, which fell out of favour in the 70s. Neurocomputing has been coined as the name of these new approaches. Results are interesting, but not yet up to conventional P.R. performances. Nevertheless, abstracting, generalizing, organizing knowledge, in other words learning, is the central question for researchers in this fascinating field of Pattern Recognition."

References

On the topic of computer vision:

Ballard D.H., Brown C.M., 1982, Computer vision, Prentice Hall.

Devijver P.A., Kittler J., 1982, Statistical Pattern Recognition, Prentice Hall.

Duda R.O., Hart P.E., 1973, Pattern classification and scene analysis, John Wiley.

Devijver P.A., Kittler J. 1987, Pattern recognition theory and applications, NATO ASI, Serie F, 30, Springer Verlag.

Fu K.S., 1982, Syntactic Pattern Recognition and applications, Prentice Hall.

Gregory R.L. 1970, The intelligent eye, McGraw Hill.

Marr D., 1982, Vision, W.H. Freeman.

Pao Yoh-Han, 1989, Adaptive Pattern Recognition and Neural Networks, Addison Wesley.

Pavlidis T., 1982, Graphics and image processing, Springer Verlag.

Pentland A.P., 1986, From pixels to predicates, Ablex Publ. Corp. USA.

Rosenfeld A., Kak A., 1982, Digital picture processing, Academic Press.

Simon J.C., 1986, Patterns and operators, McGraw Hill in USA, North Oxford Acad. in Europe.

Simon J.C. edit. From pixels to features, 1989, North Holland.

On the more specific topic of document recognition:

Proceedings of ICDAR-91, Saint Malo, Sept. 1991.

Proceedings of IWFHR-1, Concordia Univ., Montreal, April 1990.

Proceedings of IWFHR-2, Bonas, Gers, Sept. 1991.

SECOND SESSION

Life Sciences and their Global Impact

Chairman: Shuhei Aida

Towards a Molecular Understanding of Mammalian Development and Disease?

Erwin Wagner, Institute of Molecular Pathology, Vienna, Austria

"I would like to start out by thanking the Honda Foundation and in particular the Alexander von Humboldt-Stiftung for organizing this meeting and for inviting me. It is, needless to say, an honour to talk in this session on life sciences and their global impact. When I received this invitation I was all excited and I thought I will definitely choose the short form of presentation where I will give you a provocative statement and then I would be ready to discuss it with you. When I thought about it a little longer – it is like when you do an experiment, initially you are all excited, but later on when you have to evaluate it in detail it becomes much more complex. And so it was when I thought about how human societies view the 'life sciences', I got into very muddy waters. And I decided that it will probably be much better to talk about some of the frontiers in the science we are doing, try to be provocative and try to open up a discussion, where you can challenge my ideas about mammalian development and possible diseases.

I would like to start out by saying that when I think about what impact life sciences have on our society, I feel that intellectually they have a very big impact, but globally I do not think that we really foresee an impact at present. But this is my personal view, and I would be happy to discuss it with you at the end of my talk.

For the remaining, I will constrain myself to discussing basic science. And I would like to end my talk with some applied science, where I think that the society is very interested in what we are doing and is open for a public discussion.

I would like to outline to you what approaches we have today for analyzing early mammalian development. I will explain to you and exemplify with some of our own work how powerful embryonic stem (ES) cells are. I would like to elude to possibly also human embryonic stem cells to be provocative, and then I will go on and show you what we can do in terms of model systems for diseases, how we can dissect the networks of genes regulating growth control and tumour formation, where the prospects lie in the future and where life science is at the moment. At the end, as I said, if time permits, I would like to outline the experiments which have been conducted and been published on somatic gene therapy, mostly involving cells from the hematopoietic system.

A 15-day-old mouse embryo, I think you all are convinced, is a fascinating creature, and only very few probably in this audience would say that molecular

biology will comprehend the mechanisms and the genetic networks which are operating to form such a multicellular organism. I think it is very clear – at least in my mind – that we can only take certain parts and assume that maybe understanding parts of it, we might finally get a picture of how an early embryo develops, how patterns are laid down in the embryo and so forth. I think this example illustrates to you that what we are trying to understand is very complex and that the answers will be very limited.

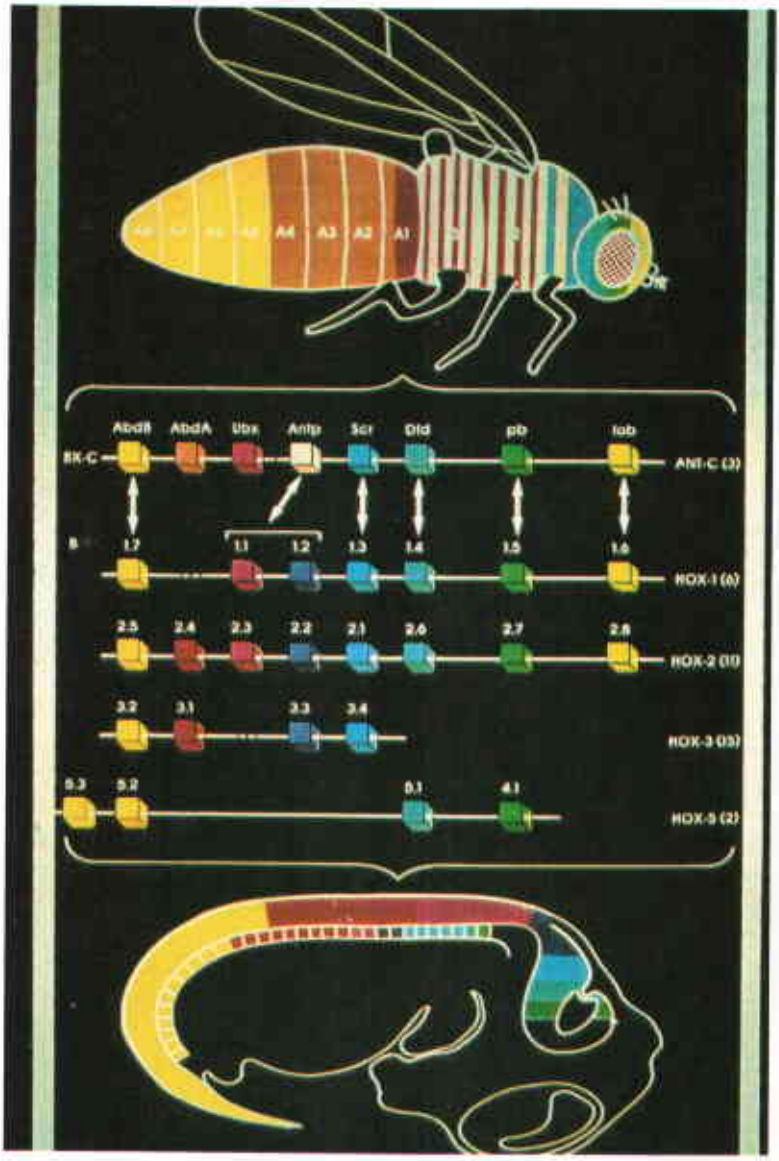
Next I will give you an idea how people in the 'mouse field' think about development and where the big unanswered questions lie. And there are a few points I want to make. I have depicted for those who are working in philosophy and law a fertilized egg with a female and a male pronucleus. The point to make is that we need a paternal and a maternal genome to make an entire organism. The recent work on imprinting has shown that it is indeed so. The other point I want to make is that this embryo at the one-cell stage egg or later in development is very accessible to genetic manipulation. We can add genes, and as we will see, we can delete specific genes. We can obtain a lot of information on how genes are regulated and how they possibly function in development. Most importantly for those of us who work with a mammalian, the mouse system, we have very powerful tissue culture techniques, somatic cell genetics, all kinds of gene transfer techniques, which can be used to obtain and to describe the genetic events, which are occurring for example in the one-cell embryo.

How would you set out to study genes which act early in development? There are many ways, and if one looks into the literature, there are many different approaches. I would just like to describe to you one powerful and very fashionable approach. I would like to briefly outline it to you, and also make a statement about what the approach might tell us.

The approach could be described as from flies to mice to man and back (Figure 1).

Why do I say this? In figure 1 you see a segmented Drosophila, and this depicts a cluster of genes, which is by no means complete. And down here you see a mouse embryo. The colours and the genes depict the sequential expression pattern along the axes of an embryo from anterior to posterior. The amazing finding is that the genes have been highly conserved between Drosophila, mouse and man and furthermore, that the sequential activation of genes correlates with the positional values of the cells along the axes. I do not think we can deduce from these particular experiments that the development of a fly conceptually is similar to that of a mouse. We can only say that evolutionarily we have conserved functional aspects of certain genes which are definitely operating in setting up the pattern and staging the expression profile within the embryo and thereby being instrumental in the development of an embryo. I think the different development of a Drosophila embryo from a mammalian embryo poses rightly the question, whether the basic mechanisms which act in molecular terms for mammalian development might be similar to the fly. I would probably disagree. If you think about the regulation of these genes, we noted that in the mouse retinoic acid is probably a key regulator. There is no evidence that this reagent

Figure 1: From flies to mice and man



The figure schematically shows the arrangement of various Hox gene clusters from the mouse (Hox 1-5) compared to the genes of the antennapedia complex in *Drosophila*. Furthermore, the specially restricted expression of specific genes and their conservation between *Drosophila* and mouse is also indicated.

plays a role in the insect, and therefore the mechanisms might be different. This is just to illustrate how one set of genes, which are definitely instrumental in early mammalian development, have been identified based on the homology to Drosophila.

How does one go about to study the function of these genes and possibly their regulation? Again many different experimental approaches are possible. One has already been mentioned at the meeting yesterday. The DNA of a particular gene can be injected into a fertilized mouse egg. This technique has been around for about ten years and has helped us a lot to dissect tissue specific gene expression, regulation of genes but also gene function. In the context of homeobox containing genes it was very instrumental to assess the specific pattern of expression of these genes throughout development, and also their functional importance. A particular regulatory region of a Hox gene has been fused to the lac Z gene. This is a very common technique, using a reporter gene, to visualize the stage and spatially restricted expression, exemplified by the blue staining of the histochemical marker ß-galactosidase. With this approach many people have dissected the transcriptional control elements important for directing expression of these genes. I should also mention that all of these homeobox containing genes are transcription factors. They bind sequence specific to DNA, they activate genes, they may repress genes. The mechanism how they talk to each other and how they recognize each other is, to my knowledge, not understood as yet. It is something which many, many groups are heavily working on.

Now what else can you do? The last experiment taught us that a particular sequence is very important for a particular pattern of expression. You can also do experiments towards genefunction, where you would ask whether it has any consequences for the embryo when you express a particular gene at a particular stage in development. You can take again DNA vectors with particular promoter elements from your gene of interest and express it in different cell types, and then ask: does it have a consequence? And the answer is yes. With homeobox containing genes but also with many other transcription factors it does have. I have one example again from Peter Gruss's lab, where a homeotic transformation was seen in the vertebrae by over-expressing one particular Hox gene. A pro-atlas is formed in one of the uppermost cervical vertebra columns, in addition to the normal structure which we have in an embryo. This is very good evidence that these genes are very instrumental in setting up the body plan. One current view is that the combined expression of sets of these Hox genes identifies the position of the cell in the embryo.

I will leave the early embryological study and would like to bring up one other example, which was already mentioned in Ernst Winnacker's talk yesterday. Many scientists are most interested in defining if one particular gene or a class of genes can specify the development of a particular organ. I should state that even in the yeast cell we do not understand the mechanisms which convert a cell A into a cell B and also forming a daughtercell A. The whole mechanism how you can change the phenotype of a cell at the genetic level is not understood. Surprising results were obtained from studies centered around sex

determination. I will give you the results and make some comments, because I think it is very important to explain some of the details.

Recently a front cover of 'Nature' issued depicting the development of a male mouse from a chromosomally female mouse, transgenic for a particular gene which is called SRY. This gene lies in the region of the Y-chromosome, which must be responsible for testis determination. And those who work in the mouse field know that this is a phenotypical male, although the chromosomal composition of the animal is XX. This result is very tentalizing and very important, since it tells you that this one particular gene has instructed the genital ridges to develop into a testis. However, this is by no means a fertile male mouse, and sex is not simply the matter of one particular gene. This is an infertile mouse, which cannot reproduce. And for those of you who were very interested in the human genes that have been tested in this context, they do not work in that particular experiment. When one injects the same 14 Kb of human homologue, no phenotype was observed. Nevertheless, these results illustrate the power of genetics, how transgenic technology is shedding important lights on the function of genes. I would like to summarize this part of my talk by saying that these studies have given us a lot of novel knowledge on how genes are arranged, how they are expressed, and partly how they function. The understanding of these genes in an interacting network which must operate during development and cellular differentiation is something which will be studied in the future. Much more work is needed to gain a better understanding of the function of these genes.

Many people might ask whether these Hox genes are involved in classical mouse mutations and if there is a relationship to disease. We are beginning to see signs where these genes may play a causal role. But one should keep in mind that these genes are possibly highly redundant, since they are always clustered in 'families'. If one compares Drosophila to the mouse, there are four classes in the mouse, and gene ablation experiments have shown that if you interfere with the network, one might disturb the system in a non-predictable way. All I want to say is that we really do not understand enough to make any predictions on the phenotype, and redundancy of the genome may be a fact which is responsible for not seeing more mutant phenotypes.

I want to switch to my second part and to something I myself am much more familiar with. This is a class of genes which are definitely causal in human disease. These genes are collectively called *oncogenes* and can be grouped into different classes resembling growth factors, growth factor receptors, transcription factors, etc. You will hear more about growth factor receptors in the talk by the next speaker, how instrumental they are to control the proliferation of a cell and also the cell cycle. It is very clear that these genes are important in growth control leading to a severe phenotype in an organism when their proper regulation and function is perturbed.

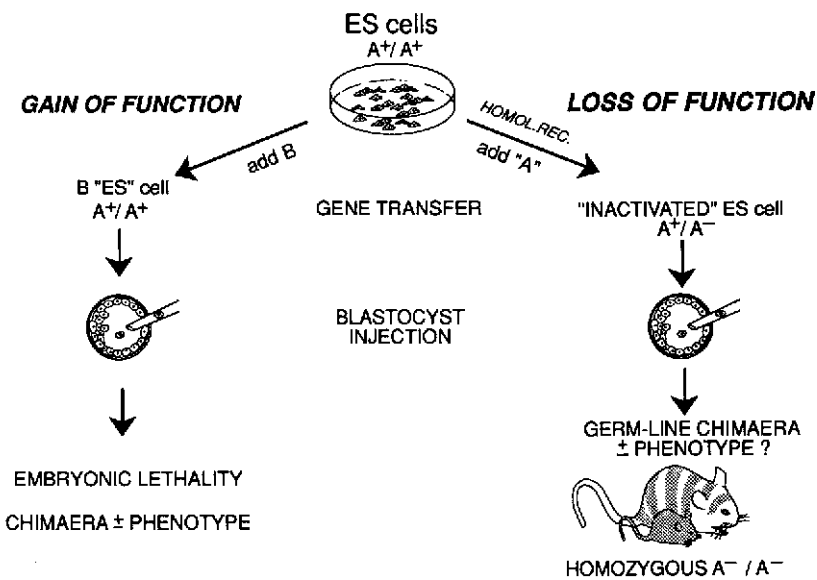
How do we go about and how do we define and study the process(es) which changes a normal cell into a malignant one? Again studies in mice, in particular with transgenic mice, may help to shed some light onto this very basic problem. I think it is clear that we have to define today a malignant cell as a cell which

has evolved stepwise and has undergone progressive alterations and genetic changes, finally leading to a cell which is highly proliferating. At a later stage a clonal expansion of this cell will lead to a malignant cell. This multi-stage model of carcinogenesis is presently being analyzed in various model systems. It is correct to state that we do not know whether the studies in mice really will tell us something about transformation of human cells. But I think that the concepts which we develop explaining the change of a normal into a malignant cell, these should be valid for mouse and man.

Let me now tell you a little bit about one system which is very instrumental for defining the function of proto-oncogenes or cellular oncogenes, as they are called. I will give you a few, very few examples.

The system has been mentioned yesterday and it is clearly a system which is revolutionizing mammalian genetics and mammalian developmental biology. It is the system of embryonic stem (ES) cells (Figure 2).

Figure 2: Scheme for studying gene function using the ES cell system



The right panel describes the loss-of-function approach involving the inactivation of one allele (e.g. A^-) via homologous recombination and subsequent transmission through the germ-line of chimeric mice. The left panel describes the gain-of-function approach involving the overexpression of a gene (e.g. B) in ES cells which might lead to an altered "ES" cell clone. Following blastocyst injection the consequences of B expression in chimeras could be embryonic lethality of the development of chimeras with or without a visible phenotype.

Those of you who work in this area are very familiar with these cells. They are derived from the explant of an early embryo, a blastocyst, and they can be cultured in vitro and permanent cell lines can be obtained. There is a number of unique features about these ES cells, not to mention that obviously they are accessible to all genetic manipulations we know by now from tissue culture cells. Moreover, these cells upon re-introduction into another embryo participate in the development of this embryo leading to a chimeric mouse. If these cells, which have been genetically altered, develop into somatic cells including the germ cells, they will pass on the genetic alteration to the offspring. Thereby we can make what I had shown in my first slide – a 'man-made' mouse, because we can add genes, we can delete genes at the level of the tissue culture cells. And we can then pass this genetic alteration through the germline of a chimera, as we call it, on to the offspring, and thereby design the mouse with the desired genetic composition. These ES cells are also very important for just in vitro experiments. I think it is very clear now that we can take these embryonic stem cells and equip them with proper signals, so that they will differentiate into one or the other cell lineage. Many attempts have been made to differentiate embryonic cells into neuronal cells or into hematopoietic cells. I think it is provocative to ask, if one had human ES cells available, why a study to convert an embryonic cell into a stem cell of the hematopoietic system would not be a desirable thing to do. I am trying to be provocative here to encourage some discussion on this topic.

For the sake of this talk, let me give you now a few examples what we can do with these ES cells. We can do basically two approaches if we always go back into the mouse. We can inactivate a gene and do a 'loss-of-function' approach, meaning that we have inactivated a gene and we ask, how does this affect the mouse if the gene is missing? I will show you in the end of this an example for this approach. Conversely, we can add genes, particular proto-oncogenes, a growth control gene, and we can ask whether the expression which has been selected for at the level of the stem cells, whether that has any consequences on development, and whether these consequences can be understood genetically and also molecularly. And I will give you three examples, very briefly, from our own work. If we express a proto-oncogene, the tyrosine kinase encoding v-src gene, we found to our surprise that although the gene was expressed throughout development, the chimeras were totally normal. You see absolutely healthy chimeric animals. They express and have a highly up-regulated tyrosine kinase activity. Important negative factors must regulate or must modulate this high activity in order not to be detrimental.

Conversely, a related oncogene introduced in the same way causes tremendous lesions in the vascular system of the mouse, and all chimeras die at midgestation. We analyzed this particular phenotype in great detail and found out that the gene acting downstream from the oncogene perturbs the normal proteolytic balance of these cells and thereby leads to haemorrhages of the blood vessels, the development of what we call endothelial tumours or hemangiomas. We are now very well ahead of experiments to try to prevent this from happen-

ing. The new concept is giving us a handle to understand how the oncogene on the one hand perturbs the system but also how we can prevent this from happening. These are experiments which are ongoing at the moment.

And yet the last example with a potent transcription factor. If we express a proto-oncogene like fos, which is involved in cell proliferation, and many experiments around the world have implicated fos as a key regulator of cell division. If we constitutively express it in many different cell types, we will only obtain one phenotype. You can see the development of severe bone lesions in these mice, which develop sequentially over time. The gene is already active at this early point, but the phenotype develops later. The bottom line from this is that these oncogenes are growth regulatory genes, they act in the context of the cell, and that additional factors in this particular cell compartment are instrumental and are cooperating to deregulate normal growth. These studies should help to find out how these genes work and how we can prevent them from working. I should also mention that these type of tumours – they are called osteosarcomas or chondrosarcomas – are also found in man. There one also finds that this particular fos oncogene is highly expressed. So it might have a relevance to society and also to the treatment of human cancers.

Let me now give you a last example of a knockout experiment which was done by two groups in the United States, by Mario Capecci and Andy McMahon, who inactivated a particular proto-oncogene, called int-1. What you can see is that if the mouse is deficient of int-1, one particular region of the brain, the cerebellum as well as part of the mid-brain does not develop. That implies this gene is very instrumental for the development of that particular part of the brain. I think these are very important experiments for advancing basic science. Whether the public can be excited and can be made interested in this remains to be seen.

I would like to leave now 'basic science' and turn to somatic gene therapy. I would like to illustrate what is possible in this field, what has been done and what is being done at present.

Gene therapy in man – there is clearly high public interest. The purpose is to correct a genetic defect, it could be gene addition therapy or a gene replacement therapy. That is what has to be discriminated. At present we can only talk about gene addition therapies. The targets are obviously somatic cells only. The indications must be that they are single gene disorders; the route of gene addition is mostly by a retrovirus at present. There are, however, many other different ways and many people are investigating novel routes. The control of these experiments must be overlooked by a national or better international body which considers all proposals and insures that the application follows national guidelines. These type of experiments are incredibly expensive. Just to file an application for a particular retrovirus to be used in a scenario involving a human cell will cost about $ 50,000, not to talk about the conduction of these experiments. I will be happy to give you some more numbers at the end of my talk. What are the targets? Can I give you some examples of somatic gene therapy experiments which have already been conducted? The answer is obviously yes.

Due to lack of time I will not go through the list of candidate diseases. I will just tell you that the prime target cells at present are hematopoietic cells. And I will not mention anything about the viral diseases but tell you a little bit about T-cells and adenosine-deaminase deficiency (ADA). Before I do this I would like to summarize the first published human gene therapy experiment from last August by Steve Rosenberg et al. using tumour infiltrated lymphocytes (TIL) cells.

They have taken tumour infiltrating lymphocytes from patients with metastatic melanoma, explanted them in vitro, genetically modified them with a retroviral vector containing a neomyan resistant gene to mark the cells and to follow them when re-introduced into the patient. The therapy relies not on the expression of the gene. All what is meant to do is to follow the fate of the cells when re-infused into the patient. The authors claimed that they have a 50%-success rate. Nowadays, they have filed applications with cytokines, with TNF, tumour necrosis factor and other genes to enhance the likelihood of killing the cancer cell.

A crucial draw-back at present may be to do long-term gene therapy experiments using bone marrow cells. And the draw-back is that we know very little about the most primitive stem cell, which gives rise to all different lineages in the myeloid and lymphoid compartments of the hematopoietic system. Great need is required to characterize and better define from the basic research stand-point the earliest stem cell, whether it can come from an ES cell, from an embryonic stem cell, or whether we can device strategies to amplify these cells by equipping them with the right cellular signals. These are all possible avenues which are followed out.

The authors of a partially successful ADA-experiment have done two things: In 'transient' experiments they have used T-cells from an ADA-deficient patient, inoculated these cells with an ADA-gene transfer-vector and then re-infused these T-cells into the patient, along with polyethyleneglycol modified (PEG) ADA. I should say that for this particular ADA-deficiency alternative treatments are possible. Therefore, it is very controversial and the risk assessment is obviously a very important aspect. In terms of long-term cure -- here are the real problems I have just alluded to. We need to take bone marrow cells, need to infect the most primitive precursor cell, the stem cell, in order to ensure long-term engraftment of these cells in the bone marrow transplanted patient.

Let me conclude by saying that I have given you some highlights on the present work in mammalian genetics, mainly along the lines of early mouse development, gene regulation and gene function, I have tried to explain some of the frontiers in that area. I think it is fair to say that the molecular mechanisms, how these genes act in a complex system, are not yet understood and whether the approach of applied science in the case of somatic gene therapy will really help and will have a global impact, remains to be seen in the future."

Regulation of Cellular Responses

Tadatsugu Taniguchi, Institute for Molecular and Cellular Biology, Osaka University, Japan

"Elucidation of the molecular mechanisms underlying the cellular responses to various extracellular stimuli is one of the most fascinating subjects in biology. In fact, the responses are tightly controlled by complex mechanisms which operate throughout from the cell surface receptor to the nucleus. Thus, elucidation of such regulatory mechanisms is not only important in basis biology but would also provide a means to modulate cellular responses by specifically targeting essential steps in the signalling pathway.

Our efforts have been focused on cytokine-mediated cell responses, particularly with respect to immune responses and cancer. Cytokines are secreted cellular products which mediate many crucial biological signals for cell growth, differentiation and transformation. Already, some cytokines have found clinical application in tackling hitherto unsurmountable disease conditions. I will summarize the present state of knowledge on the regulation of cellular responses, using some of the best characterized cytokine systems as prototypes. Understanding the cascade of complex events at different steps of the signalling pathway will ultimately lead to the discovery of novel drugs."

Mathematical Analysis of Physiological Phenomena and Future Profile

Toshiyuki Furukawa, President, Osaka National Hospital, Japan

"I think my talk is a singular one compared to the speeches of the other authors. Because I would like to talk about the mathematical laws found in the domain of the medical and biological fields. I believe that properties, natures, characteristics, and behaviours of all living organisms are restricted by the natural laws which can be described in a mathematical way. I could say that only mathematics is the method to know the external truth of our world.

Anyhow, I announced too many items in my abstract. But today I will show you two examples of mathematical analysis of the physiological phenomena. And I do hope many of you would like to agree to the important and deep meaning of such kind of mathematical methodology in science research.

At first I would like to talk about an example of the simple quantitative expression of physiological phenomena.

You many know the difference or the characteristics of pupils of several kinds of animals. The cat has a cat's eye, namely sickle moon type pupil, which is apparently suitable for nocturnal hunting.

Cat's eye gives us somehow a crafty impression. But it is not generally known that the koala has a pupil like the cat. As dark eyes make it difficult to recognize it, people can love the koala's charming look.

As is well known, the owl becomes blind in daytime. The reason is that the owl has a dilated pupil in order to keep a sensitive vision in the dark night, therefore the pupil of owl cannot adapt to the sunny bright. The reason is the limitation caused by the possible distortion of total length of the pupillary edge. I will discuss the details later.

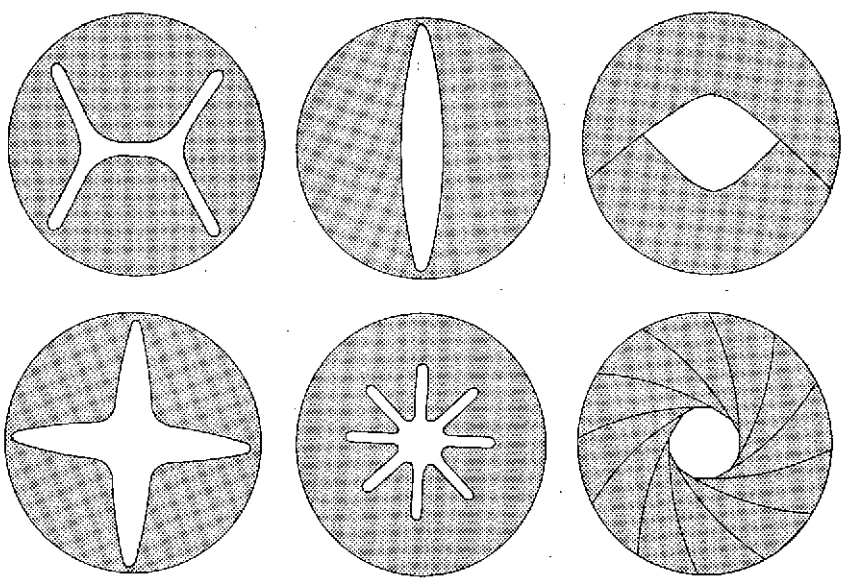
I wonder how many of you know that the pupil of sheep and goat has a rectangular form, as I suppose in European countries sheep and goat are the most popular livestock. In the laboratory of the Institute of Medical Electronics, University of Tokyo, a great number of goats has been kept for the experiment of artificial heart implant. When I found that the goat had a rectangular pupil, I frequently asked Professor Atsumi the reason why this is the case, but he is not interested in it, because his primary concern is the replacement of the goat's natural heart to the total artificial heart.

In order to take pictures of pupils of goat in the night, I had to sneak into the shed, because Professor Atsumi likes female goats and the shed is his holy harem. The pupil completely dilated as a circle in the dark circumstances.

Then, I began to pay attention to observe the pupils of different animal species. Shortly afterwards, I found that the pupil of cephalopod was very similar to that of goat. We can find many pictures or the pupil of cuttlefish in any pictorial encyclopedia. Some day, I asked a photographer to take pictures of eyes of octopus at an aquarium, and I could confirm that the pupil of octopus was rectangular.

Now, let us consider the reason of set-up of the rectangular form of pupil. The feasible designs of pupillary mechanism are shown schematically (Figure 1).

Figure 1: Possible design of pupillary mechanism

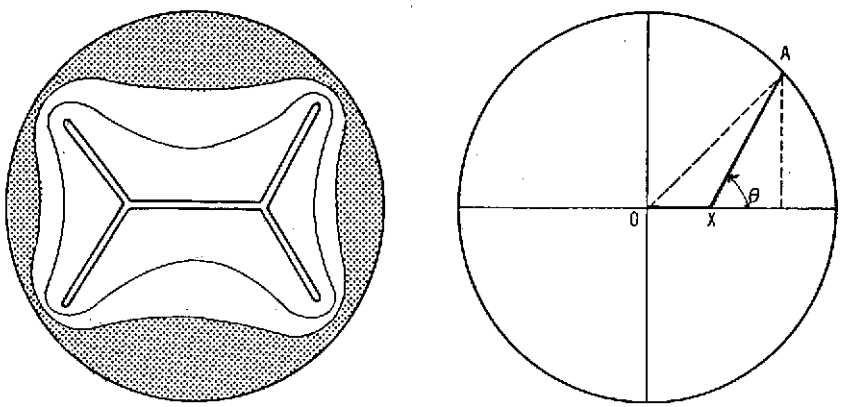


From the stand point of technology, only a small number of designs are industrialized, i.e. some are applied in the camera lens. There is one of the most popular and cheap iris of the lens consisting of two pterygoid plates. At the same time, the more orthodox iris of lens consists of a great number of plates. Anyway, the engineer is able to produce a pupil which can cover from 100 per cent to 0 per cent of opening ratio. But the concept of pupil design of living beings is different from that of the industrial engineer. The cat's eye type pupil is considered to be a very basic type. But considering the ratio of expansion and contraction of the total length of pupillary edge, it must change from two times of diameter in the contracted situation to multiply diameter by π in the dilated situation, it means $\pi/2$ times ($\fallingdotseq 1.571$). From among the other feasible designs, we can find better plans to cover the opening ratio from 100 per cent to 0 per cent. According to

the minimum energy law, the best design must have a simple structure. So, comparing several designs, we can choose the cross shape or its variation.

Now the problem comes to a simple arithmetic one. When the iris has a couple of two Ys form, the total length of pupillary edge is described as the outlines of the couple two Ys form (Figure 2). Briefly speaking, the angle of Y must be 120° if it minimizes the surface tension. Thus, the optimum design is decided estimating the point where the length of outline is equal to that of totally dilated circle of the pupil, from a simple mathematical calculation (Figure 3). I can say that the Creator or the sagacious gene gave an excellent design of pupil to the nocturnal defenceless animals.

Figure 2: Total length of Y's form



$$max \quad OX = 2\,AX$$

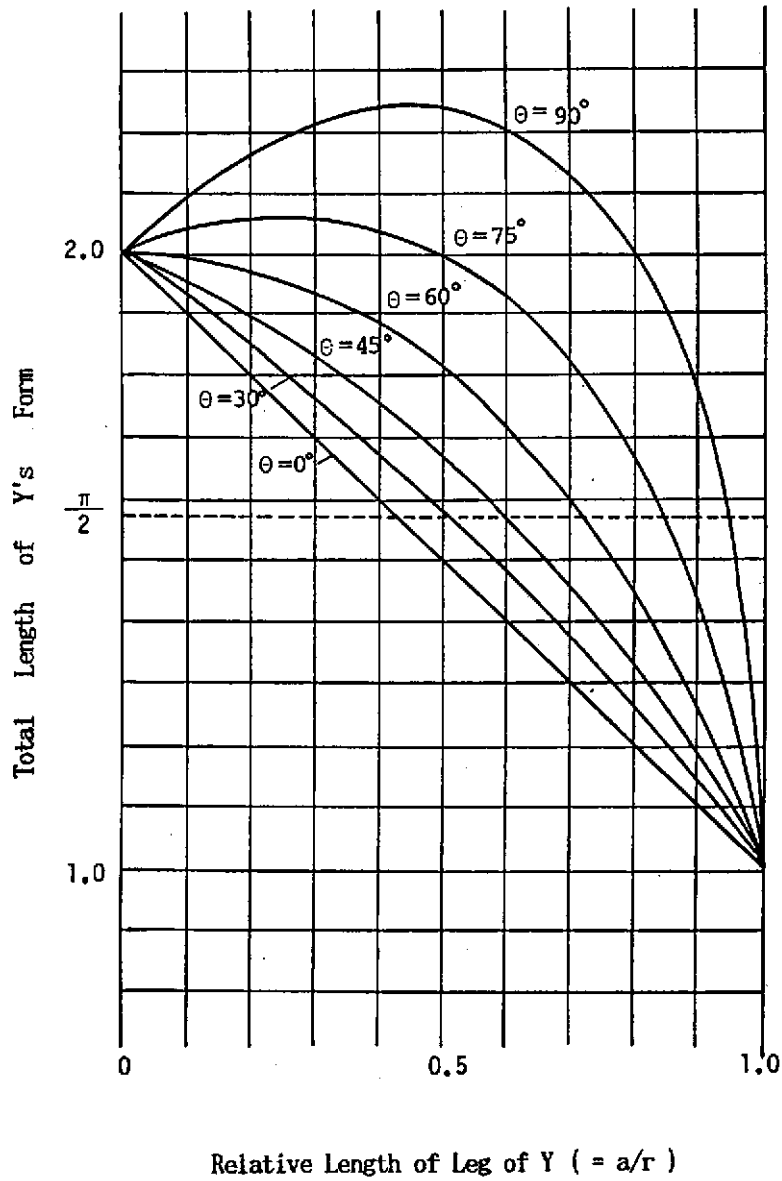
$$(a\sin\Theta)^2 + (x + a\cos\Theta)^2 = 1$$

$$a = \sqrt{1 - x^2\sin^2\Theta} - x\cos\Theta$$

$$a = \overline{AX} \qquad x = \overline{OX}$$

There has been a tremendous number of examples of such kind of manifestation of the Creator or the Gene. Why can cranes fly over a high altitude, the upper region of the mountain top of the Himalaya without oxygen mask? Not only cranes but also small birds such as canary birds and paddy birds can live in the artificial high altitude set up in the low pressure chamber. However, mice sharing the low pressure chamber with birds faint to death. The supercharger mechanism is composed of their specific respiration system. The air stream within the lung of bird flows as a countercurrent to the pulmonary blood flow. As the high efficient gas exchange is possible in that countercurrent system, the lung of bird can absorb oxygen from the thin air. In addition, the respiration system of the

Figure 3: Total length of Y's form

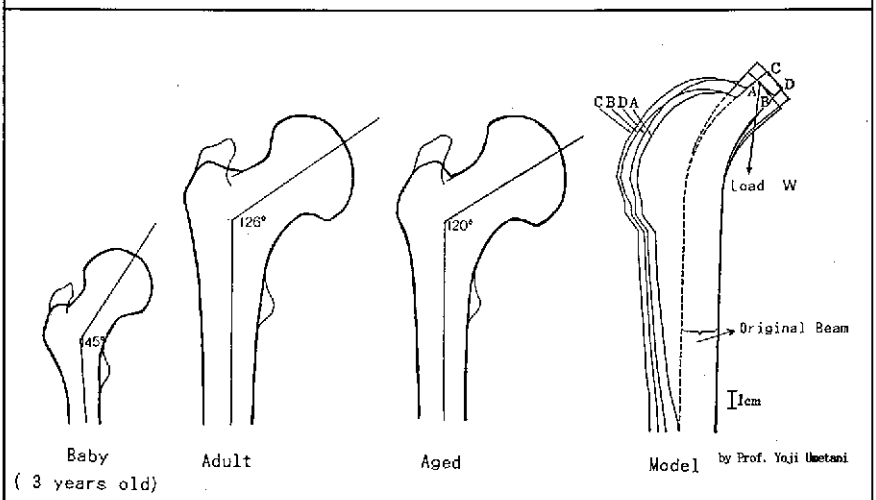


bird is cooperating under the assistance of air sacs in its body. It must be emphasized that the air sacs in the front part of the body work as the heat radiator of the high-power flying engine of the bird. It means the air sacs surround the pectoral muscle, which is the flying engine, and the exhaustion air discharges the heat produced by the flying engine. This specific mechanism allows the non-stop long range flying to the bird.

The countercurrent multiplying system in the mammalian kidney is also one of the sublime works of 'the Gene'. The whale can live without supply of pure water. The kidney of whale consists of over 3,000 units. Each unit has an extremely developed countercurrent system, namely Henle's loop, in the renal medulla. It can squeeze out the pure water from the sea-water. All of the renal physiologists cannot give any rational scenario of development of renal countercurrent system. It shall be one of the everlasting research goals of renal physiology and of theory of evolution.

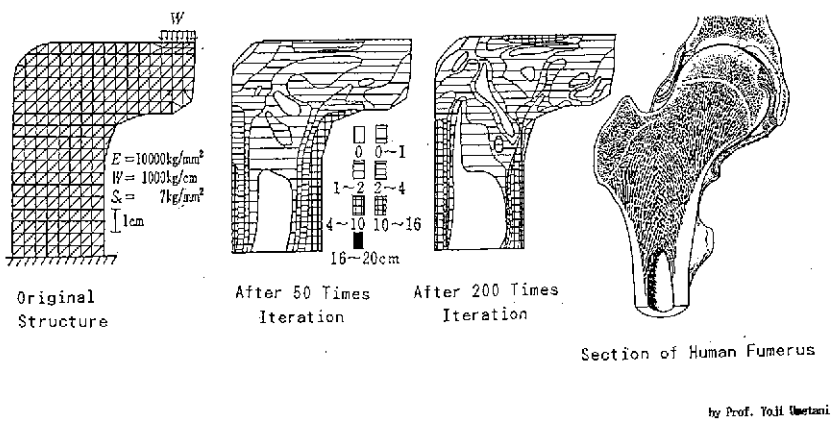
In the other cases, we can often draw a part of the unconscious intention of 'the Gene'. A couple of years ago, Professor Yoji Umetani, Tokyo Institute of Technology, simulated the unique shape of the form of prominence of thigh-bone. This bony prominence is called a greater trochanter and has been simply considered to be a connecting part of great muscle. He assumed that the bone materials distributed according to the strength of stress. His model started from a simple upside down L beam and iterated calculation was performed by a computer. As time went by, the bone material accumulated on the specific part on top of thigh-bone. Finally, the shape of the upside down L beam offered a curious resemblance to the human thigh-bone (Figure 4).

Figure 4: Simulation of greater trochanter started from upside down L beam



Professor Umetani spread out his work to another model. In this model, a restricted amount of material was relocated according to the strength of stress. The relocation of bone material was calculated using a finite element method. The results of the simulation showed an amazing resemblance to the human femur, the thigh-bone, even to the appearance of the bone marrow space (Figure 5).

Figure 5: Simulation of bone material distribution in human thigh-bone



In the latter half of my presentation, I would like to describe one of the mathematical approaches to the life span determinant. In other words, it shall offer a subjective scale to the research in gerontology.

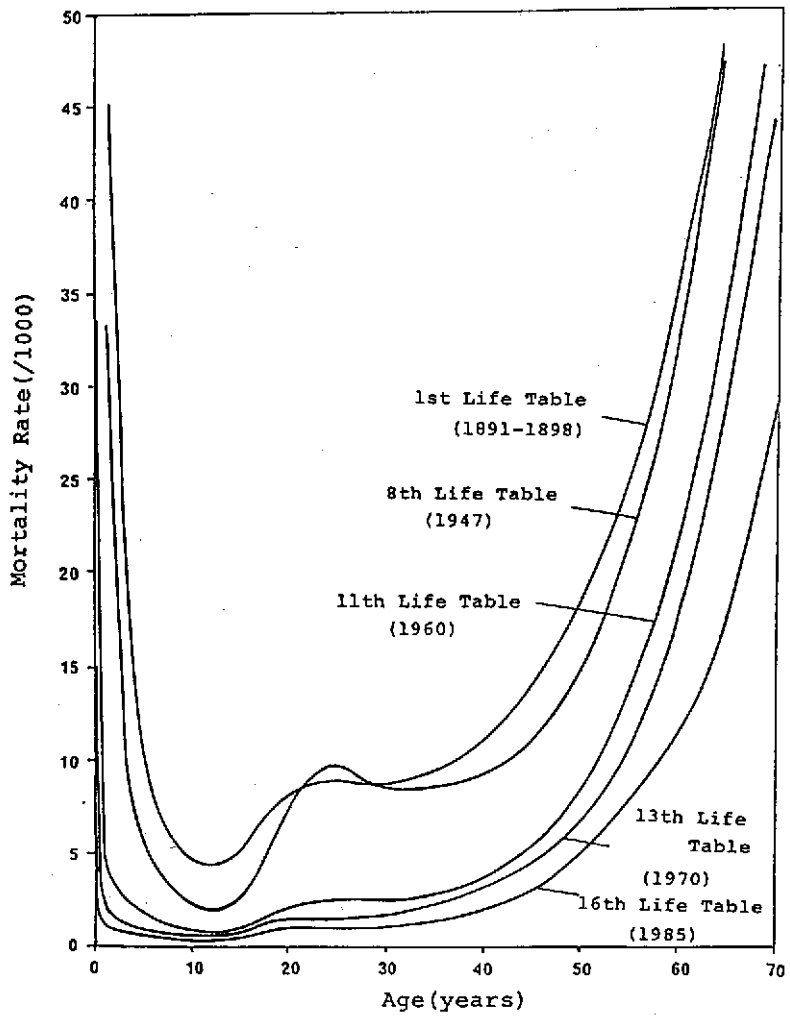
Age specific mortality rate curves resemble the failure of parts of machines and also artificial systems such as chemical industrial plants and so forth (Figure 6).

The mortality of infant babies is remarkably high even in the developed countries, and this phenomenon resembles the high initial failure of machines and systems. Low mortality at 10 to 20 years old is like a random failure mode of machines during the most reliable operation period. Machines and those parts are discarded and replaced due to wear-out after long operation. Mortality after 40 years old corresponds to the physiological senescence and is a typical wear-out failure. The failure rate curve of machine is depicted as bath-tab form, which resembles human age specific mortality rate.

Fortunately, the Japanese census is well known to be quite accurate, and about 100 years' records have been kept. Moreover, the Japanese are composed of a uniform nation, and are homogeneous with respect to the level of living

circumstances, medical services, and also healthy nutrition intake, and moderate welfare.

Figure 6: Movement of age-specific mortality rate of Japanese male

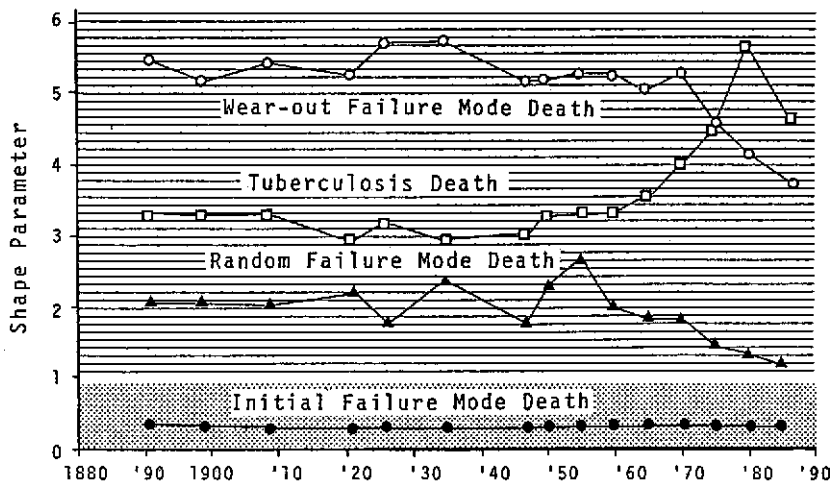


In order to estimate parameters and to confirm the Weibull model, I started from a rough estimation using a Weibull chart. It is similar to a peeling analysis of exponential function models.

Then, I proceeded to a precise solution of Weibull model using a non-linear least square method.

Thus, the age specific mortality rats of Japanese national censuses were analyzed as a mixed Weibull distribution as follows (Figure 7),

Figure 7: Movement of shape parameters of modes of death in Japanese male



$$F = \sum_{i-1}^{4} p \cdot \exp\left[-\frac{(t-\gamma)^m}{t_0}\right]$$

where
- p: mixing ratio
- γ: location parameter
- t_0: scale parameter
- m: shape parameter

The first component corresponds to the death of babies and shows a typical initial failure mode. As expected, the mortality rate decreases very rapidly after birth. That means shape parameter m is less than 1.0, namely m = 0.297. Comparing to the cases of machine, it seems to stabilize after operation more rapidly than those of Benz cars and Honda cars, which are well known to be of excellent quality. It is most impressive that the shape parameter has been unchanged during the recent 100 years, so that I can suggest the constancy of the fundamental design of molecular machine, human body at birth. In the engineering sense, the quality of the machine at shipping is completely controlled.

It is also expected that the mortality during the growing period may follow the random failure mode. But, actually, shape parameter in the youth has been over 1.0, it means somewhat wear-out failure is carried over in this period by the contamination of some few diseases, which has relatively high incidence in the past. In recent years, however, the shape parameter in the youth becomes closer to 1.0 year by year. It means the hypothesis supposing the death in youth as a random failure mode is reasonable.

Tuberculosis is not such a threatening cause of death as in the past. As it should be taken care of the developing circumstances, however, the detailed discussion will be skipped at this time.

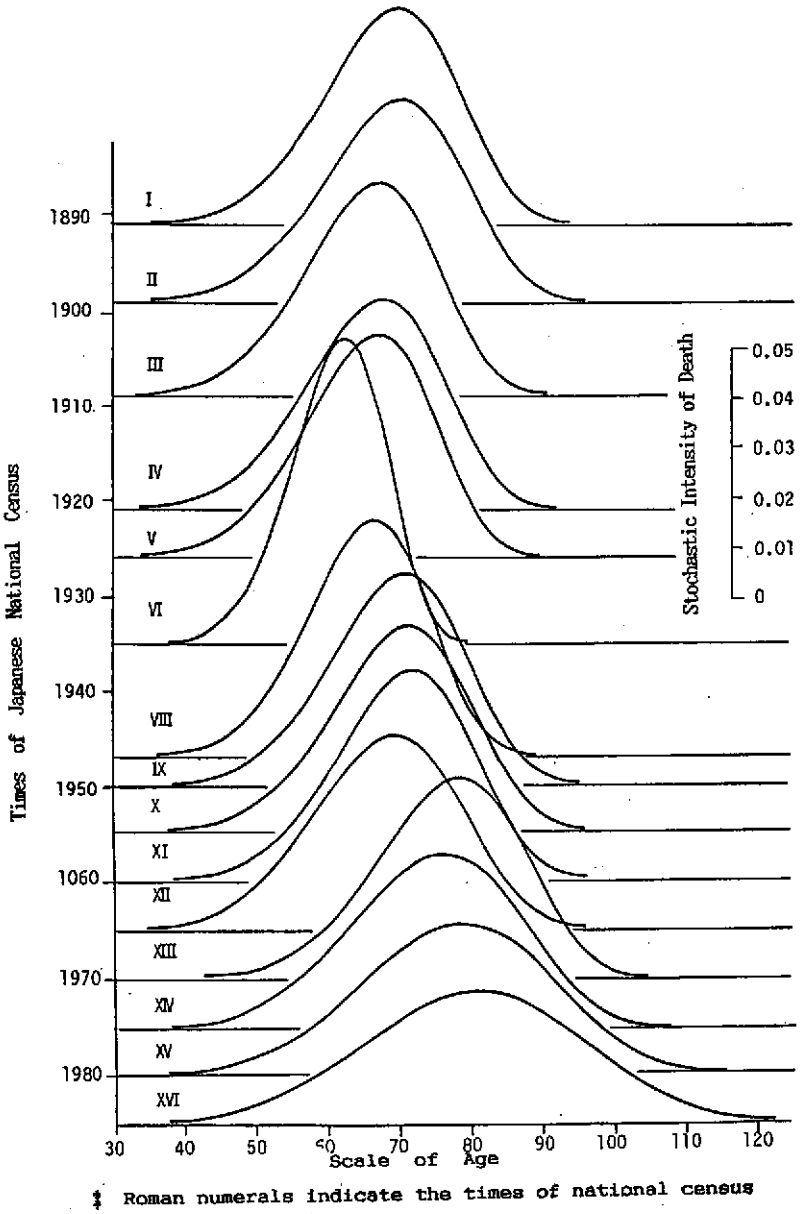
The so-called life expectancy is supposed to be the result of wear-out of vital capacity. The exponentially increasing mortality rate after 40 years old is the determinative wear-out component of human life span. The shape parameter had been around 5.0 and began decreasing from 1960 and is now under 4.0. There has been an idealized expectation that the natural life span of all individuals must certainly be equalized when the far advancement of medicine is achieved. In that case, the survival curve becomes rectangular at the species allotted life span. It is unexpected that the variance of wear-out failure mode death becomes greater. Mortal medicine has been concerned with lowering mortality rates of such adult diseases as brain stroke, cardiovascular disease, malignant tumours, and so forth. If such efforts have brought about the prolongation of life span, wear-out failure mode must become more steep a distribution with less variance. But my analysis shows the opposite results (Figure 8).

Consequently, we are forced to make a new hypothesis that once an imminent disease is suppressed, new diseases show up as more intractable causes of death. We may go so far as to say that man is doomed to death not due to the end of natural life span but due to disease. Modern medicine has been successful in lowering mortality rate in infant and youth, but, as is noted before, the shape parameter in the initial failure mode during infancy does not change. It is suggested that incoming goal of research and investigation in medicine shall be directed towards the elucidation of the process before birth. Another important project shall be the study of diseases in aging process.

Regarding the movement of location parameter, I am going to skip the detailed interpretation. But I would like to ask you to remember the fact that the location parameter of the wear-out failure has been shifting to the older age. I will discuss this fact later.

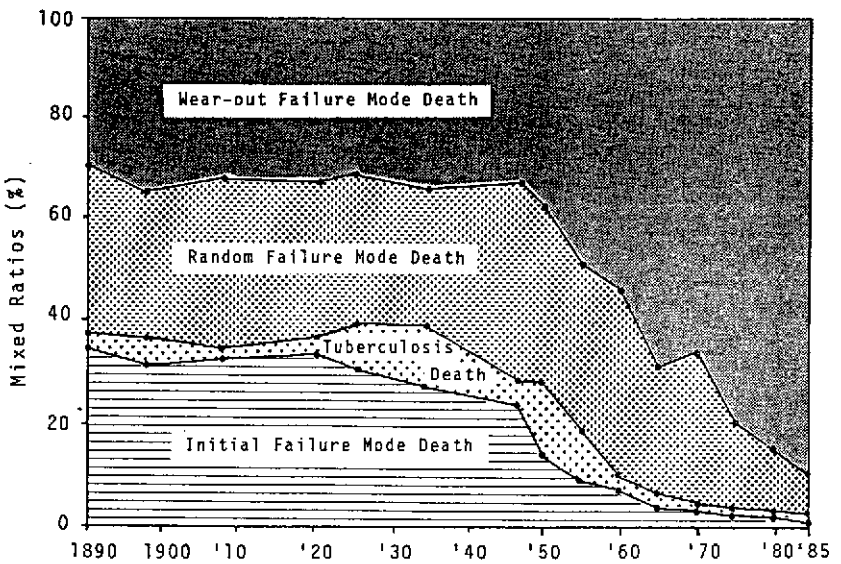
The most dramatic movement that occurred in the recent 100 years is the change of mixed rate. The mixed rate of initial failure mode death reduced most remarkably. Until the end of World War II the mixing rate of initial failure mode death had been near one third of total death. The mixed rate for the random failure mode death and for the wear-out failure mode death shared the rest two thirds equally. But, at now the mixed rate for the initial failure mode is less than 1 per cent, for the random failure mode death is 9 per cent, and for the wear-out failure death is over 89 per cent (Figure 9).

Figure 8: Stochastic intensity function of death in the aged



‡ Roman numerals indicate the times of national census

Figure 9: Movement of mixed ratios of modes of death in Japanese male



Now, let us look into the problem of the unchangeableness of shape parameter in the initial failure mode in infants. According to our knowledge of the reliability of industrial products, by prompting the initial failure under severe utilization conditions, we can retain a highly reliable product. Supposed that human infants are saved from death due to good sanitary environments, the many weaker individuals may remain alive. In reality, however, there are no such tendencies. Therefore, the model which is applicable to machine parts is considered to be not applicable to living creatures having growing stages. For a reasonable solution, we must assume a model the scale parameter of which will change with growth.

In order to conceive a concrete image, it is better to imagine a model of factory. In this factory, in the production line which will not become a completed product — as if the parts are stolen by a huge number of thieves who break into a shop. In this case, the thief is the illness which will cause the death of an infant baby. If the thieves are arrested the damage will decrease, the shipping volume of the completed products will increase, and thereafter the production line will run without trouble. The product itself has a longer life span until it reaches wear-out failure.

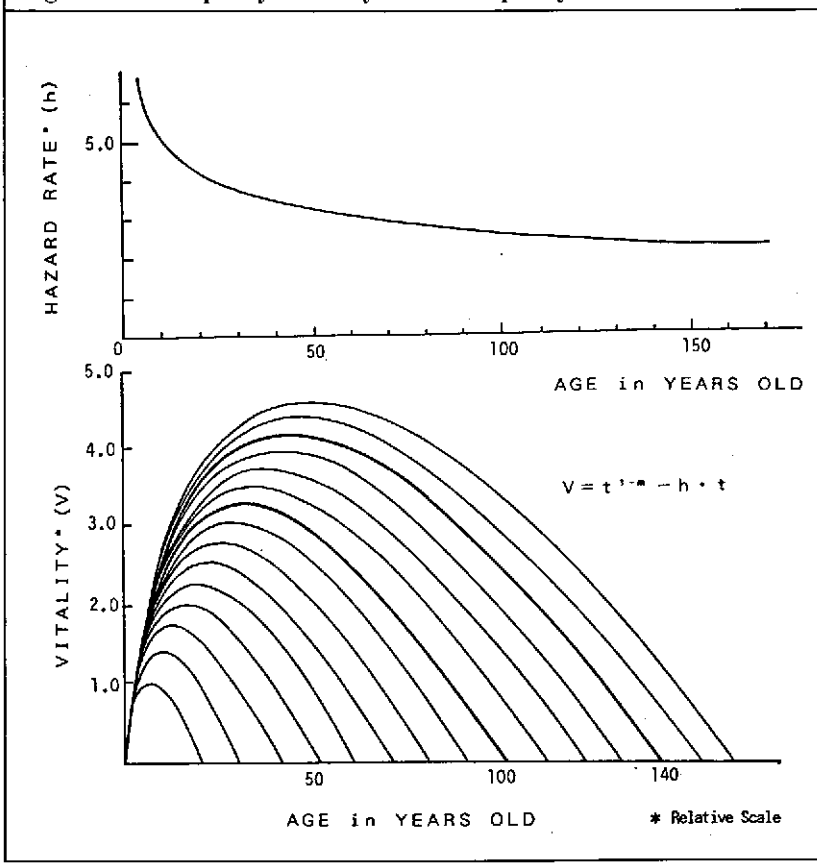
According to the opinion of a specialist in reliability engineering, the reliability of computer software will grow by the removal of bugs. Taking such an interdisciplinary example into consideration, the new model shall contain a parameter which unifies the function of growth factor and of the hazard factor.

The difference between the growth factor and the hazard factor corresponds to the conceptual volume of living power, or the vital capacity.

If the loss of the vital capacity occurs as a random mode, namely according to a Poisson distribution, the ageing process of the individual can be calculated as the difference between the growth function and uniform loss of the conceptual vital activity.

I estimated the growth function from the shape parameter of initial failure Weibull function which was obtained from the solution of actual life table. And as the hazard function, a most simple first order proportional function was introduced. The hazard function includes both intrinsic and extrinsic hazard factors. Thus, the conceptual vital capacity rises and falls as a bent parabolic curve. And the magnitude of hazard coefficient is decreased as an hyperbolic curve (Figure 10).

Figure 10: Prosperity & decay of vital capacity model



Comparing these trends to the actual vital capacity of human being, the residue indicates the size of intrinsic hazard, it means the size of congenital and hereditary lethal factors. Therefore, the vital capacity is able to be described as:

$$\text{Vital activity} = t_0 \, (t^{1\,m} - h \cdot t)$$

where the simple Weibull function is converted as follows:

$$F = \exp\left[-\frac{t^m}{t_0}\right] = \exp\left[-\frac{t}{t_0 \cdot t^{1\,m}}\right] = \exp\left[-\frac{1}{t_0 \cdot t^{m}}\right]$$

Then, this function means the dynamics model with the size of the compartment changes by time according to an exponential way as $t_0 \cdot t^{1\,m}$. In order to consider the effects of intrinsic and extrinsic hazard, the denominator of the equation can be rewrite as follows:

$$F = \exp\left[-\frac{t}{t_0 \, (t^{1\,m} \quad h \cdot t)}\right] = \exp\left[-\frac{1}{t_0 \, (t^{m} - h)}\right]$$

In this model, the size of compartment expands and shrinks when time goes by.

At this point, I may propose some suggestions and questions to the molecular biologists. The growth function is estimated to be $t^{1\,m}$, the parameter governing the growth function is (1-m), as a mathematical consequence. In the case of protocaryote, the growth function must be proportional to t, that means the growth function is $t_0 \cdot t$, and the parameter is equal to 0. So that the bacteria can divide infinitely for the breeding. In addition, the reason why the dinosaur grew up to such a gigantic size is also estimated to be the capability of endless cell division. I would like to discuss these problems together with the molecular biologists in the same ring, by the same words, and specifically by the mathematical model. Can the biology solve the meanings of this magic parameter or not? I do not know.

I can show you a supporting evidence. In a report of Hensley and his colleagues in 1964 the prosperity and decay of the physiological capacity of mouse was studied. They estimated the physiological maximum capacity by observing the gram-calorie consumption under high temperature circumstances where the experimental mouse fell into a cramp. You can find the resemblance between the experimental result to the curve deduced by a mathematical hypothesis (Figure 11).

Another supporting evidence is the chart of Japanese boys' growth curve. It apparently differs from the well-known growth functions, including logistic function, Gompertz function, and exponential function. But it is rather akin to the function I proposed above.

Figure 11: The prosperity & decay of physiological capacity in rats

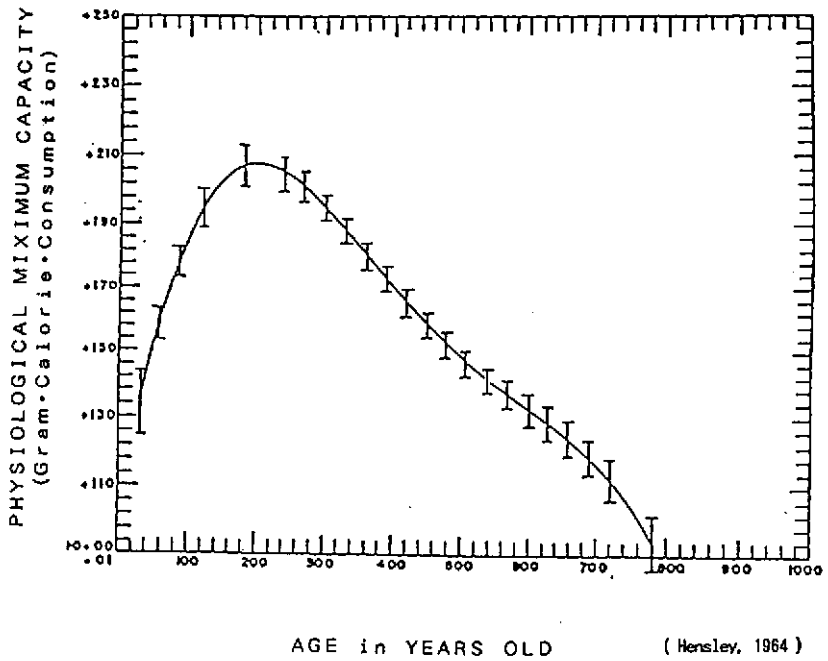
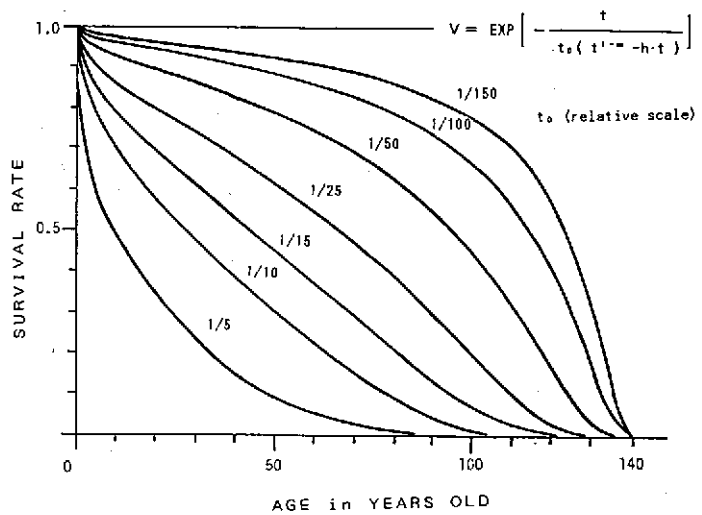


Figure 12: Survival curves of human vitality model



On the other hand, the profile of decay of the organ functions by aging is a monotonous one. In the famous test book of renal physiology written by Smith, there is a chart indicating that cardiac, renal, pulmonary and other organ functions decrease as each one owns straight lines.

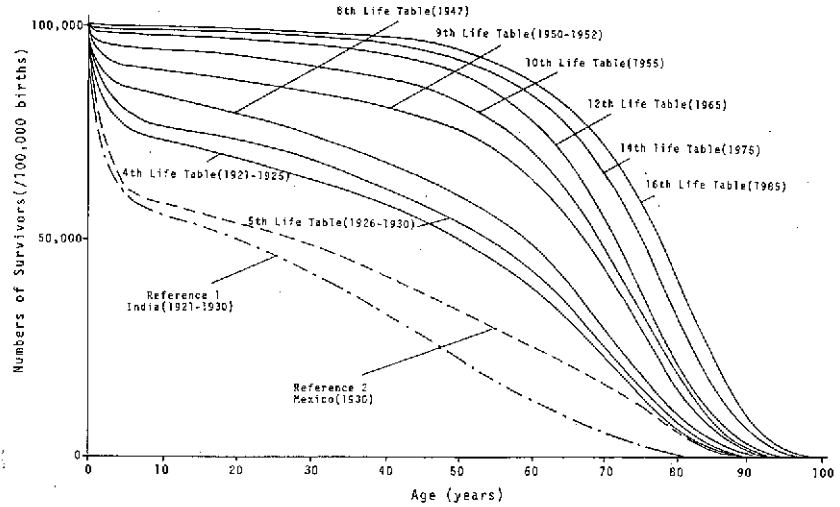
All things considered, the age specific survival curves in the different health environment levels were calculated, using the above expanded Weibull distribution function as the model of human vital capacity (Figure 12).

As a result, one can easily recognize from these curves the effects of health environmental improvement between the developed and developing stages. As a matter of course, there remains some difference to the actual survival curves of human being (Figure 13), but I think this difference itself must be the next goal of mathematical approach.

Before ending my speech, I would like to suggest that the Gene is neither almighty nor omnipotent. The history of the evolution is the history of trials and errors. We can see many examples of good design and bad design of fossil animals. Nothosaurus was designed in a complex greedy concept. It had a long head bone and longer legs with shorter palms. In addition, the webs between the fingers were also added. This awkward design was far from the high speed swimming capability. On the contrary, the design of Mixosaurus is better. It had a dolphin-type streamline shape. Only the propelling mechanism, namely the fin was a primitive system. The design like the wing of jet air plane will be most effective to deliver the propelling power. It is interesting that the Gene seems to have neither a basic idea for the evolution of living beings, nor mathematically and physically an optimum design concept. I mean the rational approaches to the biology are ever so many. The mathematical analysis is one of the minority party. But, I believe the researchers most powerful tool is mathematics.

At last, I would like to ask somebody to teach me the reason why the woodpecker can escape from the brain concussion in spite of the strong and continuous percussion. When the mechanism becomes clear, it will be helpful to protect drivers from car accidents."

Figure 13: Movement of numbers of survivors in Japanese male



How can Life Sciences create New Waves of Industrial Innovation?

Hansgeorg Gareis, Hoechst AG, Frankfurt-Höchst, Germany

"If the one or the other of you really has read the title of my talk which is in your programme, you may have been somewhat puzzled by the formulation 'industrial innovation'. When I read it in preparing the talk, I was puzzled myself: I don't think there is an industrial innovation. There is of course innovation (even if we for the moment escape a definition what innovation is) but there is certainly no industrial innovation. There is only innovation, which may be interesting and in this case it is also interesting for industry.

What the title means of course is simple: will innovations in life science create new areas of application in industry?

I could say 'Yes' and sit down again. But I will disappoint you, I will not only try to explain this 'Yes' but in addition I will also add a few more or less serious 'Buts'.

Life science searches for the understanding of life. It does not search for the answer to the philosophical question 'What is life?'. It is looking for answers to questions like 'How does life occur?', 'How functions an organism?', 'Why is a petunia pink or yellow?' etc. And I think it is not trivial to ask the question: how should the answers to these questions lead to industrial activities?

Industrial Activities out of Research in Life Science. Medicine

At the moment the largest area of application is certainly medicine. And I will also try to explain, why in my opinion this will be so also in the near future.

It is and it was always the art of the doctor to diagnose a certain disorder correctly and then think about the reason for the disorder.

In old times urine was tasted by the tongue, the experienced doctor looked careful at his patient and smelled a little bit. And then made his diagnosis. The remedies he had were little and really not very effective. So he put the patient to bed and hoped that the organism would help himself.

Today we have complicated and elaborated machines which analyse carefully every parameter of every fluid which can be found in the body and compares it automatically with the mean values which the machine knows.

The knowledge of how enzymes function and how they influence each other made it possible that medical diagnosis can be more accurate than ever before.

This has led of course to an enormous increase in many activities for the diagnostic industry. New machines, highly sophisticated apparatures have been

made available not only to the large hospitals but also to the smaller community houses and even to the general practitioner. This then has achieved two digit sales increases during the last years for industry. And there is yet no end to be seen.

At this point is the first 'But'. The question of money arises. These analyses become more and more expensive. And social insurance begins to wonder how long they will be able to afford this. The first signs of cost savings are on the wall already. On the other side it is well understood that a correctly done diagnosis can save a lot of money in hospital and other costs. But we should not neglect that money is a limiting factor.

I think one can make it very simple: without the breathtaking recent results in life science practically none of our nowadays available drugs would have been possible. Examples are plenty: ACE-inhibitors, H2-Antagonists, Sodium — or Potassiumchannelblockers, Renin-inhibitors and many others. All depend on results of modern life sciences. Without the tools and the knowledge of this science no modern drug-research would be possible.

This is the reason why the pharmaceutical industry, with all its critics, with all its difficulties, will also in future be one of the very few steadily growing parts of the economy.

Money for Research

Again there comes the 'But'! To continue this research and development is of course only possible if there is enough money to be spent. Not only does the diagnosis for the patient become more expensive. Research itself and all what is connected with it is eating up more money than ever before. It is difficult to calculate, but you are not mistaken to say that the development of a new drug, until it reaches the patient, today takes 200 to 500 mio $ and 6 to 12 years, in some cases even longer.

It would be a disaster if this industry would in future not have the funds to plough profits back into new developments and use the results of life science. The roads to cancer treatment or even cures against AIDS would be totally blocked.

We see already the first traffic-lights for the use of modern research results. If we don't watch they may easily turn red.

People

But there are not only outside constraints. The process of picking up new results does not work on its own. There must be people who know and accept this process.

Industry has to provide two types of people. First there must be a bunch of industry scientists who cry at the right moment: 'Hey, there is something which we ought to do.' They must be well informed about what is going on in the

science community and must (and I reiterate must) do basic research on their own. Otherwise they would not understand their colleagues from university, they could not smell that there is something hot and finally they would not cry at the right moment. These people are rare and they have to be raised and motivated carefully.

The second group of people is as important as the first one. There must be corporate management people who have sufficient trust and confidence in their science colleagues to provide the necessary funds. I may assure you that this is not so easy especially when you remember what we just said before. To calculate the results or the success of research in profit and loss figures is as difficult as it was ever before. Economy scientists have written books, have given lectures, university chairs have been donated and created. But the final answer has not yet been given.

It is my personal opinion that calculations about research success are possible, but what figures finally mean is a different question. It is more important that there is a high degree of motivation to create a climate for innovation. There are huge research institutions which are absolutely dry, and there are little circles of a few researchers which produce one result after the other.

To sum up already at this point: life science with all its results can but must not create new waves for industrial applications. There are certain constraints both from outside and from inside the industry. But they can be overcome if they are realized and people are convinced that this should be done.

This is comparatively easy in medicine because the chances for life science in the area are evident. There are estimates that at the end of this century there will be sales between 10 and 20 billion $ with products originating from gentechnology only. If we take life science as a whole there will be certainly products worth 100 billion $ or even more.

Agriculture, Opportunities and Constraints

But I am convinced that medicine will not be the only area where life science will have impacts.

In a time-span of a few decades the earth will have about 8 billion people to feed. 2 billion more than today. There are no more empty places to occupy and to just grow wheat or potatoes. Even if there would be still some uncultivated land, it would never be sufficient to grow the then urgently needed food.

Life science in recent years has provided the tools to increase food production. Science is convinced that there will be plants growing on dry or salty soil. There will be plants which are resistant to certain diseases and there will be plants which need less fertilizer. This then means less energy to be provided by men.

In this area I am somewhat reluctant to predict in which time frame new waves for industrial activity will come. It is obvious that they will come but may be slower than one would imagine.

The reasons are simple but not so easy to understand. The plant breeders industry is highly conservative. Since new products as we just have described, may change their industry completely, they may not be in their own interest. It is my personal notion that they did or do not want, at least until now, to understand that this impact will come anyway. And it will be the only solution to the population problem in the coming century.

On the other hand, we have food over-production today in all the northern hemisphere and the huge problems which this causes. This does certainly not cry for additional production. The problems of today totally overshadow the needs of tomorrow. Therefore to a certain extent one can understand the viewpoint of this industry.

But if this is so, one has to find ways and means to resolve this very basic future problem.

This is the reason why I do think that these have to be government projects. They may be even so costly and risky that they are too big for national governments. Therefore it should be at least a European or even a WHO problem. There are the first signs that this is going to be understood in this sense.

I am convinced that only life science has the ways and means to effectfully counteract the approaching catastrophe of over-population. To speak of a catastrophe is not just the view of a pessimistic elderly gentleman but a fact which can be calculated in very simple figures and numbers.

Life science can create enormous waves of industrial activity in agriculture. Provided however that there are a few far-sighted people who take things in hand and convince organizations and governments that there is an urgent problem which has to be solved. If we do not react, the next generation would rightly blame us of ignorance.

CO_2 and Life Science

The steadily increasing population is one major problem of our space-ship Earth. And of course one problem creates other problems. The increasing population causes increasing production of CO_2. It cannot be avoided that by the mere existence of men CO_2 production increases. It will inevitably lead to an increase of this gas in atmosphere, because the otherwise existing equilibrium between absorption and release is disturbed. And this will finally lead to a change in climate. Again this is not the view of an elderly pessimist but as clear and solid a fact as is over-population. You don't need the computer to calculate the equation. You may take a pencil and a single sheet of paper to arrive at the same result.

How to diminish the production of CO_2? The simplest would be to save energy, because energy production is one major source of CO_2. This could be most effectful if people would be really aware of the seriousness of the problem.

Another possibility is nuclear energy, because no CO_2 is produced. We know the pros and cons and the never ending discussions. Even if it may be the cleanest energy-source it may not be the only answer. Another way would be to

use much more solar energy. It is without question that the cheapest and the most plenty available energy is solar energy. But until now we are not able to use it economically. We are told that the chips which one needs to collect solar energy are too expensive, if one does not produce enough. It seems to be one of the vicious circles society has to deal with. Maybe also here government and other organizations should step in and provide funds, which could be used to bring the problem closer to a solution.

The problem which could be tackled by life science is the absorption of CO_2 out of the atmosphere by plants. To grow more plants seems to be a contradiction to what we said before: that there is no room for more plants. I have to admit this contradiction is true in the long run. But for the medium-term future we have to realise that we do not know what to do with our food producing crops. We even take large agricultural areas out of production. The situation is recognized to a certain extent. There is research to produce plants which have such a high content of oil that it could be used in combustion engines. The results show that with some more effort this could be made economically feasible.

Also here we are against a very conservative and powerful group. But just for this reason we would need people who cry: 'Hey, there is something which we ought to do.' I think such a cry and its effect would be much more useful than sending space-ships up into the orbit circling around the world. Besides a few other experiments nothing else is done but watching how the human organism behaves under conditions without gravity. This does help the space-industry but does not contribute at all to resolve really pressing problems on earth. Many people know how this money could be spent much more effectfully.

I am convinced that innovation in life science can and will produce new waves of activity for industry. This is very obvious in medicine, both in diagnostics and in therapy. This is already in full swing.

This is also obvious in agriculture. I just may mention again: pesticide-resistance, disease-resistance, defined protein producing plants i.e. insulin even up to albumin, plants of dry or salty soil, oil producing plants for combustion purposes etc.

But here is the area for very far-sighted and future-oriented not only scientists but also entrepreneurs and last but not least politicians. One only can hope that those men will be found.

Life Science and Animals

The area where I am somewhat reluctant is animal breeding. One has shown that one can produce animals which are able to grow faster or are resistant to certain diseases or even excrete substances which could be very useful in medicine.

It is absolutely clear that this is highly interesting for scientists and certainly for animal breeders or farmers themselves.

But this is such a highly emotion-loaded area that I doubt somewhat whether society is already prepared to accept, let us say, the change of animals. I am

convinced that this comes, because it is so obvious, but there are many things which have to change until such work can be used by industry.

Life Science and the Public

This leads to the last chapter of my talk. Can we expect that all things which can be done technically can also be realized?

Are men allowed to do what they can do? The question may sound trivial. Since centuries we have laws which should prohibit certain activities. There were always things which were not allowed to be done. But the more delicate question 'Can things which are technically possible be done or not?' is not trivial at all in our days.

The question our fathers never would have understood. At the beginning of this century everything which became technically possible was welcome, since it was supposed to contribute further to the well-being of men.

Today it is different. The word 'progress' has not only bright and optimistic aspects. Experience has shown that even beautiful and very useful things can have two aspects: positive and negative ones. And people have realized and started to become afraid.

We are living today, as the slogan goes, in a post-industrial society. We may like it or not but not only in Europe, also in the US and somewhat behind also in Japan environmentalists have their say. And I think one has to listen to them, because in certain aspects they are right. We cannot do everything without thinking what our doing is doing to the environment.

This does not only change the climate for science, it changes also, and I think very considerably, the climate for industry.

When I was a young man, the responsibility of the producer stopped in the moment the product had left the factory premises.

There were of course always exceptions, i.e. medicines or other products which went directly to the consumer. The carmaker always had to guaranty the safety of his product as long as it was used according to instructions. But what happened to the car finally when it could not be used any more was not his problem. Industry produced millions of tons of plastic material and forgot it in the moment it had left the factory site.

This has changed and I think we all agree rightly so.

I cannot any more do anything with things I have produced. This is the reason why I think the meaning of what is property has changed. When the Romans first started to think about property the definition was clear: if you own something or even someone, you can do with the object or the subject whatever you want to do or not to do. Today the ownership especially of industrial property is quite different. There are considerations about the community, about social implications and today also about the environment as a whole. It is not only safety but also what the product by its mere existence does to the environment. Where does it finally go, can it be recycled or will it stay forever? And we may have to accept that there may be products which cannot be produced any more.

This may rightly be so. But at this point I would like to pass the question to attorneys and philosophers who may be more apt to deal with this topic.

We should here and today try to find the answer, after all what we have said, to the question: will life science lead to new waves of industrial activity?

Constraint, Solutions, Hopes

Any activity which leads to something new has in it the unknown, otherwise it would not be new. Therefore the answer to the question 'May there be some danger in what you are doing?' must be 'Yes' but 'I believe or even I am sure the probability will be very small.' I will not be able to state that there will be no danger at all.

If we were afraid to take any risk then the solution could only be to do nothing at all. But it would be an illusion to pretend that such a non-activity would be feasible. Firstly it would have to be a world-wide agreement. And we all know which difficulties world-wide agreements have. Secondly the do-nothing attitude would mean that all the problems we mentioned would have not the slightest chance for being resolved. They are just not solved by themselves. To take the argument to the extreme: do nothing would be suicide. The third alternative could then be, let everyone do what he wants, because there is no solution anyway. But this would be chaos.

There is the dilemma! We have the dogma that research should be free and have this even fixed in our constitutions. We also firmly believe in a free economy with as much freedom as possible. But especially here it was early understood that there must be certain rules which have to be acknowledged by the players of the game: anti-trust-law in many different variants were put into effect. And industry has learnt to live with it.

I am certainly not the advocate of new laws. But we will not be able to live in this highly complicated world without rules. Since, as we have seen before, there is no alternative but to go ahead and do something, we can do this only when we accept limitations or rules.

I am a strong believer in self-responsibility. You may contradict me in saying that this is the illusion of an idealist. And you will be able to bring many examples for that I am wrong. But I still believe that the game can only be played by responsible players.

I am convinced that all of us in this room are convinced that our highly technical world can only be kept as a place where it is worth living if we bring more and even more sophisticated technology into operation. Making by its mere existence has changed this world so much that only new inventions can keep the change in limits.

I am convinced that life science will be one important means in this struggle. There will also be others but life science will have a high priority.

I am optimistic that we are aware of our responsibility and we are intelligent enough to find ways to imply the results of research in the right way. BUT ...

And there it the 'But' again. It will be more difficult to do so than it has ever been in the past. Because not only we in this closed room have to do it, but it will also be our responsibility to make these results accepted by politicians by the media and finally by the public itself. And nobody of us should underestimate this task. If we do not succeed we all are the losers.

The first and very pessimistic report to the Club of Rome was a shock. But only because it was a shock the public reacted. And finally the report proved to be wrong. Not because the report was wrong by itself but because it prompted reaction. The discussion about energy saving, treatment of waste and limited world resources started. And people found results.

What we have to do is to convey the message that our earth needs more not less technology in order to be able to survive. But of course it has to be considered very carefully what type of technology it should be and how it should be used.

This is also the reason why I predict that there will be many waves of industrial activity originating from life science innovations. But they may be somewhat different and may be not as high as we could imagine them to be today.

We may, more than in the past, first have to think and then to do."

Biotechnology Assessment – Political Figleaf or Scientific Tool?

Walter Ch. Zimmerli, University of Bamberg, Germany

"1. The most recent part of scientific development is characterized by what has been called "universal technologization", i.e. by a process of encompassing hybridization of elements formerly belonging to the strictly seperated areas of sciences and technics. From a traditional point of view, technologization consists in the mere technical application of the results of basic research. From a more advanced point of view, however, the whole process of what traditionally went by the name of "scientific progress" is now turning out to have been a process of technologization from its very beginning: The "experimental philosophy" of the renaissance, explicitely aimed at the technical benefits as it was, set the goal, and the modern period of pure basic science as opposed to applied science and industrial technology was but a compensation for the lacking applicability of the scientific results.

2. That the sciences are undergoing an universal technological change of the aforementioned kind becomes obvious when we take a look at the so-called "New Technologies", i.e. at information technology and particularly at biotechnology employing genetic engineering methods. Life sciences are on the point of advancing from the developmental stage of analytical science to the stage of synthetic technology or, to put it differently, from description and explanation to construction. And this is especially true with respect to the second-order hybridization emerging from the combination of information technology and genetic engineering.

3. At the same time (and probably not quite independent of the universal technologization) the sciences experience a paradigm shift as far as their internal orientation towards time is concerned: The future-oriented attitude of optimism as expressed in the notion of "scientific progress" is increasingly replaced by the rather pessimistic attitude of "avoiding unintended negative side-effects". Therefore Technological Assessment (TA), in its early days despised as "technology arrestment" or "technology harassment", finds itself, all of sudden, forced into the position of a scientific front-runner discipline.

4. In order to avoid the temptation of promising more than it is actually capable of achieving, TA has to carefully reconsider its own strengths and weaknesses. For methodological reasons TA has failed (and always will fail) to become a

successful instrument of technological forecasting, and it must be called in question whether TA is capable of reliably functioning ever as an early warning system. On the other hand, however, a new TA-conception has prevailed according to which TA is complex transdisciplinary tool consisting of

a) research in unintended side-effects of the application of different technologies,
b) monitoring the development of both the unintended effects and the TA-results achieved by other researchers,
c) research in the social value systems,
d) monitoring the changing these value systems undergo,
e) assessing the actual and possible unintended (and sometimes even unknown) side-effects with respect to the actual and possible social value-attitudes, and
f) preparing the techno-political decision-making.

From this it becomes evident that TA is both a scientific and a political tool, in which the evaluation of different options with respect to different value-systems plays a decisive role. The theoretical substantiation of value-oriented normative arguments therefore play an important role in TA.

5. With respect to the special problem of genetic engineering methods in biotechnology therefore five different questions arise:

a) Which are the different realms of application, and what are the specific differences between them?
b) Do any categorical (unconditional) ethical commandments and prohibitions exist, or is every application of genetic engineering methods subject to a comparative (conditional) assessment?
c) What are the rather technological risks and benefits of the different applications?
d) How could we take into account the difference between factual behavior of acceptance and rational acceptability (homo-oeconomicus-model) of risks?
e) Are there additional possible cultural/social impacts and how could they be weighed?

6. The only categorically prohibited case in the different realms of a) human application, b) animal production, and c) plant production is the case of gene-transfer into human germline-cells. All other cases including the application of genetic engineering methods to human somatic cells and animal or plant production, are subject to a comparative/conditional assessment, the most promising ethical principle of which is what I call the "principle of situationally modified biological relativity".

7. With respect to the not strictly ethical aspects the results of biological security studies are to be combined with a socio-psychological discourse-analysis, especially of the scientific, the industrial, the juridical, the political, and the public discourse (cf. TAB-project "Biologische Sicherheit bei der Nutzung der Gentechnik"). The most promising methods to calculate qualitative preferences and value-attitudes are non-transitive and non-commutative value-hierarchies

("mute value systems analysis"). Elements of knowledge from the field of the humanities must finally be used to identify and assess different cultural impacts in pluralistic societies (different esteem of an unhurt nature etc.)."

Principles of Biological Autonomy studied by the Amalgamation of the Eastern and Western Ways of Thinking

Hiroshi Shimizu, Faculty of Pharmaceutical Sciences,
Tokyo University, Japan

The Principles of Biological Computation

Introduction

"The purpose of my talk in this Discoveries Symposium is to discuss the fundamental principles of 'biological computation' leading to biological autonomy and cognition based on some theories of the oriental metaphysics and philosophy. I am afraid that you might think that this is an inconsistent and ill-defined problem. According to common understanding, the oriental metaphysics is placed at the antipode of modern science, and would be regarded as founded on an ambiguous thinking. Frankly, many years ago, I thought like this. However, at the present time, I have a different opinion. The oriental metaphysics or philosophy has logical rationality which is understandable beyond cultural background.

In 1980, I applied to a Japanese national project, the so-called 'Bioholonics Project', which was fortunately accepted in 1981 and continued for five years under international collaboration. As one of the problems in the project, a new type of pattern recognition by means of the entrainment of nonlinear oscillators was included. The new cognitive system was named 'holovision' [1-3]. What was aimed in the study of holovision was to realize what was proposed by Heidegger and by Wittgenstein; namely, recognition is the interpretation of the meaning of input signals by 'preunderstanding'. And the input signals are given as elementary signals distributed in a retinotopic plane in the form of 'dot signals'. A set of elementary signals were sent to the 'visual field' where a number of 'hypercolumns' are placed keeping retinotopic relations. The elementary signals were received one by one by the hypercolumns which were present in the same retinotopic positions. Then, owing to the network dynamics of hypercolumns to self-organize a relational order, the elementary signals were spontaneously separated into two parts in the 'visual field' of holovision; one was the connected and meaningful part called the 'figure' and the other, the ground, was meaningless and composed of elementary signals without specific connections. The figure was represented by coherent oscillations of the activities of 'simple cells' in the hypercolums in the former part of the 'visual field', the ground by incoherent oscillations of simple cells' activities in the latter part. Only the figure was connected by means of closed loops of circulating signals

with oscillating neural elements in memory where simplified characteristics of several items of 'preunderstanding' were encoded. The establishment of the closed loops means the interpretation of input signals by the connected memory item.

What I would like to note is that in our model hypercolumns were treated as a sort of originators of 'primary symbols' with elementary meaning, that is a line element with a specific orientation. Namely, the columns, their components, encode various orientations of a line element. In other words, the hypercolumns encode a possible set of elementary meanings to be given to an elementary signal introduced from environment. In our model, hypercolumns are not the detectors of line segments as had been widely accepted but the primary originator of semantic information. In the study of holovision we started from realization of important issues of the Western logico-philosophy by means of self-organization of spatyio-temporal orders in a neural net system with three logical levels.

Later in 1990, when I had a dialogue with Professor Kawai of Kyoto University, he pointed out that our theory of holovision bears a strong resemblance with the philosophy of the Hua Yen school, a school of Mahayana Buddhism, and to study Hua Yen philosophy by a paper by Izutu given in his Eranos Lecture [4]. I found that Izutsu's signs introduced to explain the origination of an ontological nexus according to Hua Yen philosophy were essentially the same with our hypercolumns as symbol originators and, therefore, that probably our approach could be connected with Hua Yen philosophy, provided that suitable extensions and modifications are carefully made keeping the basic frame of logic unchanged.

However, for completing the logic of biological autonomy, I think that Hua Yen philosophy is insufficient and that the predicate logic of the 'Place' or 'Field' which had been specifically developed in Zen had to be added. (These two kinds of logics have been treated in the oriental philosophy rather independently without clarifying mutual relations).

As a conclusion, the logics of both, modern science and oriental metaphysics, may not be complete to fully elucidate biological autonomy and cognition. However, if we properly modify both, we could hopefully be capable of discovering a new type of logic based on the amalgamation of the way of thinking characteristic to the two logics. The merit of this is of course significant even if we limit our scope only in the frame of science, because it means that we obtain the fundamental frame of the science of semantic information.

For the sake of convenience of understanding, you will, however, hear the oriental philosophy only at the final stage of my talk. Before entering the following talk, I beg your pardon for not mentioning philosophical results, in particular, in Germany and in France. This is simply because I have only rather limited time for my talk. In the long history of human being, there have been fruitful interactions between the East and the West. And both sides have received important influences in culture and in the way of thinking. It is therefore very hard for me to say what is the pure West and what is the pure East? In the strict sense of the words, my subject today, the amalgamation of the Eastern and the

Western ways of thinking, might be nonsense. The aim of my talk is to make this more and more nonsense but at the same time significant in this age of international interactions over the world.

Indefinite Uncertainty

Living system maintains its life in a complex environment, changing with indefinite uncertainty. Therefore, the system cannot predict all the states which will encounter in the future. Since living system has a limited size, it is impossible for the system to store all the operational information that might be used in the future. Hence, only one way that is possible for the living system is to create operational information for self-control in real time, depending on environmental states, of course, within its limited capability. By what principles is this 'from-time-to-time creation' of operational information for biological autonomy achieved? I would like to discuss this problem.

If one has knowledge about all the events which might appear in the future, the future can be predicted by means of the probabilities of appearance of the events. In such a case of *definite uncertainty*, operational information necessary for autonomy is Shannonian information.

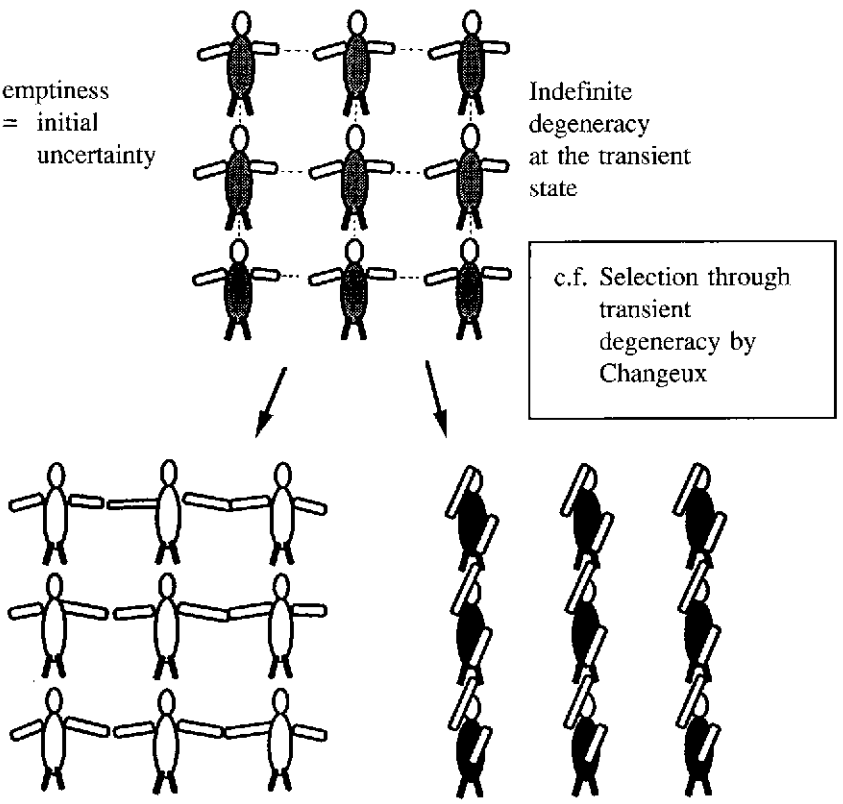
However, this is not the case for *indefinite uncertainty* when one has only insufficient knowledge about the future. Clearly, what is needed first is to obtain relevant knowledge or semantic information to teach the meaning of unknown new events. The origination of the *semantic information* for this purpose is the very problem of biological autonomy [5]. This was also the crucial problem of the oriental philosophy.

Origination of Semantic Information in Ontological Networks

How to treat the creation of semantic information in science? No clear principles have been established yet. Regarding to biological autonomy, an interesting theory, 'Autopoiesis', was proposed by Varela and Maturana [6, 7]. They pointed out living system is controlled through its boundary which is self-organized by the system itself. However, the principle that relates these two has not been shown so clearly. Therefore, we like to explore a possibility based on a theory of an ontological network developed in the oriental metaphysics. According to the theory of the oriental metaphysics, semantic information is originated in an ontological network system that is a 'relative or relational system' composed of a specific type of active elements, which I like to tentatively call elementary originators, actors or *'ontolons'*. Ontolons have indefinite property in isolated state. Only in the presence of ontological relations among them, ontolons are able to *originate* elementary symbols associated with their semantic states, depending on the relations. Consequently, an ontological system can select or originate a number of different states (see Figure 1). This is contrasting to the case of substantial system where elements with a definite property are given first,

and then suitable relations are introduced among them to construct a system. Cells in embryonic processes are examples of ontolons. Similarly, people in a social system originate their own way of thinking. They are therefore a sort of ontolons. Hypercolumns in neocortex selectively activate some of the columns belonging to them under relevant interactions. And a specific elementary symbol is encoded in the activity of each column. I therefore like to include the hypercolumns to ontolons.

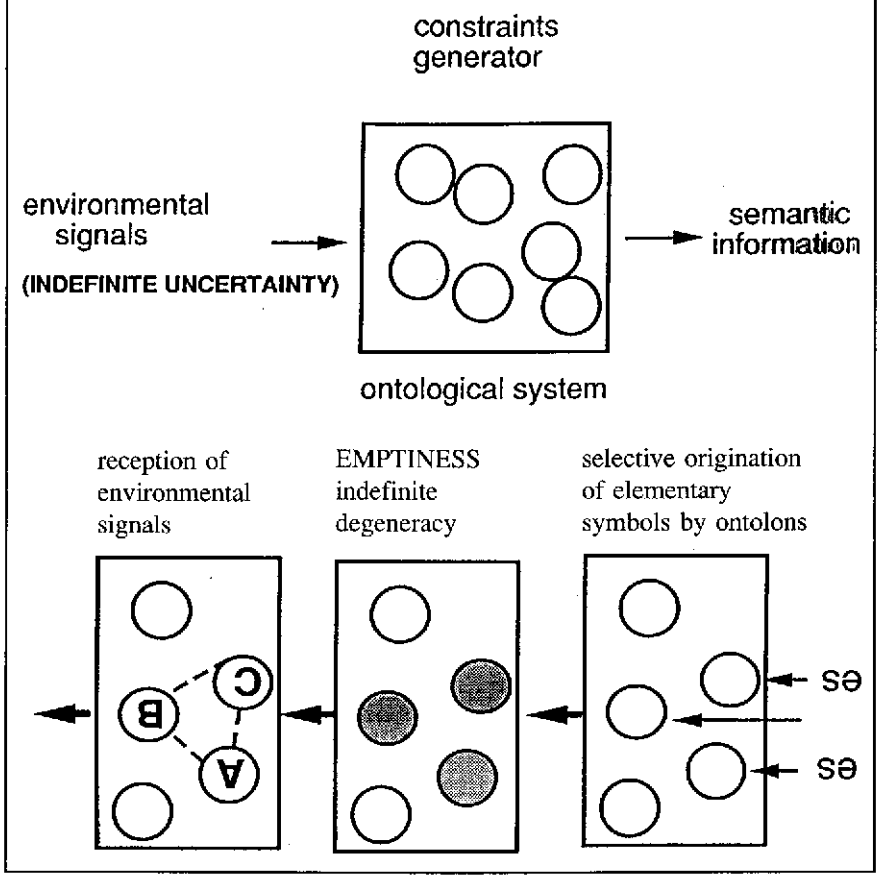
Figure 1: Relative System & Ontolons



Let us start by assuming that living system has an ontological system, and an assembly of elementary signals are received one by one by ontolons as schematically shown in Figure 2. The ontolons are then brought to an active but indefinite uncertain state, corresponding to so called 'emptiness' in Mahayana Buddhism, from which they start to originate. The indefinite uncertain state has an indefinitely large number of redundancies [8]. Then, a symbol representing the

temporal state of the environment is created in the ontological system by the cooperative activity of the ontolons, accompanied with convergence from the redundant state. More exactly, some of the elementary signals are transformed by the ontolons to the elements of symbol, i.e. elementary symbols. And a proper meaning or function is encoded or attached according to preunderstanding or relevant constraints. The symbol becomes semantic information.

Figure 2: Generation of Elementary Symbols in Ontological System



Ontological Relations with Closed Loops

What are the ontological relations and how are they related to the origination of symbolic states? The dynamics of an ontological system could be explained in terms of scientific words as follows. Ontolons in an active state are able to produce an extremely large number of symbolic states by self-organization. In

other words, the symbolic states are generally folded or hidden, but become observable only by self-organization. When some of the symbolic states are unfolded, the ontolon begins to transmit internal signals which are characteristic to the unfolded states. At the same time, it receives internal signals transmitted from some other ontolons. The received internal signals accelerate the rates of self-organization of symbolic states specific to the signals. The stronger the received signals, the larger the unfolding rate. The specificity may also depend on the 'position' of the ontolon relative to those of the transmitters of the internal signals. Furthermore, in some cases, the specificity also depends on the position of the ontolon in the group connected each other forming a figure with coherent activities.

When ontolons with unfolded symbolic states receive internal signals that are specific to their unfolded states, the weak activities of the unfolded states are amplified and begin to transmit internal signals stronger than those before amplification. This means that the activities of the signal receivers are amplified only when their symbolic states are consistent with those of signal transmitters. Thus, two interacting ontolons have the tendency to form a closed loop of circulating signals, and this is the formation of an ontological relation with distinct strength between the ontolons. The establishment of such a closed loop between a pair of ontolons is the sign that their symbolic states are mutually consistent.

Similarly, if the symbolic states of many interacting ontolons are mutually consistent, closed loops will be formed among them self-organizing a coherent network of closed loops [8]. The ontological network becomes self-complete when a set of self-consistent relations are definitely formed among the ontolons with separation from the other ontolons in the outside of the network.

(The symbolic state of the coherent network as a whole is able to have a self-complete form only under the condition that a proper meaning can be encoded to it. And the symbolic states of the ontolons in the coherent network will spontaneously encode the elementary meanings coherent with the whole meaning).

Synchronic Originations

Relations among the ontolons in an ontological system must vary from time to time for constant originations of symbols, depending on environmental states. On the other hand, the semantic or functional consistency among the elementary symbols can be examined through closed loops. This is possible only when all the ontolons participating in the origination of a symbol are activated at the same time. This leads to the important conclusion that the symbolic states of all the ontolons originating the symbol must be activated all at the same time to make their mutual consistency sure.

As is indicated in Figure 3, in Hua Yen philosophy, the mechanism of the interdependent coordination of ontological states was studied. And two important principles were proposed. Namely, they are the synchronic originations of the

symbolic states and the non-equivalent distribution of 'powerfulness'. The latter concept 'powerfulness', the amplitude of the symbolic states, was introduced to explain the originations of different unfolded states from identical ontolons. The distribution of 'powerfulness' will be caused by non-equivalence in the initial conditions and also in the positions of the ontolons with respect to the boundary of the coherent network.

Figure 3

Hua Yen philosophy

Fa Ts'ang: 643~712

Interdependent Coordinations of Events

(yüan ch'i ; *ENGI* in Japanese)

(1) Synchronic Origination of Events by Ontolons with Interpenetrations

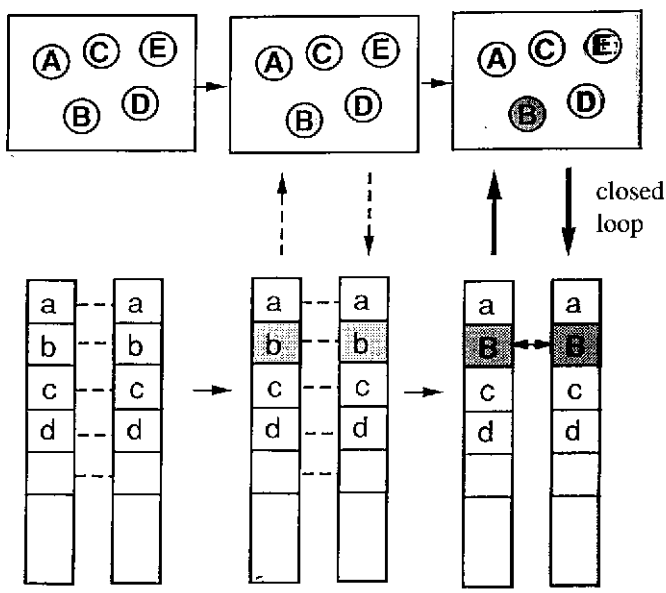
(2) Nonequilibrium Distributions of "Powerfulness" among the Ontolons

I would like to point out that the principle of synchronic origination is satisfied, if the activated ontolons have oscillating activity and then an originated symbol is represented by means of synchronized or coherent oscillations. In such a case, closed loops relating the coherent ontolons will be regarded as a sort of phase-locked loop. This would be necessary for the representation of plural symbols at the same time.

Constraints Generators

An ontolon is incomplete in a sense that it cannot determine a symbolic state of its own by itself. As illustrated in Figure 4, even when two interacting ontolons converge together to identical states, they are not able to uniquely specify symbolic states. They will behave together as a sort of ontolon. Similarly, in the case of convergence to nonidentical states, two interacting ontolons may be regarded as a complex ontolon. In any case, the two interacting ontolons cannot converge to definite states by themselves. In this sense, they are not able to uniquely transform elementary signals to elementary symbols only by themselves. This conclusion can be extended to the case of many ontolons. Chaotic changes may emerge in such an indefinite state. Therefore, the origination of symbolic states in a self-complete form is possible only when the huge number of excess relations among the ontolons are suppressed by means of suitable 'constraints', which must be provided from somewhere. In this sense, any ontological system is an *ill-structured* system. However, only ill-structured systems have the capability of origination.

Figure 4: Self constraints generator



In the theory of self-organization, constraints have been treated as fixed parameters. However, for the from-time-to-time origination of symbols in an indefinite environment, living system must have its own constraints generator in it, which I would like to call the 'self' of the system [5, 8]. According to the theory of self-organization, only in the presence of relevant constraints, a coherent pattern can be self-organized. It means that only in the presence of relevant constraints the symbolic states of the ontolons in an ontological network spontaneously becomes consistent not only mutually but also with the state of the network as a whole where a symbol is represented as a sort of collective mode of ontolons' dynamics. Only in such a condition, the elementary meanings to be encoded to the elementary symbols become consistent mutually and with the meaning of the symbol as a whole.

The meaning of the symbol, that is the meaning of the environmental signal, will be discovered by the self, that is also a sort of ontological system, according to the mechanism which will be introduced later. And the meaning is transmitted to the ontological system through constraints. Therefore, I will call the constraints semantic constraints. Essentially the same scheme will be applied to the autonomic control of biological functions in indefinite circumstances.

The above principle of the origination of semantic information explains the so-called 'hermeneutic circle' between the elementary meanings and the context. As pointed out by Heidegger, this logical circle converges only in the presence of preunderstanding of the context. The hermeneutic circle is caused from the indefinite and non-convergent state of an ill-structured system, and the preunderstanding is a sort of constraints for convergence.

The Predicate Logic of Identity

Thus, the next problem to be asked is the dynamics of the self, to generate semantic constraints. Kitaro Nishida, grandfather of modern Japanese philosophy, asserted that the logical function of the self was characterized by the *predicate logic of identity* but not by the *subject logic of identity* as it had been believed [9]. The self working with the predicate logic of identity was called the 'place'.

The characteristic feature of the *predicate logic of identity* is in its general and comprehensive property. The 'predicate logic' was studied by Frege, a German logico-philosopher, which could be very roughly outlined as follows. The logical relation between the subject and predicate can be expressed by the following function-variable relations. Imagine that there are subjects, x, y, z, ... and predicates F, G, H, ... For instance, let me define x, y and z are, respectively, a dog, a car, and a tree. And we introduce predicate part in the form of predicate operators F(), G() and H() as

F() = '... runs.'
G() = '... has a flexible form.'
H() = '... are hard.'

In the predicate logic of identity, two elements x and y are regarded as identical if they can respectively generate a self-complete form with the same predicate operator. For example, x = y because x and y can be respectively included in the same predicate operator F() = '... runs.' to produce a complete statement, F(x) and F(y). Similarly x = z because they can produce self-complete statement G(x) and G(z) with the same predicate operator G().

Induced-Fitting between Subject and Predicate Parts

As schematically illustrated in Figure 5, the relations between the subject variables and the predicate operators are not rigid as the key and keyhole relation, but more flexible and comprehensive, something like induced-fit relations proposed for the spontaneous deformation of steric structures of enzyme and substrate molecules to fit them completely. Or the subject variable and the predicate operator are related by 'mutually entrained' to make a self-complete form. Due to the original property of the self, semantic constraints as predicate operators must have flexibility which allows to converge to make a self-complete form with various information. For complete fitting, not only the information but also the constraints are needed to vary. Complete fitting means that subject and predicate parts are consistent in a self-complete form. Therefore what we have is a set of linked convergence processes of the ontological system and the self to a state where both are related with a closed loop.

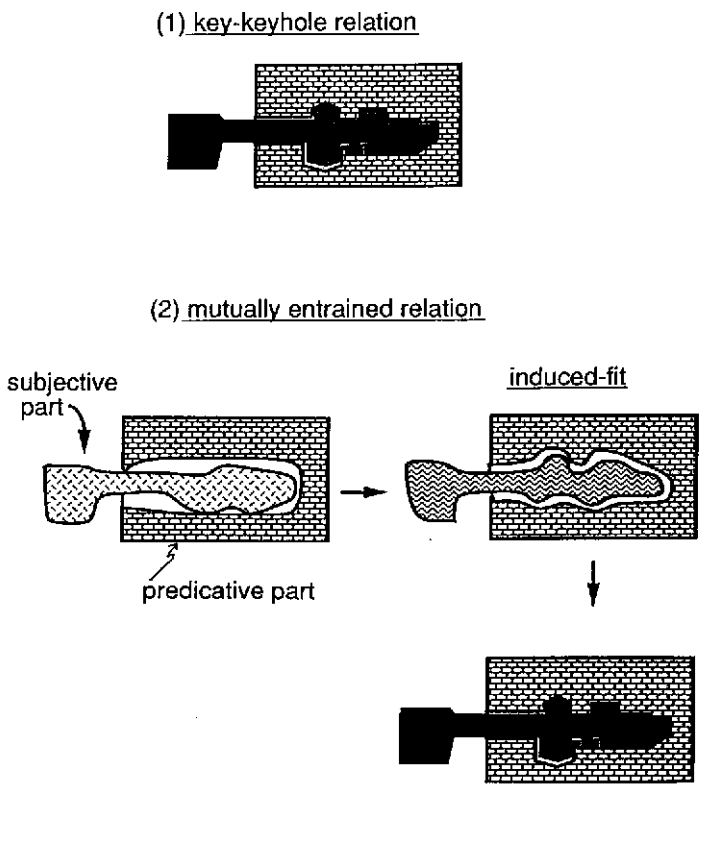
Our discussion could be extended to the problems of judgement. Predicate operators correspond to pre-understandings or semantic constraints while subject elements correspond to environmental signals to be transformed to semantic information under suitable constraints. And complete statements could be regarded as semantic information with meaning given through the constraints. Recognition of the environmental signals is the creation of semantic information with a self-complete form by induced-fitting between the signals and the stored information in the form of a predicate operator. The self is able to know the meaning of the environmental signals through simply judging whether or not generated constraints that are able to be successful in forming a closed loop between the ontological system.

Double Convergence of Ontological System and Self

Semantic constraints originated in the self is a sort of hypothesis. To have definite convergence, it must not be changed for some characteristic time which is needed for the ontological system to examine the characteristic origination of symbolic states under that hypothesis. This is the phase of the origination of a symbol. Then, we have a switch to another phase, that is the semantic phase to generate or modify the hypothesis against a temporal structure of ontological network which is tentatively fixed. The two phases may be switched on and off alternatively to have convergence to a self-complete state. This is the only way

to get a self-consistent state efficiently. And such processes are recorded in time for the sake of comparison, and would make a story and history.

Figure 5: Induced-Fit of Constraints



This could be compared with the following example. The elected members of the Diet generate law, i.e., constraints to suppress civilians' irrelevant behaviours, then after some years that to make the judgement of the relevancy of the law possible, the civilians elect the members of the Diet again. This alternative influence between information originators and constraints generators causes induced-fit between both sides and makes adaptation to indefinite environment possible.

Environment as Place: Logic of the Oriental Philosophy

To live in a complex environment, living system has to discover its behaviour to be relevant to environmental condition. How does the self generate the relevancy of the constraints to determine or control its behaviour? Let me introduce 'Place' which includes a place in it. According to Nishida [9], the critical point is in the utilization of the predicate activity of the 'Place', that is the environment with predicate activity where living system is embraced as its part by induced-fitting as shown in Figure 5. It means that not only a change is induced in the environment, but also a concomitant change is generated, or more exactly in the self of the living system, for the induced-fitting to create a global or holistic order in the Place. In the process of induced-fitting, the self will obtain relevant constraints. And, at the same time, the living system will discover the meaning of the constraints in the Place.

As far as my limited knowledge on the oriental philosophy concerns, the logic or the oriental philosophy to creatively adapt from time to time to indefinite environment is as follows. The only way that is left for living system to accept the indefinite state of the environment is to generate an indefinite state, i.e. 'emptiness', in the system itself, and then starting from the indefinite state, relevant information is created from time to time, making a cycle of perpetual destruction and creation of internal information. For this purpose, a *symbol originator*, a relative system composed of ontolons is utilized, and the indefinite state is represented in the ontological system as an unstable state with an indefinite number of possibilities or redundances to relate ontolons to each other. A relevant set of ontological relations will be selected forming a coherent network, depending on the temporal state of the environment.

However, the selection of the ontological relations, i.e. the origination of a symbol, in the relative system becomes a sort of ill-structured problem. Therefore, a *constraints generator* becomes necessary, in addition to the symbol originator. The constraints generator corresponds to the self of living system. In other words, the self is regarded as an organized assembly of predicate operators and makes the indefinite state of the symbol originator of the living system converged to a self-complete state by induced-fitting. To generate constraints relevant to environmental condition, an important concept, the Place, was introduced. The Place is constituted from the self and the environment. It was assumed that the Place has an intrinsic tendency to self-organize a global order by embracing various elements. Due to the predicate activity of the Place to cooperatively accomplish the global order, the self is able to know the relevancy of cognition or behaviour if and only if the living system becomes a member of the Place. Relevancy of the meaning to be given to the symbol by the self will be found in the Place through participating to the self-organization of the global order. According to Weizsäcker [10], the relevancy of cognition is verified by a cyclic consistency between cognition and action against environment, which was called *Gestaltkreis* by him. However, only a self-referential approach might be

possible. The amalgamation of the self to the Place is, therefore, the most important practice in Zen.

Temporal Coherence in Constraints Dynamics

In the dynamics of the above processes, three types of oscillatory or alternative changes are involved. One is the oscillatory changes in the ontological system when consistent relations are self-organized among various ontolons, and the second one is the alternative switching in the type of changes between the ontological system and the self, i.e. between the symbol originator and the constraints generator, to produce semantic information with a self-complete form by induced-fitting. The former type of oscillations is directly related to the synchronic origination of interdependent events. Eye movements in visual cognition may be related to the induced-fit with alternative switching. (The study of hippocampus will be interesting from the point of view of constraints generation in brain. Koerner [11] proposed a mechanism called 'the parallel in sequence' which is coupled with eye movement.) Generally speaking, the former type of oscillations will vary much more rapidly than the latter type of oscillations. These two types of oscillations will respectively become coherent only when consistent relations are established among the elements and between the elements and the whole.

The third one is oscillatory changes due to the destruction-construction cycles of self-organized symbols for the from-time-to-time creation. This was also studied in the oriental philosophy, in particular in Zen, and one may point out a similarity of this concept with 'deconstruction' by Derrida. This may have a tight correlation with the second one.

Recently, oscillatory activities were reported in visual cortex [12, 13] of cat's brain and oscillations with slower frequencies were also observed in hippocampus in particular in voluntary movements [14]. They may be related to the synchronic origination of semantic information in the information originator and the constraints generator, respectively. In 1981 we started the theoretical study of pattern recognition with these two kinds of sub-systems, and in 1985 in this country [1], I reported some results which were essentially the same as those I talked about today. Constraints dynamics based on the concept of the Place.

Yesterday, we had an interesting presentation by Professor Changeux on information processing in brain. I would like to point out that his idea, selection of neural connections through transient redundancy, has similarity to our selective origination of symbols by ontolons through emptiness where relations among the ontolons are indefinite and unstable."

References

[1] H. Shimizu, Y. Yamaguchi, I. Tsuda and M. Yano, in: Complex Systems — Operational Approaches in Neurobiology, Physics, and Computers, ed. H. Haken, 225-239 (Springer 1985).

[2] H. Shimizu and Y. Yamaguchi, Synergetic Computers and Holonics — Information Dynamics of a Semantic Computers. Physica Scripta **36**, 970-985 (1987).

[3] H. Shimizu, Y. Yamaguchi, K. Sato, Holovision: a Semantic Information Processor for Visual Perception. In Dynamic Patterns in Complex Systems. S. Kelso et al. eds., 42-76 (World Scientific 1988).

[4] T. Izutsu, The Nexus of Ontological Events: A Buddhist View of Reality, in: ERANOS 1980 Jahrbuch-Yearbook-Annales Vol. **49**, 357-392 (Insel Verlag 1981).

[5] H. Shimizu and Y. Yamaguchi, 'How animals Understand the Indefinite Information from Environments?', Prog. Theor. Phys. Suppl. **99**, 404-424, (1990).

[6] F. Varela, Principles of Biological Autonomy. (North Holland, 1979).

[7] H. Manturana and F. Varela, De Maquinas y Seres Vivos, (Editorial Universitaria, Santiago, Chile, 1973).

[8] H. Shimizu, A Dynamical Approach to Semantic Communication — the Significance of Biological Complexity in the Creation of Semantic Information, in: Biological Complexity and Information. H. Shimizu ed., 145-185 (World Scientific 1990).

[9] K. Nishida, The Collected Works of Kitaro Nishida IV (in Japanese) (Iwanami 1965).

[10] V. von Weizsäcker, Der Gestaltkreis. (Thieme, Stuttgart, 1950).

[11] E. Koerner, H.-M. Gross and I. Tsuda, Holonic Processing in a Model System of Cortical Processors, in: Biological Complexity and Information. H. Shimizu ed., 86-116 (World Scientific 1990).

[12] R. Eckhorn, R. Bauer, W. Jordan, M. Brosch, W. Kruse, M. Munk and H.J. Reitboeck, Coherent Oscillations: A Mechanism of Feature Linking in the Visual Cortex? Biol. Cybern. **60**, 121-130 (1988).

[13] C.M. Gray, P. Koenig, A.K. Engel and W. Singer, Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. Nature **338**, 334-337 (1989).

[14] For example, W. Seifert ed., Neurobiology of the Hippocampus. (Academic Press 1989).

The Impact of the Progress of Science on Modern Human Society

José Llompart, Faculty of Law, Sophia University, Japan

"It is a fact that not only our legal system but even our basic morality is at a loss before the increasing progress of modern sciences. Science was supposed to help us to change and to control the world around us, but life science is able now to change and to control our life as human beings. The kind of science tells us how we are able to manipulate life, but not how we ought or ought not to do so. Robert Edwards, father of the test-tube baby, is reported to have said at a congress in Berlin that ethics must be adapted to science, not the contrary. I will not comment on this opinion, but this is the problem.

Due to the lack of time I will make only some reflexions on the impact made already by modern sciences in our human society, showing what they have changed and what they were not able to change, and finally say a few words about the future as it can be foreseen from our present time.

1. It is easy to give a catalogue of what has changed due to the progress of science and the so-called applied sciences:

- We have more free time because our machines and robots can do our manual work. Nevertheless, this blessing has created new problems. How can we spend our leisure or fill the time when we have nothing to do? Narcotic traffickers for instance take advantage of this situation.
- We have more information and in order to get it we need only to turn on the television or to press a few keys on the computer. However, we have less need to think. A calculating machine works faster and with more accuracy than our brain, so our children need only to learn how to use it.
- Medical science has given us better health. The death-rate has decreased, and life can be prolonged for an indefinite period. However, now there are people who wish to be allowed to die with dignity. At the same time the birth-rate has decreased too, more babies are unwanted. I do not know whether mental health is now more endangered than ever before, but it is a fact that the countries with higher suicide-rates are those that have the greatest benefits of progress and applied sciences.
- We know better how to use natural sources of energy, but we have also found that they are limited and that in a predictable time they will be exhausted. We cannot discover new continents, but we have discovered nuclear energy. However, this complex source of energy has already been used to kill human

life and can easily run out of human control. The tragedy of Chernobyl can be repeated.

- We have succeeded in using nature for our purposes, but we have also disrupted the life environment of the whole world. It is not known whether our applied sciences will be able to stop and to repair the destruction of nature.
- The rhythm of time has accelerated. Nature never grows old-fashioned, but if we buy the best computer or the best instruments for research, in a few weeks they will no longer be the best. The same applies to industry and commerce. Not to produce something new means to be disqualified in the world of competition. Hence the increase of stress. Less contemplation and more action. The homo faber, the man who makes things, is no longer needed today. All we seem to need is the homo activus, the man with a little act in one of the many systems. It is the system that is expected to learn, correct itself and produce wonders while people become nothing more than subsidiary elements of the system.

There are still two more aspects of the impact of modern scientific progress on human society which I would like to dwell on a little more.

One is already implied in the title of this symposium. We speak — it is obvious — of 'human society', but generally not of 'human life sciences'. Life science is generally understood as a 'natural' science, as *Naturwissenschaft*. It uses empirical methods to try to make clear the mechanism of life but nothing more. It tries to clarify step by step the mystery of life, but this kind of life is only biological life. It is beyond the grasp of empirical science to tell, for instance, if a body with a healthy, beating heart but with a so-called dead brain has any 'human life' left or not. Science has made it possible to keep this heart beating or to stop it and send the body to the cemetery. It gives us the choice, but it cannot tell us which choice is right.

This problem cannot be solved by the methods of the natural sciences. They only deal with empirical facts. Empirical facts teach us what is or what is not, but not what we ought or ought not to do. Obviously this kind of problems belong to the realm of what Germans rather inappropriately call *Geisteswissenschaft*. However, it has been the consensus that de facto has given a practical solution to this problem. It is the empirical fact of a consensus about brain death that has given the green light to dispose of such a human body under the assumed premise of not being any more a living human being. I can of course not prove that such a premise is mistaken, but at the same time nobody has been able to prove in a convincing way that such a human body is a corpse. I fully admit that in law and politics many times there is no other way to solve a problem than by consensus. My point is only that the non-empirical fact that 'a human body under such conditions is not any more a living human being' cannot be proved with the empirical fact of consensus. It is the essence of positivistic philosophy to solve human problems only with empirical facts, but I am of the opinion that the truth of an anthropological statement like this cannot be proved by a majority vote.

I have raised this problem only to show the great and unavoidable impact of natural sciences on human sciences. I am aware that in this kind of consensus also the moral feelings of the people involved are at work and that many times in problems of morality it is necessary to take a decision even if we do not know the whole state of affairs. But in no case can we escape from responsibility for our decisions.

A heavy burden of responsibility is finally what the progress of science has brought us. The physical and biological world has its own laws which act under necessity and have nothing to do with responsibility. The laws of nature can never be illegal, immoral or inhuman. However, the more we can make use of these laws and manipulate nature, the more we must take responsibility of what nature alone cannot achieve.

In my opinion, many times we have no obligation to interfere with the course of nature. Nevertheless, once we have made a free decision to alter the course of nature, we are always responsible for all the effects of the new situation we have brought into existence. In Japanese I call this principle '*shinjitai-settei-setsu*'. It seems to me self-evident, if we are responsible persons. This principle is very practical, but at the same time does not solve all problems, since in the stage of research not all the effects of the manipulation of life can be foreseen. They may prove a blessing, but at the same time they may produce an irreversible catastrophe for future generations. (Here I am thinking of genetic engineering as one possible example.) This is clearly not only a problem of individual responsibility and private morality but also of legal-social responsibility concerning the future of humanity.

2. I am, however, of the opinion that we can detect at least three factors in our human society which, despite the great impact of science and technology, have remained unchanged and which we have no reason to expect to change. I will not comment on these three invariables, but leave them open for discussion. They are:

a) Even if the pursuit of happiness has been included in some constitutions (for instance in Japan, but not in Germany), we cannot prove that human beings now have more happiness or less happiness than before the birth of modern science and technology. We cannot say that a child playing with the most sophisticated toys is happier than a child playing with sand on the beach.
b) We cannot prove that our human society has become better or worse in a moral sense. The means of punishment we use now are really more human, but not the crimes which are being committed. Science may help to prevent crime, however the so-called prevention of crime does not mean that crimes are being actually prevented. We no longer need to include in our criminal code some offences related, for instance, to sexual morality, but the progress of science and technology has made it necessary to include other offences which were completely unknown a hundred years ago.
c) Finally, we cannot be proud of producing more beauty and better masterpieces of art than our ancestors of remote ages. The technical means they used

were primitive and for us obsolete, but not what they produced in the fields of literature, music, painting, the plastic arts and the like.

These are the three invariables of our human society which seem to be unrelated to the progress of natural and applied sciences, yet, at the same time, very important for us as human beings in a human society.

3. Finally, a few words about what can be foreseen from the progress of modern science in connection with the above mentioned invariables of human nature.

It has been said that history is the master of life and that history repeats itself but never in the same way. Actually what changes history is not so much the bright ideas of first class scholars or the sermons of people of good will. What many times changes history radically is rather the bitter experience of having done what never should have been done. If now, for instance, the dignity of man is the basic principle of the legal system provided by the German Constitution, it is due to the experience of the atrocities of the Nazi regime. If after World War II, and not only in Germany, the so-called basic values and respect for human life became self-evident, it was because we had the experience of seeing with our own eyes what happens, when these basic values and respect for human life are ignored.

Many years have passed since we had this experience, and now the content of human dignity is less evident, and it seems that we do not know any more how to apply this principle which was supposed to be the best guarantee for a human society. Social welfare and financial security have increased, but it seems that the level of the so-called 'fair expectability' *(Zumutbarkeit)* on the side of the citizens has sunk so far that the power of the state is powerless to protect human dignity and human life.

I am not a pessimist and do not foresee the day, but it is possible that some day the basic values become completely devalued turning human dignity into a slogan which can be used for everything. Such a development could produce a catastrophe different from war, but with similar or even worse results. The experience might teach us how to make a new start. The limits of the ways we may manipulate human life would become, no doubt, self-evident, even if it were too late for the victims of such a catastrophe. No new theory and no sermons about human dignity would be needed.

Thanks to the progress of applied sciences we now have more information and more communication at an international level. We can share better our anxieties and our responsibility. Little by little, international collaboration is replacing international confrontation. An increase of diversity and at the same time an increase of universality are the trends of our times.

The history of our human society is in a way the history of war and peace. Again and again different countries have tried to destroy each other fighting for a piece of land. The progress of science and technology has made possible in our century even the so-called World Wars. We have already experienced two. At the same time we have destroyed the environment of the whole world and what remained intact of nature. It is possible that in the near future a peaceful

coalition of all countries of this world to fight against the common enemy of environmental pollution will be the only means to survive. Then all human beings will become friends and join hands in using the means of the most advanced sciences for a better human society. This is not a prophecy. It is only a possibility for our future which, as such, can never be predicted. Even for human sciences the future of human society is unknown.

What do we have to do now at present?

At least to be more aware of our responsibility at an international level before it is too late. Responsibility for future generations is our present responsibility. To feel this responsibility is not enough. We have to act according to this responsibility."

A new Aspect of Life Sciences

Yoichiro Murakami, Research Center for Advanced Science and Technology, Tokyo University, Japan

"First of all let me tell you one thing. A long time ago, I established a very important hypothesis in the field of comparative studies of culture, particularly Eastern culture and Western culture. That is, the speakers from the West or the Western culture start their talk with a joke, whereas the speakers from the East or of Japan start their talk with an excuse. And this hypothesis had been supported by my empirical evidences and observations, but unfortunately this hypothesis saw a negative evidence this morning. You must remember clearly that Dr. Taniguchi started his excellent talk with a fantastic joke. But I myself would like to stick to my hypothesis, so let me start my talk with not a joke but an excuse.

As the Chairman introduced me, I am not an expert of life sciences nor of any particular exact sciences, and my academic background is history, philosophy and sociology of science. So what I am going to talk here is something not *from* science but *on* science, or more specifically on life science. And the subject I have chosen for my talk is to identify some, not all, but some impacts and influences that the emergence of life sciences had on the existing situation of natural science in general, *not* the society in general but natural science in general.

First of all, I will spend a few words on the institutionalization of biology. Institutionalization of science in general started in the mid-nineteenth century in the West, but interestingly enough, compared to physical or chemical sciences, the institutionalization of biology came rather late, although some constituent subjects of biology, such as zoology, botany, taxonomy, and so on, were institutionalized much earlier than even physical sciences. There were several factors, internal and external, that assisted and supported biology to be institutionalized, particularly in early twentieth century. One factor was the shift of interest at the forefront of physical sciences, not biological sciences. As is well known, around 1925 due to the works of Schrödinger, Heisenberg and so on, long-lasting pre-history of quantum physics came to an end and quantum mechanics was firmly established, at least at a theoretical level. Since the establishment, not a few theoretical physicists have begun to show their interest in the biological field in terms of applying their newly acquired physical ideas to life. Niels Bohr and Erwin Schrödinger were the remarkable examples. Bohr published his famous paper 'Light and Life' in 1933, and he reconfirmed his idea in his last lecture 'Light and Life Revisited' in 1962, which appeared

posthumously in 'Essays on Atomic Physics and Human Knowledge'. Schrödinger's 'What is Life?' was published in 1946. Another remarkable example is Max Dellbrück. As you know, he started his career as a theoretical physicist, and became a — or might be *the* father of molecular biology. And this taking over phenomenon of physicists in the biological field supported the institutionalization of this field, but both at external and internal level. At external level, the institutional equipments of scientific community of physics were brought into the biological field.

These outsiders of biology changed in effect techniques and methods of traditional and conventional biology, and it followed that the whole structure of biological research, which used to be quite broad and vague, was reorganized to be exact and solid as a well-defined field of scientific research. And this induced the financial supporters of scientific research to have an increasing concern in this field. In connection to this, particularly in the United States, the activities of the Rockefeller Foundation may be worthwhile to be referred to. The assistance of this influential institution to the biological field has been enormous.

At internal level, I would like to mention the influence of reductionistic attitude shared by the physicists on this field. As in physical sciences, reductionism introduced into the world of life by physicists formed the fundamental principles of disciplinized biological sciences. And distance to this fundamental principle came to play the decisive key role to determine whether a biological science is located at the core of life sciences or rather at the peripheral part of it. This institutionalization of biology can be regarded as one typical case of the same phenomenon, proceeding in every corner of sciences. But it implies, at least to me, some different aspects which are more or less specific to this particular field. These specific aspects of institutionalized life sciences are now giving a new colour, so to say, to this particular area. I would like to call it openness, because we can recognize something open in several ways in life sciences, which are not shared by other institutionalized natural sciences, I believe.

The second part of my talk will be dedicated to the openness at external level. Again, I would like to discuss the openness at two different levels, external and internal. As is well known, the mid-1970s saw the emergence of new technology in life sciences. I think some of our colleagues at this meeting may be quite familiar with this process, because they are direct witnesses of the historical process. This in the splicing technology of DNA sequences, invented by Paul Berg, Stanley Cohen, H. Boyer and others. Immediately after the invention of this technology, or even during — in the midst of — the process of the invention, the voices of warning could be heard, warning of various dangers, anticipated in the exercise and application of this new emerging technology. Of course, the memory of a precedent desastre in physical sciences helped them to take the matters serious, I think. Berg himself listened to these voices, and admitted to have his own experimental programme suspended. In the midst of this suspending situation in 1973, as you know well, Cohen and Boyer published their

historical paper, in which a rather simpler technology of splicing than Berg's was proposed.

So it was Berg who took the initiative in appealing the dangers they were confronted. He and his colleague researchers sent a letter to two journals, 'Nature' and 'Science', in 1974, where they proposed the moratorium of the experimental research based on the new technology, addressing to all the researchers of this field in the world. I think this was a monumental event in the history of science, because these letters were the first case where the active insiders of an institutionalized research field intentionally and voluntarily proposed the moratorium of their own research activities. Up to then, for the insiders of, let's say, compartmentalized scientific discipline, everything that hinders the development of their research activities had been considered absolutely evil. Of course, I do not forget one exception. In the field of physical science, Leo Szilard once tried hard to stop using the disasterous product of their research activities at the end of World War II in vain, but this was not the proposal of the moratorium of the research activities themselves, but the one of the suspension of mal-application of what they produced during the research.

Berg's action triggered off organizing a series of conferences to discuss how to carry out the moratorium programme. The first conference of the series was held in Asilomar, Conference Center in California, 1975, collecting about 140 participants from 16 different countries. The so-called NIH guide-lines established in the following year eventually resulted from this Asilomar Conference.

All the participants of the Asilomar Conference were only the insiders of this particular field, and in that sense, the conference maintained a still rather closed atmosphere. Nevertheless, this movement of the institutionalized research field almost inevitably destroyed the closed atmosphere which all the members of all the scientific community had been enjoying from the very beginning of the institutionalization of scientific research. By means of the acceptance of new institutions based on the guide-line, such as IRB-systems and so on, life science as a compartmentalized research field was for the first time forced to open its compartment towards the outsiders.

The insiders of every scientific compartment now begin to learn and realize from the experience in the case of life sciences that this openness is necessary for them, not only to carry out their research activities without serious conflicts with outer societies, but also to do them both smoothly and in some appropriate manners. Awareness of needs for critics and advices from outsiders — I hope and I believe — is beginning to be shared among the researchers in other compartments as well. So, a scientific compartment equipped with certain institutionalized channels with outer society is a new stage of institutionalization of science, or rather a new concept of institutionalization of science. And the way toward this new stage or new concept was opened not by physical sciences but by life sciences.

The third point is the openness at internal level. Another new openness brought into science by life sciences is rather a theoretical openness. It can be safely said that one of the prerequisites for something to be science is to have a

closed structure in referential relation. To put it in another way, it is required that our fields of knowledge should have no self-referential openness so that it can be classified within the realm of science.

First of all, viewed from formalism, if it does have self-referential structure, a field of knowledge cannot avoid having formal paradoxes in one way or another. Even for that reason alone, self-referential structure tends to be rejected in the world of knowledge. Furthermore, in natural sciences when you write a technical paper you are strongly advised to use the first person plural, namely 'we' instead of using the first person singular, 'I'. Episodically I would like to refer to the episode immediately after the outbreak of rebellious anti-establishment movement of students, which began in 1968. Especially in the United States, not a few researchers tried to go against this implicit rule, in writing academic and technical papers, and they voluntarily used many 'I' in their papers. But this rebellion, so to say, did not bear any significant fruits. And the reason why 'I' is strictly rejected in scientific papers seems to me that science needs to pretend, I dare say to pretend, to be objective. Scientific propositions should be true not only to a particular individual observer but to any possible observer, whoever the observer may be, or rather even to no observer. And since the first person singular is a particular individual, there should be no room for it in scientific description of nature. Thus the scientific propositions describe natural phenomena as if there were no observer. It means that the description of nature in science is closed and complete within itself. I sometimes call this scientific picture, or the nature of this scientific picture of the world by a 'God's eye view'. Of course this is the paraphrased expression of 'bird's eye view', but the scientists want to draw a picture of the world from the viewpoint of God. This implicit but strictly observed rule has been a considerable success as far as one stays within the realm of matter. But when one goes out from the motherland of matter, one cannot follow the rule any more, just as you heard yesterday morning in Dr. Yanase's keynote speech.

To explain, let me take a rather simple example, that are the environmental problems. What makes them unique in the scientific context is the fact that they are open in the relation between the things observed and those who observe them, or in more simple expressions, the objects and subjects. The problems of carbondioxid, the problems of ozone holes and so on are in a way of course natural phenomena, but at the same time it is clear that they are in a way human phenomena. The problems are produced by the human activities. And when you try to have a picture of the problems of that kind the picture inevitably includes yourself in it as one of the indispensable factors of the problem. In other words, these problems have a self-referential structure, which you do not care as far as you are in the realm of ordinary sciences.

And life sciences seem to me to share almost the same cognitive structure as those fields have. Of course, molecular biology, the most dominant field of the life sciences, has so far gained a success to some extent in excluding those who describe the picture from the picture described. Molecular biology now looks to wear a quasi objective coat on it. So if you are fully satisfied with taking

reductionistic attitude towards life, you may not have to be open to the perpetual movement of self-referential structure. But the nature of life itself — this is my personal opinion — but the nature of life itself does not allow one to stay within the realm of closed descriptive picture of reductionism. One should open up the picture toward an endless self-referential structure, if one steps in the world of meaning, I think which is one of the most remarkable features of life. Just as Professor Shimizu described the importance of semantical information in his lecture.

To conclude, I have mentioned so far only two types of openness that have something to do with life science, but even only those two are significant enough to change the nature of conventional framework of science. I think that the development of life sciences almost inevitably implies some conceptual shift of natural science, which is — if you wish — called the paradigm shift.

Thank you very much."

THIRD SESSION

How can Biotechnology contribute to new Concepts for Chemistry, Medicine, Engineering, Agriculture, and Environmental Protection?

Chairman: Rudolf Rott

Protein Structures and what we learn from them about Chemistry, Physics, and Drug Design

Robert Huber, Max Planck Institute of Biochemistry, Martinsried, Germany

"On the occasion of a recent doctorate's feast we were shown a cartoon which illustrates two aspects of protein structures. First, the fact that those sticky materials of our breakfast egg consist actually of protein molecules with stable, very well defined, and often aesthetically appealing structures. The other aspect concerns the work involved in elucidating these structures, work usually done by doctoral students, represented by the doctorandus crystallographiae shown here.

My lecture today is accordingly split into two parts. In the first part I show the methods we use to derive three-dimensional protein structures, the developments in the last ten years, and future prospects. The second part will be devoted to protein structures themselves. How do they look like? What do they do? Why are they interesting and how can we use them eventually?

In order to make it easier for you to follow, I have made a number of transparencies, which will be on during all of my talk, where I point out specific problems and lines of development. I will then illustrate these specific points using slides.

The main and most important method we use in order to elucidate three-dimensional structures is protein crystallography. We have to use x-rays because we need light of a wave length corresponding to the atomic dimension, which is in the order of Angstroms.

The basic crystallographic experiment is shown next. This is a lattice with a basis. The basis is a phtalocyanin molecule. The lattice gives rise to a diffraction pattern illuminated when with light. There is a simple relationship between the object and its diffraction pattern; a simple relation between the lattice constants here and the mesh of the diffraction pattern there, and also a simple relationship between the intensities of these diffraction spots and the structure of the basis. The relationship is just a Fourier analysis, i.e. the addition of sinus and cosinus terms, which can be calculated from the geometry of the atomic positions of this phtalocyanin. But the way back — to derive the structure from the diffraction pattern — is principally impossible, because an essential information is lost when we record the diffraction pattern. The essential information is the *phase*. We can record the intensity, the blackening of the diffraction spots. We lose the phase information, which is necessary for the back transformation, which mathematically again is a very simple Fourier inversion operation. We need the phase information. The phase problem is the central problem of crystallography, which of course can be solved, as shown in any of the structures I am going to present.

There is a straight-forward solution to the phase problem in protein crystallography because protein crystals form very open lattices. There is may be up to 80 per cent of solvent in these crystals; they are more or less order gels. We can diffuse heavy atom compounds into them, which bind isomorphously, i.e. without disturbing the protein structure. And they give rise — as you see in a pair of derivative and native protein crystals — to small intensity changes, which we have to measure. This was the basic discovery of Max Perutz and John Kendrew in the fifties in England, who founded protein crystallography by discovering these effects and how they can be used to derive phase information.

There is a very elegant alternative method discovered by my teacher, Walter Hoppe, also in the fifties, which becomes more and more important, because of the increasing number of known protein structures. The basis of the method may be shown with a simple tri-atomic molecular structure. From it a vector set can be constructed connecting vectors between the three atoms. This gives rise to a hexagram. The essential point is that this vector set is represented in the Fourier synthesis of the diffraction *intensities*. We do not need phase information in order to derive the orientation and the position of the vector set. When we know the orientation and position of the vector set, which we can construct from the underlying object, we have solved the crystal structure. We do not have to know the structure of the underlying object exactly, a related molecule is sufficient. For example trypsin and chymotrypsin are sufficiently similar. Obviously, with the increasing number of known proteins this method became very powerful.

At the end of crystallographic experiments stands an electron density distribution which is easily interpretable modelwise. However, the starting electron densities are by far not as good as the findings, have breaks and require skill to interpret them. They require refinement. This was another line of development in the last twenty years, refinement by using model information. Of course we know the exact geometry of the protein's amino acid building block. The use of this information and its implementation in protein crystallography was a major progress in protein crystallography. Last not least, protein crystallography requires computing. There is close correspondence between progress in protein crystallography and in computing facilities.

An important new technique of structure analysis is magnetic resonance. There is no time to go into any detail. The information from magnetic resonance about protein structures is totally different from diffraction experiments. It is a distance relationship. As we can construct a three-dimensional landscape from a series of distances so we can construct a protein model from a series of distances. There are limitations for structure determination by magnetic resonance — size, we usually can analyze only small proteins of about 100 amino acid residues. But there is the advantage that proteins in solutions can be analyzed. A very interesting new line of development indeed in the last fifty years, mainly due to work of a group in Zurich, Ernst and Wüthrich.

Let me come to the second part, proteins: Versatility of proteins. There are only 20 amino acid residues linked by peptide linkages, a very simple construction scheme, arranged in secondary structures, helices, beta-sheets, which then

may be assembled to the three-dimensional structure of this water-soluble protein molecule. The assembly of two beta-sheets gives rise to this globular protein, which is water-soluble. Proteins may bind co-factors which then change their functional properties in a fundamental way. I will come to this important point later, when I discuss photosynthesis and photosynthetic proteins. Proteins may be membrane-bound; sub-units may assemble to aggregates with water-soluble components and lipid associated parts. There is also flexibility of proteins, as proteins may be constructed to enable hinged type motion.

Proteins as catalysts: The example is citrate synthase. The protein in its closed form encloses the two substrates of oxaloacetate and acetyl-coenzmye A, brings them together and reaction occurs in the special environment of the enzyme removed from water. This is an important aspect. The reaction would not occur in water but requires the special environment of the protein. However, a closed form is a contradiction to catalysis, because permanent binding would allow one turnover only. There must be a second open form of the enzyme, which indeed exists. The small domain moves away by about 20°, by a hinge-type motion which allows substrate-binding and product release.

The aspect of compartmentation is even better demonstrated in the complicated enzyme riboflavin synthase, where 60 sub-units of one type make up a capsid. The capsid is cut through the middle in order to allow a glimpse into the interior. Here catalysis goes on, removed from water like in a biological reagent tube.

The capsid is composed of 12 pentameric substructures, where the sub-units embrace each other by using their interminal arms in a cyclic way. This is the basic building block and twelve of these are assembled in the whole capsule.

Antibodies – prototypic recognition molecules made of framework and loops. But unfortunately, I see time runs out, I have to go on.

The basic problem with antibodies is to generate with a limited amount of genetic material an unlimited capacity to recognize foreign molecules. This genetic problem has an important structural correlate. Antibody molecules are constructed from framework and loops, which stem from different genetic segments, and are combined during the generation of the immune response.

Protein structures and physics: I would like to demonstrate this aspect with proteins serving as light guides and photocells, an unusual property of proteins but the central functions in photosynthesis. Proteins are transparent and may gain these functions only by binding co-factors. These endow colour and electron conduction properties. The basic components of the photosynthetic apparatus are a light harvesting system and a photocell, the reaction centre, which is membrane-bound and generates an electron current across the membrane. This is the primary reaction of photosynthesis. It is quite remarkable to mention that the number of proteins and pigments involved in light harvesting exceeds those in the reaction centre by 100. The green colour in plants is essentially due to light harvesting components, which are chlorophylls. Let us just have a quick look at the light harvesting component in cyano-bacteria. In an electron micrograph, at low resolution, you see aggregates associated with the photosynthetic membrane which have rodlike sub-structures. Let us focus on these and look at them at

atomic resolution. They are huge protein components forming the rods and the tiny blue co-factors in them, which are responsible for coloration and for light conducting properties. They are slightly differently coloured, light blue and dark blue, indicating their slightly different absorption properties. The components are arranged to generate an energy gradient. Light flows from top to bottom and from periphery into the centre. The rods act as a funnel and a concentrator of light to the reaction centre, the photocell.

All components form wonderfully coloured crystals, a pleasure to study.

Just a few words about the photocell, the reaction centre: The structure analysis of the reaction centre of a purple bacterium – together with Hartmut Michel and Hans Deisenhofer – shows four protein sub-units and chlorophyll and heme-co-factors. The heart of the system is a pair of bacteria chlorophylls absorbing light of the lowest energy. The light energy from the light harvesting complexes excites it, ejects an electron which travels down to the other side of the membrane. This is the primary step in photosynthesis. An interesting point of this reaction is its efficiency. There is always the danger of deactivation, mainly by fluorescence. The intrinsic fluorescence life time as a critical time limit is nanoseconds. The electron transfer processes in the reaction centre are in the picosecond range and much faster. In fact, the quantum efficiency of the primary light reaction of photosynthesis is one. Ideal – there is no physical device which majors this. But there is much energy lost by conversion and transfer (60 to 70 per cent). This is an important aspect in the comparison of biological and technical materials for photovoltaic processes, as some technical materials reach 90 per cent energy conservation.

An interesting aspect of the reaction centre concerns membrane binding – how is this achieved? Very simply by an appropriate surface. In the case of water-soluble proteins this is salty. The reaction centre molecule is partly exposed to water, partly located in the membrane. The form has a salty surface with many charged residues, the latter lacks charged residues.

This was a simplified picture of proteins in membranes. It does not explain how the proteins are transported from the cell into and through the membrane. The four components of the reaction centre are located differently, intracellular, in the membrane and extracellular. How are they targeted? That is a most interesting question, which we cannot address from the structure alone. But the observed orientation of the reaction centre molecule in the membrane is thermodynamically and kinetically favoured.

Proteins mediate oin transport across cell membranes. They may form voltage-gated channels. We have recently studied such a structure with proteins called annexins. They have a salty surface and are indeed water-soluble. But they show a very special feature, which we saw for the first time in this protein. There is a central channel in the protein which is also salty. Annexins are membrane associated in the presence of calcium. As shown by electron micrographs in projection, the membrane protein complex superimposes perfectly on the protein structure seen in crystals. There is no significant structural rearrangement. The protein as we see it in solution attaches to the membrane. What

function does the protein membrane complex have? Membrane binding occurs in the presence of calcium. The membrane becomes permeable, and calcium from outside flows through the membrane part through the proteins's central channel. This is a first picture of a calcium specific channel, which is regulated by transmembrane voltage. But annexin is not an integral membrane protein. It is water-soluble and membrane-bound and has properties which usually are associated with integral membrane proteins.

The last few minutes I would like to address the aspect of application in drug design and medicine of protein structures. So far, I discussed some protein structures which may be useful as catalysts to make precious chemicals. Enzymes are regio- and stereo-specific. I discussed the photosynthetic proteins and their possible use to substitute technical devices. These are interesting fields of research. However, the greatest promise lies in the application of proteins in the design and development of drugs for therapy based on structural information, 'rebind drug design'.

For demonstration I use blood coagulation, a complicated process of activation and inhibition, many proteins are involved. This activation cascade serves to activate the protese thrombin which cleaves its substrate, fibrinogen leading to bloodclots. It is quite obvious that thrombin is a central target for drug design. For this purpose we have to know its structure.

The human thrombin structure (work to which Wolfram Bode was mainly contributing) has a very narrow substrate binding the active side of ... where the fibrinogen comes to lie. It is a very long channel, a very complex surface and a deep canyon. This structure now offers a way to derive inhibitors to thrombin rationally.

Inhibitors may be designed on the basis of a vast number of natural inhibitors, which exist in animals and plants and which have been studied in structural terms. These inhibitors are not directed against thrombin but towards other protoelytic enzymes. On the basis of the structure of the thrombin we can modify them in a rational way so that they fit into thrombin's deep canyon. Many possibilities exist, which can be realized using recombinant technology on the basis of the three-dimensional structures.

Most natural inhibitors are known to bind to proteolytic enzymes in a similar canonical way. However, an inhibitor from leech, hirudine, binds very differently. The molecule has a globular part and a C-terminal tail, which exactly fits into the thrombin's canyon. The work going on aims at dissecting hirudine to use different parts of it which still strongly bind to thrombin. It is quite clear that this mode of inhibition of hirudine was unpredictable. Only by analyzing the real structure this new field was opened.

Despite the enormous accumulation of knowledge about protein structures we still do not understand them. There is no way so far around experiments, and these experiments show surprises. Whenever we look at a new protein structure we find something unusual and unpredictable."

How can Biotechnology contribute to new Concepts in Medicine?

Hans-Gerhard Schwick, Behringwerke AG, Marburg, Germany

"It is difficult, and sometimes impossible, to predict the future. A scientist who gave a lecture on a similar topic some twenty years ago began his remarks with a quotation from Goethe:

'Crucify every visionary by the time he is thirty; Once he knows the world, every dupe will become a villain.'

(Goethe: Venetian epigrams)

However, since I am a notorious optimist, I prefer the view expressed in the first part of Clark's Law:

'When a distinguished but elderly scientist states that something is possible, he is almost certainly right. When he states that something is impossible, he is very probably wrong.'

It is perhaps easier to talk about the future influence of biotechnology on medicine if we remember that biotechnology began to influence and change medicine to a major extent at least fifty years ago.

Definition of biotechnology:

Biotechnology is an interdisciplinary field of work. It uses the biological synthesis capacity of living cells or enzymes produced from them for extraction or transformation of substances in industrial production methods.

If we accept this definition of biotechnology, then it is clear that for the past half of the century, biotechnology has had a considerable effect on medicine in many areas. I would like to mention only three examples, which I think are extremely important. These are: Vaccines, antibiotics and blood plasma proteins.

Today, more than twenty vaccines are being used world-wide. They are produced with biotechnological methods, using bacteria that are cultivated in bioreactors with suitable nutrient solutions, or using virus grown in suitable cell cultures.

The consistent use of vaccines, at least in the developed or industrialized parts of the world, has led to the practical elimination of many infectious diseases. Such vaccinations deserve most of the credit for the drastic reduction in infant mortality since the beginning of this century, and for the drastic increase in the average life-expectancy of the human race.

Whereas vaccines are used prophylactically to combat infectious diseases, the antibiotics, beginning with penicillin, are indicated for therapeutic purposes. To an even larger extent than vaccines, these antibiotics are obtained from various microorganisms in bioreactors. I do not think it is necessary to emphasize the significance of antibiotics in modern medicine. I am certain that most of you have already been treated successfully with antibiotics at least once so far in your lives.

Blood plasma proteins are also obtained with biotechnological methods, and administered as prophylaxis and therapy for a wide range of diseases. Here, large amounts of human blood plasma are separated into their individual proteins and then used to produce more than twenty different medications. They are frequently used for substitution purposes, that is, to replace a protein that is lacking in the patient. Among others, immune-deficiency diseases caused by a lack of immunoglobulins can be treated by administering the missing immunoglobulins, or a deficiency of the antihemophilic factor in cases of hemophilia can be treated with antihemophilic globulin obtained from blood plasma. Less than fifty years ago, shortly after World War II, hemophiliacs had an average life-expectancy of fourteen years, whereas today, thanks to substitution therapy with antihemophilic factor obtained from blood plasma, their life-expectancy is within the general norm. I believe that these examples convincingly demonstrate the extent to which medicine has been influenced by biotechnology.

It does not require too much imagination to project this picture into the future: The progress that has been made in biochemistry, molecular biology, and immunology in recent times justifies our hopes that further developments in biotechnology will lead to further important advances in medicine during the coming years. Indeed, there have been many predictions in the past years regarding biotechnology, and all of them express the same high expectations.

At the exhibition ACHEMA Ninety-One, which took place in Frankfurt very recently, biotechnology was presented in various demonstrations and lectures as one of the key fields that will determine the progress of medicine in the coming millenium.

What is the basis for this optimism? First, new possibilities have been opened up by the scientific advances made in the last two decades, particularly during the nineteen eighties, which is being referred to more and more as a decade of biological revolution. These new possibilities have already been described and discussed repeatedly at this meeting, so let me briefly mention only a few of them:

- the discovery of monoclonal antibodies
- the production of recombinant proteins by means of genetic engineering
- the major improvement provided by the breeding of mammalian cells in large-scale cultures.

Up until quite recently, cells could be multiplied only in so-called roller cultures, or on large-surface glass plates. Today, however, they can be cultivated in bioreactors in the form of submersion cultures with small plastic pellets on which the cells grow and multiply. Here I should also mention that advances in

computer technology have made it possible to equip bioreactors for cell cultivation with measurement and regulation instruments without which, in many cases, it would be impossible to grow certain particularly difficult cell types. All these developments work hand in hand, so to speak. Today, for example, we have a good deal of reliable information regarding the surface of mammalian cells, their receptors and other components, and their soluble factors, and we owe this knowledge to a great part to the analytic use of monoclonal antibodies. Because of their high specificity, these antibodies are able to differentiate among small molecular areas on the cell. Once they have been identified and characterized in this manner, these receptors and factors can be produced by means of genetic engineering. For this purpose, cell cultures are often required again as vectors. In order to obtain the desired factors in the necessary highly purified form, monoclonal antibodies are again frequently used.

To put it in the simplest terms, gene technology makes it possible to produce all endogenous substances, once they have been identified and characterized. Gene technology also makes it possible to obtain protein molecules which have been altered in such a manner (protein engineering) that they possess greater efficacy or a longer half-life.

Now I would like to look into the future in regard to infectious diseases:
How biotechnology contributes to combating infectious diseases (e.g. HIV, HCV):

- Definition of the infectious agent by genetic engineering.
- Investigation of the pathogenesis in humans by new diagnostic methods (e.g. PCR) and in new animal models (e.g. transgenic animals).
- Prophylaxis by vaccines based on recombinant antigens (e.g. production of rec. antigens in large fermentors).
- Development of specific therapeutics based on the results of genetic engineering and protein modelling.

Resulting new concepts:

- A specific infectious disease will not any longer be treated symptomatically, but a specific prophylaxis (vaccination) and therapy will be available in the future.

New biotechnological methods will enable us to obtain faster and more accurate diagnosis of the pathogenic agents. New vaccines based on gene technology will permit more effective vaccinations, as well as therapy for diseases for which there is as yet no vaccine available.

Biotechnology will allow the development of a multi-component live vaccine for the eradication of several infectious diseases:

- The efficacious components of all vaccines needed for the protection of children will be combined on the gene level.
- The combined vaccine gene will then represent the protective antigens of for instance polio, measles, diphtheria, pertussis, tetanus, malaria etc.
- This combined antigen will be inserted in a harmless, non-pathogenic, viable germ, for instance BCG or salmonella.

— One annual vaccination of children will warrant protection from a variety of infectious diseases; consequently many of these diseases will be eradicated worldwide.

Resulting new concept:

— A series of vaccinations using various, complicated vaccination protocols will be replaced by one preferably oral vaccination.
— By this means the worldwide eradication of a number of infectious agents can be achieved.

One concept that we are working on at present is the development of a multi-component live vaccine incorporating several protective antigens in a non-pathogenic living microorganism.

The challenge here is great. There are still no vaccines available for numerous diseases, and many of our present vaccines require improvement. If we consider the annual incidence of infectious diseases, the frequency of parasite diseases, such as malaria, is striking. However, it now actually seems to be possible to develop vaccines for treating parasite diseases. In virus vaccines, the entire virus is frequently contained in killed or in altered living form in the vaccine, but in regard to parasites, it is essential to find the protective antigens of the parasite and to produce these antigens on a biotechnological basis for use in the vaccine.

Another major challenge to biotechnology is presented by oncological diseases. Deaths from cancer are increasing and are age-dependent. Our average life-expectancy is going up, thanks to improvements in preventive medicine and therapy, among other things. This means that in the future we can expect cancer rates to increase.

There are good reasons to assume that prevention of, and therapy for, cancer can be approached on the basis of biotechnology. Let me give only a few examples:

Biotechnology will permit prevention of cancer by vaccination (e.g. HPV):

— A virus will be defined as at least one causative component inducing the development of cancer in humans.
— Recombinant antigens of such a virus will be produced in test tubes and fermentors.
— The protective role of certain antigens will be proven, probably including studies in transgenic animals.
— The efficacy of a resulting vaccine will be tested in long term clinical trials (decades rather than years).

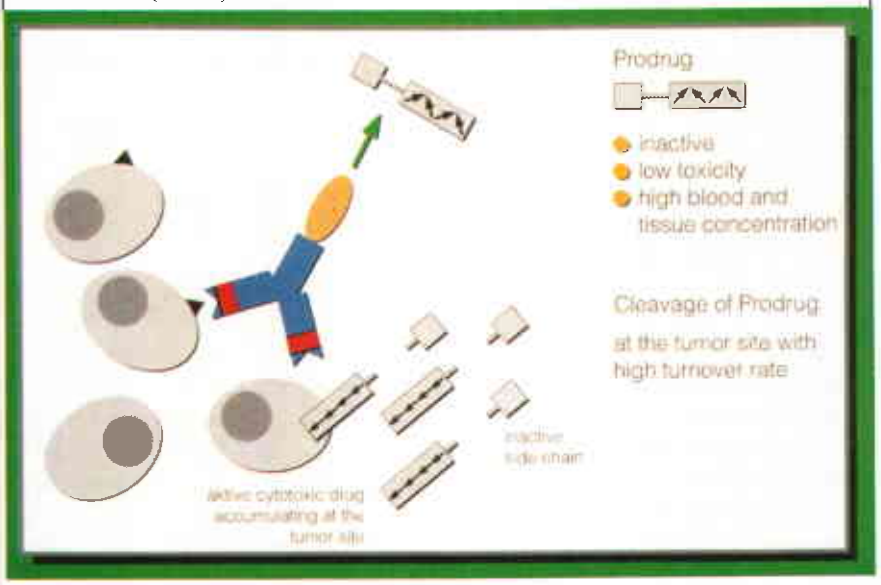
Resulting new concept:

— Prevention of cancer by vaccination.
— Based on this prophylactic approach specific immune therapy in the early phase of cancer development might also be possible.

In the future, vaccination can prevent at least certain neoplastic diseases, especially, of course, those diseases that are demonstrably caused by a virus.

Increasing knowledge of oncogenes will provide biotechnology with points of departure for developing therapeutic measures which can serve to regulate the mechanisms involved.

Figure 1: Immune Specific Enzyme – Mediated Chemotherapy (ISCE)



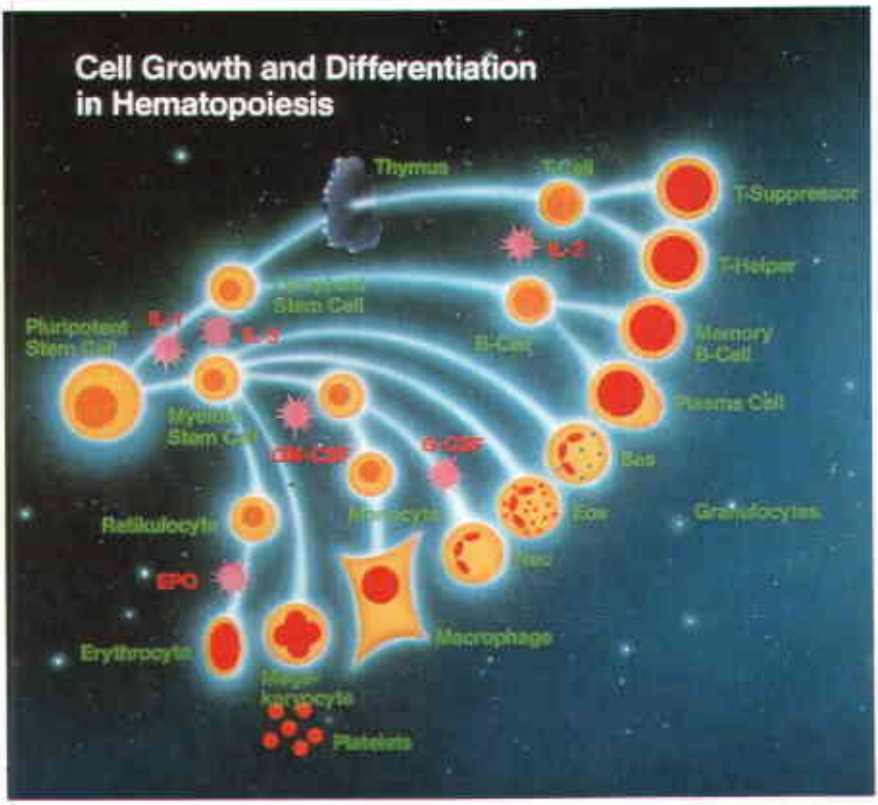
From the beginning, tumor-specific monoclonal antibodies have been discussed and clinically tested as a possible therapy for cancer. Here, one strategy consists of providing such antibodies with enzymes which convert pro-drugs into active drugs at the proper site, that is, in the cancer cell itself, and thus destroy the latter.

Thanks to new techniques, a large number of cell growth and differentiation factors have been identified in recent years, and it has even been possible to produce some of them.

These immune factors are of extreme biological significance, since on the one hand they are responsible for cell growth and reproduction, and also for cell division and renewal, and on the other hand they can cause cell maturation and differentiation. There is apparently a unified scheme in accordance with which a small pool of uncommitted stem cells produces, via many stages of maturation, all the cells of the blood, including all the immune cells, as well as the platelets and erythrocytes. Growth and maturation are largely subjected to stimulation and control by growth and differentiation factors which are effective in either earlier or later stages of maturation.

A large number of these factors have been cloned in recent times with the aid of modern molecular biology techniques and produced in adequate quantities, and some of them are already undergoing clinical trials.

Figure 2: Cell Growth and Differentiation in Hematopoiesis



Recombinant hematopoietic growth factors:

- Proliferation of specific hematological cells: granulocytes, monocytes, platelets, erythrocytes.
- Stimulation of functional effector cell activity: antiinfectious activity (intracellular bacterial killing); tumoricidal activity (NK cells, antigen/MHC presentation).
- Protective effects: hematopoietic stem cell protection (radio-protection IL-1).
- Enhancement of antitumor therapy effectiveness: leukemic blast recruitment.

Some of these factors are being clinically tested at present for their effectiveness in oncological diseases. There are other factors which we hope will provide good therapeutic results in other types of disease.

The cell growth and differentiation factors, the cytokines are generally estimated as being of considerable medical importance. An editorial article in *Science* in 1987 expressed great hopes for these factors in medicine, and in the same edition a leading scientist stated his opinion as follows: 'In my judgement, it is a revolution in medicine equal to antibiotics'.

Today, there are still only a few diseases that can be treated causally. There are many so-called autoimmune diseases which so far do not respond at all to causal therapy. Here, too, we have great hopes that the cytokines I just mentioned will lead to improvements. The same is true of allergic disorders.

Today, a great deal is known about the regulation of IgE synthesis, an immune globulin which is of central importance in allergies, and here too, as you can see from this slide, the cytokines play a decisive part. We now have a fairly clear idea of the mechanism by which these cytokines become effective on the cell surface by attaching themselves to specific receptors. So we have begun to produce naturally occurring soluble receptor molecules by means of biotechnology, with the goal of using them therapeutically as inhibitors in undesirable immune reactions, for instance in transplantations and in the autoimmune diseases I referred to earlier. Following preliminary estimates, there will be considerably more transplantations within in next ten years.

At the beginning of my remarks, I mentioned the blood plasma proteins. In the meantime, some of them have been produced with biotechnological methods. The outstanding example here is antihemophilic globulin, which is presently being developed for clinical use. If we should succeed in producing albumin in the same way, and also hemoglobin (and this should be possible, according to recent reports), then we would no longer require human blood as a basis for medications. The advantage is obvious: Human blood is available only in limited quantities, and there is always the danger of its being contaminated with unknown viruses.

Ladies and gentlemen: The future has already begun.

Recombinant therapeutic products on the market:
- Replacement products:
  Insulin (1982)
  Hepatitis-B-Vaccine (1986)
- New products:
  Growth Hormone (1986)
  alpha-Interferon (1986)
  t-PA (1987)
  Erythropoietin (1988)
  gamma-Interferon (1989)
  Interleucin 2 (1990)
  G-CSF (1991)
  G-CSF (1991)

Almost ten years ago, the first recombinant insulin, a human insulin, appeared on the market. In the past six years, additional products have been developed, including certain cytokines.

It is conceivable that one or more of these preparations will be produced, not in bioreactors, but rather via transgenic animals. The ability to introduce foreign genes into the germ line of animals makes it possible to obtain animals with altered phenotypes, and these new genetic traits are passed on to subsequent

generations in a Mendelian fashion. The mammary gland could serve as a bioreactor after appropriate genetic manipulation, and would do so as an economically viable alternative to existing tissue culture systems.

Now, before I finish my remarks, let me mention very briefly certain advances in clinical diagnostics that would not have been possible without biotechnology.

'Physicians without laboratories and diagnostics are like moles: They work in the dark and produce only mounds.'

For the clinician, and naturally for the patient as well, laboratory examinations and diagnostics are just as important as prophylaxis and therapy.

The relative sensitivity of diagnostic techniques has increased more and more in recent times. One outstanding method for increasing sensitivity, with the goal of detecting minimal amounts of the agent under investigation, is the polymerase-chain reaction (PCR). With it, every nucleic acid can be multiplied in vitro, assuming that parts of its sequence are known. The DNA of the specific agent to be demonstrated can be multiplied a million, or even a billion times.

This principle of amplification reminds one of the ancient story from India, where the king wished to reward one of his subjects by making him a gift. The subject's request: 'Put one grain of rice on the first square of the chessboard, then double the number of grains for each successive square', and so on. On the other hand, we need such sensitive methods in order to permit the early detection of tumors, a goal that is still far away at the moment.

Figure 3: Impact of Biotechnology on Medical Diagnosis

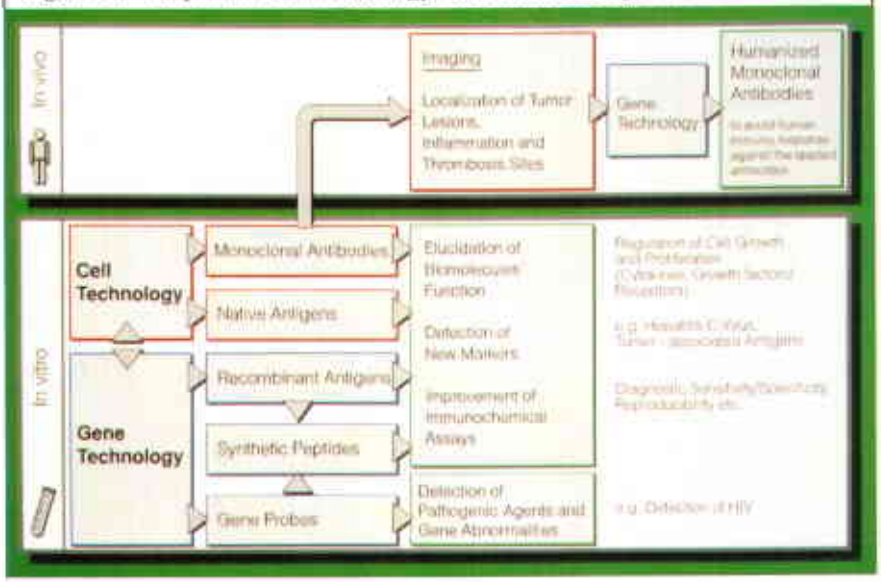


Figure 3 shows in summary form how biotechnology can affect medical diagnostics as well.

In conclusion: The recent scientific advances in biochemistry, molecular biology, microbiology, and immunology will lead to biotechnological developments which in turn will provide better diagnosis, therapy, and prophylaxis in medicine. At the same time, we must remember that all these developments will not come overnight, since they require lengthy and painstaking clinical testing before they can be put to practical use."

Plant Biotechnology: A Powerful Tool to use Plant Resources and to improve the Environmental Impact of Agriculture

Jozef Schell, Max Planck Institute of Plant Breeding Research, Cologne, Germany

"I have learnt from the previous talk by Dr. Schwick that when one gets to be elderly, as unfortunately happens to all of us sooner or later, you get in the comfortable position that, if you say that things 'are possible', you will always be right. So with this warning I will admit my bias: the way I am going to talk about plant science is to discuss what in my opinion 'is possible'. If you find that I exaggerate, please put it down to my elderly condition.

On the other hand, in the previous days we had many discussions about science and society and the value of applied science relative to fundamental science and about how one can and should integrate both and move from one to the other. The subject I am going to talk about is an illustration of how, when one focuses on fundamental aspects but keeps applied aspects very much in mind, there is no real contradiction between the two approaches and they sometimes blend together very rapidly.

In March 1987, the German science magazine 'Bild der Wissenschaft' showed a picture of a giant potato tuber with my colleagues F. Salamini, H. Saedler, K. Hahlbrock and myself sort of climbing all over this monstrous potato. It was definitely a humorous picture meant to focus attention on an issue of this science magazine in which the research done at the Max-Planck-Institut in Köln on the potato plant was described and discussed. Science journalists of the better quality had spent a whole week in our institute and were reporting quite accurately on what it was that we were trying to achieve with our research. In order to be popular with the general public, however, the journal thought it a good idea to show a monstrous potato. Although the major reason for doing this was doubtless a sense of good humour, the picture nevertheless reinforced the mental picture propagated widely by the media in Germany, that the new biotechnologies in general and plant biotechnology in particular were out to produce biological 'monsters'. The picture possibly also conveyed the motion that scientists often think that they are sitting on top of the world (the potato in this case!).

Where in fact is plant biotechnology taking us? In my opinion the future of plant biotechnology is extraordinarily bright, provided plant breeders with the help of good and responsible farmers, ecologists and environmentalists make optimal use of these new technologies. I was very impressed by the brilliant lecture of Ernst Winnacker, who quoted from Bertolt Brecht's 'Galileo' the comment that those who speak too soon are idiots. The 'idiot' in this case being Giordano Bruno who indeed got burned at the stakes. The question, however, is:

what would have happened to Galileo and to his scientific concepts, if Giordano Bruno had not spoken so soon, so that the scientific arguments brought by Galileo would not have found a properly prepared audience?

It may well be that much of the promises that have been made about biotechnology in general and about plant biotechnology in particular have been made too soon, although this is not my opinion. Dr. de Nettancourt said that the promises of biotechnology for agriculture have not been kept yet. We should worry therefore whether one has spoken too soon. But my question is, what happens if one does not speak in time and does not illustrate the potentials of a crucial technology? The consequence might be far worse than simply be thought of as an idiot. Be this as it may, the subjectivity of it all is that you will be listening to somebody who would rather be classified as an idiot since he might be speaking too soon!

With these warnings I would now like to proceed with my presentation. First of all I would like to consider some of the demands facing agriculture. There are many constraints. Yesterday Professor Gareis mentioned the obvious one of population growth. But there are many others, e.g. how much of the total land surfaces that are available for agriculture (arable land) are needed assuming modern agricultural productivity? Whereas up till this century only a rather small proportion of the arable land was required, this situation changed dramatically in this century and it is predicted that in the year 2000 (a mere 9 years from now) all arable land will be needed! Assuming a doubling of productivity, one gains perhaps 20 years and another doubling would give the world perhaps another 50 years before one reaches the absolute limit.

Whatever projections one makes about population growth, potential increases in agricultural productivity etc. etc., it should be obvious that time is running out on us very, very rapidly and that we may not have the time to quietly and patiently wait until the goals of our political and industrial leaders or the media-induced popular opinions have come to grips with this problem.

There are other constraints as well. It is often said in the developed world that we do not need more productivity in agriculture since we already suffer from overproduction. Not only is this a very short-term view, but when one analyzes this problem from an economic perspective, increasing productivity could in fact help us in achieving an economically coherent system. Indeed, without subsidies a higher degree of productivity does not have to lead to overproduction, on the contrary it might be easier to achieve an economically sound and balanced production when production costs are offset by a higher productivity.

And finally possibly the most important constraint on a global scale is that the present high input agriculture cannot be sustained or expanded without major improvements. Indeed, present day high input agriculture is too damaging to the environment. One therefore needs to increase productivity in order to drastically reduce the demands made on the soil, the groundwater, the other forms of life and reduce energy demands as well as the need for environmentally damaging chemicals.

This is why I find myself to be in complete agreement with Professor Gareis when he said that this is a challenge not only for industry but also for the public sector. It is to be hoped that good and relevant research on plants, which has been lacking in the past decades, will increasingly be supported and stimulated both by the private industrial sector and by publicly funded research institutions (as was already pointed out in this meeting by Dr. Nijkamp).

Let me once again discuss the constraint of time: I went back to the archives of our institute, the Max-Planck-Institut for Plant Breeding in Cologne, which existed and was active long before the advent of gene technology. One of its successes was a barley variety, which was given the beautiful name of 'Vogelsanger Gold' (Vogelsang is the name of the district in which our institute is located). According to these archives breeding, leading to this new variety, was initiated in 1938. The idea was to take a barley that had reasonably good agricultural properties but had one major flaw: it was very sensitive to a fungal disease. There was, however, a wild barley, that was sufficiently related to the domesticated variety that it could be crossed with it, as is done in classical breeding schemes. This wild barley had the property to be resistant to the particular mold that was attacking the domesticated variety. The idea was simply to mix both genomes to combine the genetic properties of both lines in a hybrid variety. This first hybrid was, however, totally useless since it exhibited many of the agriculturally undesirable traits of the wild parent. Classical breeders solve this problem by repeatedly backcrossing the hybrid to an agriculturally desirable variety all the while selecting for offspring combining the best yields with the capacity to resist fungal attack. This series of backcrosses and selections took from '38 till '62. Indeed classical breeding techniques take a very long time to achieve their goals. Although genetic engineering techniques combined with classical breeding schemes may somewhat shorten the length of time needed to produce better varieties, it remains fact that the creation of improved crops by the most advanced breeding techniques is a very time-consuming endeavour.

All available as well as considerable new know-how will be needed if one is to achieve the proposed goal in time (i.e. in a few decades). Modern plant breeding relies on several different techniques ranging from crosses and selection over tissue cultures all the way to the integration in the plant hereditary programme of single well defined genes. In this presentation I shall focus primarily on the latter technique. I am, however, aware, that this technology cannot be really discussed or understood in isolation, but has to be seen in the general context of plant breeding. I also want to be very clear about another point: it is not conceivable that any improvement in breeding will by itself solve the general problem if we do not remain aware of the impact of agriculture culture on the environment and carefully plan and organize agriculture accordingly. Whatever progress we make, there will be no way around the necessity to have bioconservation, that is to say to conserve the genetic potential and diversity that is available in our world.

After these general comments, we would like to focus on the impact of gene technology on plant breeding. First of all we argue that gene technology is an

essential and crucial element in modern plant breeding and that this technology does not represent per se a new danger to the environment, quite the contrary!

Our present capacity to introduce well defined genes into plants is based on the study of certain types of plant tumours. The regulation of the growth properties of cells in these plant tumours have been modified by the activity of oncogenes. The function of these oncogenes is to produce growth factors or to change the signal transduction that regulates growth in plants. In the particular case of so-called crown-gall tumours induced by the bacterial pathogen *A. tumefaciens* it was found that the tumorous or neoplasmic transformation is the direct consequence of the capacity of some soil bacteria to transfer well defined sequences of genetic information to the nucleus of plant cells. These transferred genes will, in the plant, lead to the deregulated production of growth factors or to a modification of the signals by which these growth factors regulate plant growth. We are in fact looking at a natural instance of genetic engineering. These bacteria indeed introduce defined genetic properties in plant cells with the result that the modified plant cells will proliferate and produce nutrients for the benefit of the bacteria. It was relatively straightforward for scientists to modify this system and to develop it as a general gene-vector system for plants by removing the oncogenes from the bacterial Ti-plasmid and by replacing them by any gene of interest for research or for agricultural purposes. The soil bacteria *(Agrobacterium tumefaciens)* will transfer to plant cells any gene sequence that is introduced in the appropriate way into their gene transfer system. With this method as with several others (e.g. so-called biolistics in which small particles of gold or tungsten covered with a DNA solution are shot into living plant cells) that have since been developed, it has become a practical reality to introduce at will in plants defined segments of DNA, i.e. of new defined units of genetic information. A major advantage of this approach to plant breeding is that the source of the new genetic information to be introduced in plants is essentially unlimited. Thus genetic information from bacteria or from other plants or from animal cells or from yeasts — in short from whatever source — can be added to the genetic information already existing in crop plants.

This new technology therefore represents an important additional possibility for plant breeding. One can leave the genetic properties of crop plants as they are and add to them well defined new properties through the addition of single genes to the existing genetic programme of plant cells. Thus 'elite' lines can be improved without loosing their useful properties. The use of gene vectors, such as those derived from tumour-inducing plasmids (Ti-plasmids) of Agrobacteria, combined with the general methods known as recombinant DNA technology, allowed the kind of manipulations that I alluded to, i.e. to remove pieces of DNA from one organism, study their function and add them to the existing genetic properties of plants. An important element for the use of this system was an understanding of the structure and function of individual genes in plants. Mainly we needed an answer to the question: what does it take for a foreign segment of DNA to become active after transfer and integration in the plant cellular nucleus? Indeed, when e.g. bacterial DNA sequences were first introduced in plants in the

late seventies and early eighties, the presence of this foreign DNA in the plant cells usually did not affect in any way the properties of such plant cells. This was shown to be due to the fact that these 'foreign' genes were not expressed in their new cellular host, i.e. no messenger RNAs or proteins were made. Notwithstanding the fact that the genetic code is universal and that therefore a given gene should code for the same protein whether that gene is part of its natural cellular host or part of new host cells, it became apparent that plant genes as well as animal or yeast genes carry specific so-called 'regulatory' sequences. These 'regulatory' sequences govern gene expression (i.e. transcription in messenger RNA and subsequent translation in specific proteins). A foreign gene that carries its own regulatory sequence will usually not be expressed in plant cells. It was, however, reasonably straightforward to show that one could circumvent the problem by constructing so-called 'chimeric' genes. These 'chimeric' genes combine regulatory sequences derived from 'foreign' genes. A large number of experiments with various chimeric genes introduced in plants have shown that this simple strategy works and that one can construct new plant genes with predictable and specific properties. For instance, if the goal would be to construct genes with which one wants to change the colour of flowers or produce nematode controlling proteins in roots, the principle of the method is to take any plant gene that is active in the part of the plant that one is interested in giving a new property to (e.g. flower or root), take the regulatory sequences from this gene and link them to protein-coding sequence of foreign genes that control pigmentation (flower colour) or nematode growth and thus construct chimeric plant genes which, upon transfer to a particular plant, will convey onto the flower or the root of this plant the defined new property aimed for. In summary recent research has provided us with the following tools: one can isolate genes and introduce them in living plants so that they become a stable component of the genetic programme of these plants. Provided the foreign genes are appropriately restructured they will usually function in a predictable fashion after their introduction in the plant cells. In the following we shall describe how this knowledge has thusfar been used in actuality.

Certainly the most important progress has been made in the field of herbicide resistance. This is also one of the most debated examples of genetic engineering in plants. Herbicides are widely used all over the world: the total market is currently around $7 billion. It is also well known that some of the herbicides presently used cause environmental concerns, one reason being that they accumulate in the soil, in the groundwater. This is because until now one has often used so called pre-emergence herbicides, i.e. a herbicide which can be applied prior to emergence of the crop and will kill the weeds as they come up. The problem is that the agent must remain stable in the soil environment in order to be functional, but it can be so stable that it accumulates and causes a problem. A new category of herbicides has been developed more recently: the so-called post-emergence herbicides. These herbicides are used only once the weeds come up: one simply sprays them on the weeds. It has turned out, not entirely by design, that some of these products are quite unstable in the environment. Some

of these new herbicides are also so effective that one only needs to apply gram amounts per hectare. Their weakness was that they are not selective, i.e. they have not been developed to be used in conjunction with crops and will often kill the crops as well. It is very unfortunate that in the debate some time ago people talked about these as total herbicides, which immediately suggested to everyone, even to fairly informed people, that a total herbicide is a total poison, which is not the case. It is better to be more specific and call them 'non-selective'. Other herbicides have been designed to attack the weeds or some weeds and not to attack the crop. This is possible because some crop plants have mechanisms to detoxify these particular 'selective' herbicides. The question therefore is whether one can find mechanisms to detoxify the 'non-selective' post-emergence herbicides. In a number of cases chemicals have been found which are competitive inhibitors of enzymes involved in the synthesis in plants of essential amino acids.

One example is that of phosphinotricin, an analogue of glutamic acid, which interferes with the glutamic acid pathway. This is a potent competitive inhibitor of the enzyme glutamine synthase. Its use leads to the accumulation of ammonia in plant cells which is toxic and kills the plant.

In nature a product very similar to phosphinotricin (in fact identical to it with the exception that instead of being a single amino acid it is a tripeptide), called 'bialaphos', is produced by some soil microorganisms. Microorganisms use such products to compete with other microorganisms. The bacterium *(Strepromyces hygroscopicus)* which produces this tripeptide protects itself by detoxifying the product via acetylation. The acetylated product is no longer a competitive inhibitor because it cannot bind to the enzyme glutamine synthase, and it is therefore no longer toxic. We are looking in fact at fairly 'natural' products which in the soil can easily be degraded and which come close to the ideal of a modern-day herbicide, i.e. a herbicide that will disappear from the soil after its usefulness in controlling weeds has gone. In order to protect plants specifically against phophinotricin, the strategy was very straightforward. From the streptomyces strain that produces the detoxifying acetylase enzyme, one can isolate the corresponding gene and then modify this gene so that it will work in plants. This turned out to be relatively simple and has been done by several groups. The results were as expected. The growth of transgenic plants expressing the transacetylase gene cannot be distinguished, even in the presence of the herbicide, from the control normal plant grown in the absence of the herbicide. Transgenic tobaccos were field-tested already in 1987. There was no difference in growth between these plants and controls grown in the absence of herbicide, whereas in the presence of the herbicide only transgenic plants grew normally. In this case the goal of breeding by the addition of single defined gene was thus achieved: Genetic information, originating not from another plant but from soil microorganisms, was used in order to contribute to an important agricultural goal. Such a foreign gene is functional after transfer into a crop plant as long as one provides it with the necessary plant – specific upstream regulatory sequences.

Another illustration of the specific usefulness of isolated genes in plant breeding is that when a particular gene has been isolated and reconstructed and

used in one variety or one crop, the chances are that it will be just as useful for other crops. The gene conveying tolerance to the phosphinotricin herbicide, first tested in tobacco as a model plant, has already been introduced into a variety of crops and shown to be effective. This is a very important aspect of plant genetic engineering. Once functional genes have been isolated and tested in one plant species, they can also be introduced into other crops.

A somewhat different approach has been used by researchers interested in providing crops with a gene that would render these crops insensitive to the herbicide 'glyphosate'. Glyphosate is a highly effective and relatively low cost herbicide. This herbicide is also rapidly degraded in the solid and does therefore not cause environmental problems. It is known to inactivate an enzyme involved in the synthesis of the essential amino acids, tryptophane, tyrosine and phenylalamine. By identifying genes that code for enzymes with the same function but insensitive to glyphosate and by introducing these genes — via plant gene-expression vectors — into various glyphosate sensitive crops it was shown that these crops became tolerant to the action of glyphosate. Similar examples could be cited for a number of other nonselective herbicides.

The examples given with herbicide tolerance can also be used to discuss the possible impact of plant genetic engineering on the environment. It is clear that these same methods can be applied to environmentally less desirable pre-emergence herbicides such as paraquat, atrazine or 2.4D. Whether herbicides which are environmentally deleterious or environmentally neutral are used, will be determined by economic considerations and, one hopes, also by well considered regulations, not by plant breeding methods.

I want to use the opportunity afforded by these examples to discuss some of the aspects of the so-called 'public acceptance' problem. As I explained earlier, these non-selective herbicides were also referred to as 'total herbicides'. In a public context where there is growing concern about the negative effect some 'pesticides' can have on the environment, many people and especially many representatives of the media felt that 'total herbicides' must be 'bad pesticides' and that the science-industrial community was trying to increase the market for such 'bad' chemicals by breeding crops that would allow their expanded use in agriculture.

Once this misconception was launched through the media and was also used as an argument against the use of biotechnology by some political parties, such as 'The Greens' in Germany, it turned out to be very difficult if not impossible to correct the misconception. Too many vested interests now had committed themselves to an anti-attitude. The practical consequences of this 'acceptance' problem in Germany is that on the one hand industry is reluctant to make use of this important technology and on the other hand further research is made more expensive and cumbersome.

To date only one field experiment with a transgenic plant has thus far been conducted in Germany and was the object of totally disproportionate media attention (mostly negative). This experiment, which was conducted by my colleagues Professor H. Saedler and Dr. P. Meyer, was, however, extraordinarily

benign — since it dealt with Petunia plants — with a new flower colour (pink) resulting from the introduction and expression of a corn gene.

To illustrate how rapidly this science is progressing, I should mention that transgenic plants were first obtained in the laboratory in 1983 and field tests with transgenic tobacco and tomatoes were already performed in 1987 and that to date several hundred field tests with transgenic plants have already been performed world-wide. Certainly one of the most important goals of plant breeding must be to produce plants having properties that will help yield stability and sustainability. In consequence, significant research is presently geared towards engineering pest tolerance (against insects, fungal pathogens, viruses and nematodes) and, in a longer time-frame, improving drought and cold tolerance. Let me illustrate these attempts by discussing another example based on the use of bacterial genes. Some bacteria produce peptide toxins which bind to receptors in insect intestine and are thus specifically toxic to certain insects. By taking the gene that codes for these peptide toxins and expressing in plants, several groups have been able to produce transgenic tobaccos, tomatoes, potatoes and cotton which express the bacterial toxin and are thereby effectively protected against attack by some insects as was very convincingly demonstrated in a number of field tests. The insect larvae will feed from these plants, but as a result of the presence of the toxin their digestion is severely impaired, they stop feeding and ultimately die.

The results demonstrate that a significant measure of additional crop protection can be achieved by genetic means. It would in my opinion, however, be unrealistic to think that biological protection can ultimately totally replace the use of chemical insecticides in intensive agriculture. However, the combination of breeding plants harbouring not one but several genes which reduce their sensitivity to pests (in order to avoid the emergence on resistant insect populations) with responsible use of environmentally acceptable pesticides can be expected to provide great advantages both in making agriculture more efficient and economical and in reducing its negative impact on the environment. Indeed, by combining several different methods to achieve pest control, one will drastically reduce the probability that any of these methods will soon become obsolete as a result of adaptation by the pest.

Thus, pesticides could be used over longer periods of time and probably at lower concentrations and the biological control achieved by products of specific genes would not be as readily broken down. In this respect it might be of importance to mention that various other strategies aimed at the genetic containment of deleterious insect populations can now be investigated. For example, one could try to have crop plants produce insect specific growth factors that would interfere with insect reproduction by preventing larval development into adult insects.

Thus, one could keep insect populations in check and by appropriate regulations and agronomical procedures one could also prevent the total eradication of certain insect populations. The aim cannot be and does not have to be insect eradication but instead control over the size of insect populations. (This approach is known as 'pest management'.) It can be expected that the first insect-tolerant

crops that will actually be used in the field as early as 1995 will be so-called 'Bt-cotton'. Much progress has recently been made in protecting crops against viral diseases. It was found that if one breeds plants so that they will express a particular protein which is normally part of the envelope of the virus particle, this virus-derived protein will under field conditions prevent infecting viruses from multiplying in these plants. This strategy appears to have general value and might well be used to control several different plant viral diseases. It is important to realize that no chemical agents that protect plants against viruses are presently available and that other anti-viral strategies based on single gene transfer are possible (e.g. antisenese, RNA, ribozymes etc.).

The introduction of isolated genes into defined crops, although sometimes difficult, can be achieved with relatively low-tech methods and does not require very heavy investment. This is of particular importance for crops of limited regional importance, e.g. in the developing world. Even if it is true that in its initial stages genetic engineering was developed with high-input agriculture as an economic target, the methods and the genes that are being produced by this research will ultimately benefit agriculture world-wide, and will also help low-input regional agriculture.

Let us now briefly mention a few areas that are still at an early research stage.

I. Resistance to plant pathogenic bacteria

Some bees happen to have in their lymph glands some smaller proteins that have the capacity to insert themselves into the membranes of bacteria and as a result bees protect themselves against bacterial infection. It is fairly straightforward to use techniques of gene technology to isolate from the lymph of bees some of the liquid that contains the protein, isolate the protein, and from the structure of this protein deduce the structure of the corresponding bee-gene. After isolation of the relevant gene from bees, a chimeric gene can be constructed and transferred to plants. It can then be tested whether such modified plants have become resistant to attack by plant pathogenic bacteria. (This approach is currently under study in Plant Genetic Systems, Gent, Belgium.)

II. Fungal diseases

Fungal diseases are a major problem in agriculture and their control by fungicides is essential but sometimes problematic. Various soil microorganisms (bacteria or fungi) compete with plant pathogenic fungi. Such competing microorganisms often produce various enzymes (e.g. chitinases) that attack the cell wall of plant pathogenic fungi. Attempts are being made to isolate the genes that are responsible for the production of the lytic enzymes that attack the fungal cell wall. Preliminary green house tests indicate that plants expressing such new chitinase genes are more tolerant to fungal attack. Several other anti-fungal proteins, e.g. from barley-seeds, are presently being studied in our institute.

III. Stress tolerance

Environmental stresses severely affect the sustainability of crop fields. In order to attempt to understand the mechanisms that are responsible for the fact that certain plants can tolerate extremes of temperature (high or low) or water and salt stresses better than others, plant molecular biologists are presently in the process of identifying and isolating genes that play a role in the physiological adaptation of plants to environmental stresses.

Several approaches are being used, among them one should mention:

1. Differential hybridization of cDNA banks to plant m-RNAs isolated from stressed and non-stressed tissues and from tolerant and sensitive cultivars.
2. Inactivation of stress tolerance by 'gene-tagging'. Transposable DNA elements and T-DNA inserts are used to inactivate genes. Subsequently the transposable element or the T-DNA sequence are used as probes or 'tags' to isolate the inactivated genes and subsequently to corresponding active genes. In this respect it is important to mention that transposable elements from corn have been shown to function in transgenic dicotyledonous plants. Transposable elements and T-DNA vectors have been developed specifically for the purpose of gene-tagging. Thus, it was possible to not only develop 'tags' that can inactivate genes but also some that will produce gene fusions and some that will activate silent genes and turn them into dominant, deregulated alleles.
3. Identification and isolation of complex loci involved in stress tolerance or quantitative traits, by looking for their linkage to carefully mapped restriction fragment length polymorphism sites (RFLP mapping). This method promises to be very valuable to most plant breeding programmes.

   Much progress has recently been made in the identification of genes regulated by the plant hormone Absisic Acid (ABA) and presumably involved in conveying tolerance to dessication to plants and to their seeds.

   It is to be expected that the genetic control of complex physiological process such as stress tolerance and yield will depend on the proper combination of a fairly large number of genes. It is nevertheless essential to study these genes because one might find some 'key' genes that regulate the complex process, or one might find that relevant genes are linked in complex loci, or one might discover that in some cases only a few genes are involved. It is clear, however, that without the new cellular and molecular methods it would be unrealistic to hope to study these complex processes.

IV. Nuclear male sterility and the production of hybrid seeds

Heterosis has been shown to be a very desirable property of plants since it affects several important properties (e.g. yield). Recently new approaches have been developed and are presently being used to construct dominant chimeric genes causing male sterility. The general approach is to construct genes that express a lethal function only in tissues involved in the formation of pollen.

Promoter sequences derived from genes that are expressed only in anthers, can be combined with DNA sequences coding for cell-lethal enzymes, such as for instance RNA's or DNA restriction enzymes.

This approach might soon make it possible to produce hybrid seeds of many different crops for which no effective cytoplasmic male sterility system is presently available.

V. Nutritional quality

Most of the major plants are defective for some essential amino acids. Work is in progress to attempt to express or over-express genes coding for reserve proteins rich in essential amino acids in the seeds or tubers of various crops.

Promoters directing the organ specific expression of such genes (seed or tuber specific) are presently available. Research is also aimed at analyzing and changing the biochemical pathways responsible for the synthesis of essential amino acids.

In particular, it is attempted to express in plants bacterial genes that code for enzymes involved in amino acid synthesis and that are insensitive to feed-back control by the synthesized amino acids.

VI. The use of plants to improve the quality of food or to produce important commodities or to produce valuable pharmaceuticals

Whereas improvement in plant protection has been the first goal of molecular breeding several other important breeding goals are presently being pursued. Thus a bacterial gene introduced and expressed in tomato plants, the product of which interferes with the synthesis of the plant ripening hormone ethylene was shown to improve the solids content and the taste of green tomatoes that are easily shipped and conserved and that can be turned into red tomatoes after harvesting and shipment, by treatment with ethylene.

Major progress has also recently been reported in the molecular breeding of potatoes with increased starch contents and of rape seed with tailor-made lipids (e.g. of use in soap production).

In another approach plants expressing valuable proteins (such e.g. human serum Albumin) or important commodity enzymes have recently been tested.

VII. Gene technology as a tool to understand and possibly control plant growth and morphogenesis

One of the very useful properties of many plants is that they can be grown and multiplied in tissue culture. This is already of considerable applied value, in particular for the production of ornamentals and some vegetables and in the near future for the production of transgenic cereals. However, the methods used are still largely empirical since little is known about mechanisms underlining plant

growth and differentiation. Recently, however, a number of genes were isolated in our laboratory that can drastically modify the growth properties of plants. It is expected that the study and the use of these genes will in the future lead to a better control of plant growth both in tissue culture and in the fields.

Conclusion

Plant biotechnology can significantly help to make intensive agriculture less damaging to the environment or to make low-input (organic) agriculture more productive. It is now possible to improve both major crops (rice, wheat, corn, soybean, potato etc.) as well as more regional crops. It can lead to the breeding of crops with improved capacities to resist biological pests as well as chemical and physical environmental stresses. If used wisely and responsibly, there is no inherent danger in these new methods. It would be shortsighted and irresponsible not to make optimal use of these methods to relive at least some of the tensions that already exist, and will dramatically increase, between agriculture and the environment and between agriculture and the production of food for very large and still growing populations.

Last but not least these technologies are very likely to help the economic value of agriculture both in the developed countries and in the developing world. We, however, witness at this moment in time increasingly strong opinion movements that question the value of this technology. Imaginary dangers to the environment that would result from the application of these technologies are feared. No doubt, these opinions are based on a complex mixture of emotions, experiences and interests. Objectively, however, it is mostly the damage done to the environment by large scale, very intensive industrial agriculture, with its sometimes inconsiderate use of land, pesticides, fertilizers etc. that motivates these reactions. There is also unavoidably the fear for complex new technologies that seem mysterious, are not well understood and continually modify the quality of our life.

In a situation such as in Europe, where food is abundant, of high quality and relatively cheap, it is perhaps understandable that people would concentrate on the potential dangers of new developments. This apparently favourable situation is, however, extremely labile (a few poor harvests in succession quickly bring down what is sometimes seen as 'mountains' of food reserves. World food reserves are now at their lowest level since World War II.) It would be very dangerous and, in our opinion, shortsighted and therefore irresponsible not to aim for increased productivity (not be confused with increased production) in agriculture just as it would be very irresponsible to ignore the absolute need to preserve the environment."

From the Information to the Biomation Age

Reikichi Shirane, Tama University, Tokyo

"1. Social System Evolution

The theory of the information society first suggested in Japan has been the theme of interdisciplinary research since the middle of the 1960s and has aroused the interest of various fields.

With regards to social evolution, the 19th century philosopher, Herbert Spencer (British, 1820-1903), advocated a theory equating society to an organic body. This theory has been verified by the progress of information technology.

This theory of Spencer, which is said to have been influenced by the utilitarianism of Jeremy Bentham and John Stuart Mill who pursued the greatest happiness of the greatest majority, and by Darwinism, is an excellent hypothesis that can be projected into modern society.

Alternately, the goal concept of the information society in Japan seeks to realize 'a society where each citizen can voluntarily exert diversified individuality, and can actively work in social, economic and cultural terms' with the assumption of 'affluent, safe and unassailable society'.

What should be noted here is that the concept of the information society in Japan originated with 'the theory of the information industry' published in 1963 by Professor Tadao Umesao, a specialist in cultural anthropology and ecology. He described the development process of industry and society in comparison to the embryology of animals; for example, in place of the normal classification of the history of industrial development into the ages of agriculture, manufacturing, and services, he described them as the ages to satisfy the functions of the endoblast, the mesoblast and the ectoblast, respectively.

He used the analogy of the evolution of creatures which progresses from the digestive system, through the formation of a skeleton, muscles and a circulatory system to the advanced development of cerebral nerves and a spinal cord system to compare the progress of the social infrastructure.

2. Advanced Technology Paradigm Conversion

The importance of having a global consciousness is increasingly realized in the face of environmental and resource constraints and the concomitant population explosion. With the advent of the 21st century, a paradigm conversion is sought in the area of advanced technology which pursues expansion of human capacity and economic affluence.

If this is expressed in key words, it means technology is converting from explosion-type to implosion-type. As seen from the social needs which beget the technology, emphasis is not to be placed on the evolution-type where the first priority is growth, but placed on the internal progress of the involution-type which enhances the quality of life.

With the development of advanced technology, we have challenged various frontiers and have achieved external expansion of the human capability. However, an ironic phenomenon has emerged which has made the internal aspect hollow. From a review of such phenomenon, the pursuit of 'techno-amenity gentle to human beings' and also truly amenable for human life is required. From the viewpoint of returning to the original point once again, the concept of 'learning from creatures' becomes an important pillar in the development of advanced technology.

Table 1: International Comparison of the Rate of Population Aging

Country	Achievement of Population Aged 65 and Over		Required Years
	7%	14%	
Japan	1970	1995	25
U.S.A.	1945	2015	70
United Kingdom	1930	1975	45
West Germany	1930	1975	45
France	1865	1995	130
Sweden	1890	1975	85

Source: Collection of Population Statistics, Institute of Population Problems, Ministry of Health and Welfare.

Table 2: Projection of the Ratio of Population Aged 65 and Over in Major Countries

Unit: %

Country / Year	Japan	U.S.A.	United Kingdom	West Germany	France
1990	11.9	12.6	15.5	15.5	13.8
2000	16.2	12.8	15.4	15.4	15.3
2010	20.0	13.5	16.1	16.1	15.6
2020	23.6	17.3	18.7	18.7	19.1
2025	23.4	19.6	20.1	20.1	20.6

Source: Collection of Population Statistics, Institute of Population Problems, Ministry of Health and Welfare.

The above tables are quoted from Industrial and Technological Perspectives Vol. 4, a report by the Daiwa Research Institute, Co., Ltd.

To illustrate by a concrete example, the rapid structural change of the Japanese society can be cited. As shown in the tables, Japan is transforming into an aged society faster than any other country in the world. This is likely to competitively influence the principle of economic growth as top priority. It is inadequate to view this phenomenon as the response to the 'silver business market' such as development of medicine to prevent geriatric disease and senility as well as development of home care and home-based medical equipment for the aged. The need is being presented to establish social policy, making the lives of aged people worthwhile and to advance philosophical propositions concerning the status of human life.

3. Information Technology Trends

Advancement of the information society continues to progress from biomation to humanization. The same flow of innovation is guiding the advancement of information technology to support infrastructure of such a social system.

NTT, a representative common carrier in Japan, announced last year its service vision for the 21st century: VI & P (visual, intelligent, and personal communication services) were the key words.

Preparations are being made for the 1996 start of commercial serve for high-speed broad-band B-ISDN (a comprehensive 620 megabytes/second digital communication network). This network has already entered the experimental stage as a trunk communication network for the 21st century. This will allow the

provision of various multi-media services including sound, data, still pictures and moving pictures depending on the application. It will definitely establish a two-way intellectual network. It is estimated that at least 1/3 of all the telephone subscribers will be the recipients of this advanced service by 2015.

The service menu also includes pocket telephone, text mail, and visual telephone advancing individualized communication. It is hoped that 20 million units of the first two items and 5 million units of the third will be in circulation by 2005.

On the other hand, as an example of an available technology to advancing the biomation of communication, there exists a molecule-collection device which is composed of organic molecules. This has two implications: The first is that the molecular electronic device uses the quantum status of the molecule as the unit of information. Molecular switches, molecular memory, molecular wire, etc. will be experimentally produced in the early 21st century. The second implication is that the bio-electronic device, which is highly integrated with molecules as the building components, utilizes the self-organizing capability of the bio-molecule. The realization of the practical application of this device is expected in the early stage of the 21st century. As the technology to advance humanization, research and development of sound recognition, sound synthetization, character and document recognition, image recognition, natural language understanding (translation), knowledge processing, fuzzy logic computers, neuro-computers, etc. is being actively promoted as technologies to promote biomation and humanization of communication. They will greatly impact information and communication fields in the beginning of the 21st century.

The above discusses network-type information technology. Another important development trend is taking place in package-type technology. As seen in the popularization of such phrases as virtual reality or artificial reality, the information environment of individuals will experience great development. The improvement of the interactive features and the linkage functions of the package-type media through addition of advanced intellectual processing to multi-media has coined a new word, hypermedia.

As a concrete example, a hypermedia personal computer with a built-in CD-ROM is beginning to exert its power in creating a new package-type information environment.

Another technology to be surely commercialized in the beginning of the 21st century is a large 'liquid crystal' screen (120-200 inches). The progress of the TFT (Thin Film Transistor) colour liquid crystal and its projection technology along with introduction of the HDTV system will have a great impact on the visual world. Display terminals have become commonplace to the extent that, today, each individual can have a personal terminal. HDTV would change this trend to individualization and, as a result, alter the current lifestyle of the people, for example, the family gathering would be restored in front of a large HDTV display.

4. Challenges for the Japanese Society

Over the past 40 postwar years, the Japanese society was fortunately able to overcome many difficulties, succeed in the establishment of an advanced industrial society, and become one of the members of the economically advanced countries. In order to make the Japanese-style economic system have universality in the international society and make it acceptable to other countries, Japan has many more hurdles to overcome.

First, Japan has to break through the exclusiveness and closure still remaining in the Japanese society and establish an externally open and flexible system suitable for the biomation age.

Japan has to acquire more flexibility by outgrowing the practice of corporate affiliation through the mutual holding of stocks of domestic companies. It is important to accept the participation of foreign companies and facilitate their entry into the affiliation.

Efforts for the coexistence of the pursuit of efficiency and social fairness are also important. Just as individuals have personal virtue, companies should have corporate virtue. In specific terms, companies are required to nurture higher ethics and aesthetics in their actions. The words recently stated by a top official of a certain large company are worthwhile repeating: 'The company is not going to have culture per se, but it is our goal to have a company where individual people of various cultures gather.'

In politics, the behavioural pattern of 'protection of partial interests' on the basis of vested interests must be changed. In administration, more effort is needed to quit the vertical system which is unclear and maintains to the territory of the ministries and agencies.

The above matters show that securing evolution from the mechanical and rigid social system of Japan to establish a more flexible and generous biological system is an urgent task for Japan.

The second important consideration is that Japan is integrally located in the Western Pacific and Asian sphere. This area has high economic growth and is the most active in the world. The success of these countries will prove the universality of the Japanese economic system.

For the first time in history, this sphere has formed as an independent trade sphere; Japan is no longer isolated. The progress of the NIES (Korea, Taiwan, Hong Kong and Singapore which are called the Four Tigers) and the DAE countries including (Malaysia, Thailand and Indonesia which can be called the Three Children of Tiger) has been remarkable. (As an aside, in Japan, the child of tiger refers to the most important thing). This situation has been aptly tagged as a flying geese formation; a very energetic biomated system has begun in this sphere.

Fostering close relationships with these countries and establishing interdependent and open systems with the other economic spheres must be the direction of Japan in the new age."

FOURTH SESSION

Interaction between Scientists and Engineers on one Side and Industry and Governments on the other Side

Chairman: Josef Rembser

Tools for Transnational Cooperation in Biotechnological Research and Development: Experience from EC Programmes

Dreux de Nettancourt, European Community Commission, Brussels, Belgium

"I do not know if I am at the centre of biotechnology, but certainly the Commission would like to play a decisive role in this area. What we are trying to do is to promote research efficiency and technology transfer through international cooperation. Actually, this objective is not over-ambitious because scientific cooperation is easy to induce and because scientists are naturally willing to share and to work together.

We started ten years ago with a small programme of 15 million ECU, and we are now implementing a somewhat larger programme of 100 million ECU for the period 1990-1992. This amounts to 25 million ECU/year, that is to say less than 3 per cent of the money which the Member States spend on public biotechnology. We hope to launch a somewhat larger programme of 164 million ECU next year which should cover the period 1992-1994.

What I want to discuss with you are the instruments which we are trying to use for promoting transnational cooperation. I want to discuss them with regard to our current programme, BRIDGE. I do not have the time to go into the details of the research objectives. Just remember that in BRIDGE we have four main sectors; the first one concerns *'information infrastructure'*. We do not want to create new structures, but *to make sure that what exists already in the Community*, as far as *data banks* and *culture collections* are concerned, is placed at the disposition of all scientists in the twelve Member States. The second sector covers *'enabling technologies'*; there we are trying to promote cooperative research in bioengineering, protein design and genome sequencing. I will come back to that later on. The third sector deals with *'cellular biology'*, where we support very fundamental research, oriented towards the analyses of the molecular biology of plants, microorganisms and animal cells important to man. Finally, as you can see from the transparency, the fourth sector is devoted to *'prenormative research'*. What we want to do in this sector is to assess possible risks which could be associated to the release in the environment of organisms resulting from genetic engineering. We also want to develop in vitro tests for the study of structure-function relationships in new molecules, particularly from the point of view of their toxicologic and pharmacological properties. So much for the content of the programme.

The instruments — how do we implement the BRIDGE programme? We have three instruments at our disposition. The first one is what we call *European Laboratory Without Walls*. I will go into that in a few seconds. The second one

is new, we have not much experience with it and it corresponds to what we call 'targeted projects', which are relatively close to industrial objectives. And finally, the third one which I want to mention in view of its importance in other European programmes is the European Grouping of Economic Interests. It is not used in the current biotechnology programme.

I will start with the first instrument, the 'European Laboratory Without Walls'. What do we mean by this? If a number of laboratories in the Community have a specific problem — for instance the immobilization of a given enzyme, the characterization of a gene, the control of a specific process ... — if they have a specific problem and if they accept to try to solve this problem together and to this effect accept to share information, to exchange material and staff, to plan and evaluate together their research, to execute together their research efforts — if they accept all this, we construct or create what we call a *European Laboratory Without Walls (ELWW) which is an association for the laboratories willing to integrate their work for the solution of a common problem.* Usually, this work is basic in nature, and the research partners, from four to ten on average, composing the ELWW are universities and national institutions. Once this is done and cooperative research is taking place, the next task is to promote technology transfer, which is one of the conditions for the survival of basic research ultimately. To this effect we try to attract industries within each ELWW. And it is very easy indeed because industries always welcome the possibility to integrate a structure where scientists have accepted to work together, to share their equipment and have a specific problem already defined which, in the long term, is of industrial interest; industries are therefore quite interested in our Laboratory Without Walls. Among the brochures I have brought with me, one of them contains a description of each of the Laboratories Without Walls created by the Commission. We have constructed 38 Laboratories Without Walls up to now, and you will see that in each case industries have been attracted and have been associated to the ELWW, under three different conditions: they can co-finance the research, implement part of the research or, more simply, pay a small accession fee, which enables them to attend some meetings and have access to some of the results rather rapidly. However, ultimately, all the research results obtained by a ELWW are published and the programme is transparent. If the relationship between the industries and the laboratories composing a given ELWW tends to be confidential, then we close the laboratory and stop the implementation of the research but we consider that we have reached our target which was to transfer technology. I do not have the time to give you examples of Laboratories Without Walls in the framework of the biotechnology programmes; one of the largest is the Laboratory Without Walls which was created for the sequencing of chromosome III in yeast. If you want details, for each laboratory we have published a small booklet, which is available upon request. The oldest Laboratory Without Walls concerns the biotechnology of lactic acid bacteria. You will see that it has evolved into what we call a 'T' project. I will come to that in a second. First I want to apologize to our German friends because the maps of ELWWs which I am projecting were prepared before the re-unification

of Germany. New editions are in press. So much, Mr. Chairman, for Laboratories Without Walls.

We have another instrument, which we are just starting to use. If a group of laboratories, for a specific problem which we have identified and advertised in our calls for proposals, wants to unite efforts and work together, we can launch what we call a 'T-project'. Such a launching involves the creation of bi-partite structures bringing together, for each T-project, a transnational team of contractors and a monitoring unit composed of representatives of the Commission services and of the Member States who advise the group of contractors on all matters concerning the implementation of the project. In several instances, groupings or 'platforms' have been created by industrial enterprises of the EC interested in the area covered by a given T-project and wishing to establish a dialogue, through the monitoring unit, with the contractors. Such platforms are open structures, depending on the initiatives of industries, and there is no involvement of the Commission services in their organization or function. The data which the contractors decide to pass on to the outside world will be ultimately published by the laboratories or by the Commission services. Thus, the platforms do not have the exclusivity of the information and, in no case, would the information released by the contractors be withheld from other EC industries which either individually or as a group would request it.

The launching of ELWWs and T-projects is announced through official channels and widely publicized.

In each case, *peer reviews* are organized which enable experts nominated by the Member States and by the Commission services to meet during two or three days in Brussels for reading, assessing and rating each of the proposals submitted to their evaluation. The number of proposals (always transnational) assigned to each evaluation group varies between 10 and 25.

Just to give you an idea of the current situation, I would like to present in a few transparencies some of the T-projects which are under way. There is one on industrial lipases. I will not go into the details, but you should know that there are 26 laboratories organized in five teams, each corresponding to a specific lipase, working together. Here, in case you are interested, is the composition of the monitoring unit. Another T-project — we only have seven at the moment, because those T-projects are more expensive than ELWW — concerns the *biotechnology of lactic acid bacteria*; 34 laboratories, organized in five groups, work on different components of the problems which the laboratories have identified together. You have here, on the following transparency, the membership of the monitoring units. The molecular identification of new plant genes is a T-project which Professor Schell knows very well. And there we have 35 laboratories organized in three groups, which cover floral induction, seed development and embryogenesis, respectively. And there is also a central core for bringing together resources and technological inputs. We have also created a T-project for sequencing the yeast genome. I told you that as far as chromosome III was concerned the work had been completed entirely within a ELWW — and this I think is the first time in the world that the chromosome of a eukaryote is

entirely sequenced. And I also told you that we did this through the network approach. Now, for the sequencing of chromosome II and chromosome XI, we have organized a T-project with a budget of 5 million ECU. However, in spite of the increased size of this activity, we have maintained the network approach. There are other T-projects which I would have liked to present, but I am afraid that time is running short. I would like, very briefly, to introduce the third instrument which is available to the Community for trying to induce the pooling of efforts, and this is the European Economic Interest Grouping. It was established in 1985, and its aims are not necessarily restricted to research; as far as research is concerned it can bring together big and small industrial laboratories which can decide on common ways for disseminating the information. Within BRIDGE, as I told you, we have not yet used the instrument.

This is what I wanted to say with regard to instruments. Their use is not always easy, in spite of the fact that scientists are most eager to cooperate, because we have to deal with several languages, with a large Community and because the Commission was not initially created for the administration of research. Progressive adaptation is, however, rapid and it is very rewarding to measure the road accomplished in the past. The following table is a small summary of what we have done since the last ten years, when we started with our first programme in 1982.

3,550 days of Community R&D in biotechnology What happened?	
4000	research proposals received
600	laboratories undertaking contractual research
350	industrial firms involved in ELWW and industry platforms
85	industrial firms undertaking contractual research
400	articles published every year by the contractors
200	review articles and proceedings of meetings prepared by the services of the Commission of the European Communities
640	man/month in BAP as exchanges of staff between laboratories participating to the programme
80	training contracts per year
10	summer schools per year
38	ELWWs, grouping 250 laboratories, created in BAP (65 new ELWWs presently launched in BRIDGE)
7	T-projects grouping 162 laboratories created in BRIDGE."

Technoglobalism by Scientific Option-Sharing Scheme of International Cooperation

Fumio Kodama, Harvard University, USA

"Last year, news about cold fusion grabbed the world's attention. Before that, the central topic was warm temperature superconductivity.

These two examples made clear to the general public that as we strive to achieve a certain goal, such as securing new sources of energy, science and technology present us a variety of different options.

In the above case, development of the next generation of energy supplies can follow at least two distinct routes. One would bring an increase in energy supplies by developing a new form of nuclear power. The other would take advantage of superconductivity to eliminate energy loss during the transmission of electric power.

The two cases acted as a stunning reminder that science and technology entail a vast area of options and alternatives. A thorough search of all possible options, therefore, should be made the chief aim of future international cooperation.

Another illustrative case relevant to a new approach to international technology cooperation can be found in last years' controversy over joint Japan-U.S. development of the FSX fighter aircraft, which climaxed with a U.S. congressional resolution in opposition to the project.

The issue stirred up such widespread controversy not only because the project involved military technology, but also because the form of the joint development effort was substantially different from what had prevailed in the past.

The U.S. congressional resolution, while imposing various limitations on the transfer of technology from the U.S. to Japan, required that Japanese corporations transfer of U.S. corporations their carbon fibre technology, developed in Japan's civilian sector, without condition and without payment for the technology.

The past approach emphasized the transfer of technology from the U.S. to other countries. It could be said, however, that a new paradigm has become necessary in determining what form international cooperation should take.

International cooperation has traditionally been dominated by the notions of 'cost sharing' and 'task sharing'. Both refer to dividing up costs and tasks among participating nations, in order to pursue an option that has already been selected. They also emerged for purely economic reasons.

These concepts have not, in other words, derived from the logic of science and technology itself, which appears to have been left thoroughly out of the equation. This fact highlights the need for a new concept of international

cooperation, based on an understanding of the dynamics of science and technology.

'Option sharing' is a concept which would fill this need. Specifically, option sharing would entail dividing up the various burdens and responsibilities for pursing each of the possible scientific and technological options in a given area.

In their early stages, research and developments projects, especially those identified as national projects, are characterized by a high degree of fluidity. No individual or country can be certain about the proper standards for evaluating the performance of a certain technology or judging which alternative is best.

In this regard, the dividing up of responsibilities for pursuing all possible alternatives would represent an effective and constructive role for international cooperation. Conversely, only through international cooperation would it be possible to pursue all potential options.

Through this form of option sharing, moreover, it becomes possible to resolve the inherent tension that exists between international cooperation and national autonomy.

This cooperation scheme should not permit one country of force on other countries the specific alternative it has selected. Each country would have the right to choose which alternative it wishes to pursue. Given the need to ensure that all possible alternatives are covered, however, there would also have to be a certain amount of compromise and adjustment of each country's interests.

In addition, information about which alternative is best must be shared openly among all participating nations. Determining the most desirable alternative is possible only if all the alternatives are tested and compared. This sharing of information could be assured by allowing a free flow of researchers across national borders. Specifically, researchers from each country would freely choose the alternative they wish to pursue, in accordance with their own views, convictions and career objectives, and would participate in the project of the corresponding country. After it has been determined which alternative is best, the researchers would return to their respective countries.

The participation of researchers from various countries in each project would ensure that, once the researchers have returned home, the information on the alternative ultimately selected would be automatically disseminated throughout the participating countries.

At present, there are growing fears that moves in the direction of technological protectionism will turn into a minus-sum-game for the world as a whole. It could be said that only through option sharing could a plus-sum-game be assured.

In a world where 'techno-nationalism' is the prevailing mood, international cooperation through option sharing may offer the conceptual breakthrough which can make 'techno-globalism' the new reality."

How to establish an Innovative Research Environment in the Life Sciences

Lennart Philipson, EMBL, Heidelberg, Germany

"Life originated on this planet as a low probability chance event several billions of years ago. It is now clear that all forms of life are very related since they use the same basic machinery to reproduce, metabolize their nutrients, interact with the outside world and store the basic information. We know already that bacteria, yeast, plants, animals and man must have originated from the same primeval form of life and many of the life processes are shared between all living species on this earth. Since Charles Darwin referred to the apes as our cousins we must now recognize that the yeast fungi mainly used to make bread, beer and wine are our second cousins.

Basic biology is currently studying the detailed pathway for passing information from the genes to the final protein products during development, differentiation and in tissue organization, as well as the evolutionary pathways that have governed these processes over millions of years. It may also provide basic insights that can completely change several applied areas including ecology, livestock and plant production, as well as human health. The driving force and the ultimate goal is to understand the details of the life processes to such an extent that we can correct many mistakes made in the past. Using biological processes we will probably be able to provide safer routes to accumulate agriculture products, counteract the increasing environmental pollution and also enhance health and be able to treat diseases of animals and humans.

Throughout evolution of life from bacteria to man, massive transfer of genetic material between species together with a natural selection have been the major forces. We should, therefore, not be afraid of the new methods offered through gene technology but use them to our advantage to improve the world around us. Nature has already taken advantage of gene technology.

Due to the rapid development of basic molecular biology we in Europe have introduced extensive collaborative programmes on the applied side primarily through the EC and Eureka but we have overlooked the necessity of supporting European collaboration in basic life sciences at an appropriate level. Molecular biology, or biology in general for that matter, does not require enormous instruments and technological facilities like those required for physics, astronomy and space research. Success in basic biology requires foremost a different type of research structure than the one presently prevailing at national universities and in addition a broader base for scientific interaction.

I represent a Laboratory that has attempted to set an example of how to build up an international recruitment system leading to more mobility and interaction between the scientists in Europe. It has flexibility in organizing research programmes through turnover of staff allowing for rapid introduction of new research areas. It can easily engage in interdisciplinary research, allowing new combinations of technical development and integration of science over conventional faculty borders. It also provides young scientists with an innovative environment for independent research which is not available in many countries in Europe. The independent scientists after their service at EMBL return to and strengthen the national university systems. The EMBL also provides a training ground for pre-doctoral and post-doctoral students at the European level and introduces and teaches new technologies to existing national laboratories.

The mother organization of the EMBL was a group of scientists who came together in the 60s and founded the European Molecular Biology Organization. The EMBO now, with a membership of around 750 of the most highly qualified European molecular biologists, has governed extremely successful exchange fellowships and course and workshop programmes for over 25 years. The experience from these programmes has unequivocally demonstrated the benefit of promoting European collaboration by pooling national resources. Although several of the large countries and some of the small countries in Europe have excellent national centres in molecular biology, the number of graduates being trained is still not enough to meet future applied and industrial needs. The flexibility is also hampered at the national level due to stagnation in the research support. Furthermore the expertise in each individual country is not of sufficient depth or breath to allow for an anonymous and qualified peer review system of every project. The scientific evaluation process thereby suffers from lack of expertise and subjective elements tend to enter into the evaluation procedure in Europe.

Strong basic science is extremely important for the establishment of a flourishing industrial environment, and there are numerous examples of the importance of a strong science back-up for commercial organizations. Many examples can be given where a decline in the science base has caused a downward trend in industrial enterprises. The basic dilemma is that breakthroughs in science can never be planned or predicted but they require a critical mass of scientists in an innovative research environment guided by scientific rather than political or tactical considerations. The time has probably passed when a single individual can make major contributions to science.

I would, therefore, like to take this opportunity to plead for a flexible European basic molecular biology programme that can provide substantial intellectual resources. The very best scientists should be free to develop their creativity without resorting to applied developmental or earmarked projects to secure the necessary funds. Only by an objective international peer review which considers each proposal on its scientific merit without consideration of applied goals can Europe build up the quality and quantity of trained recruits and new ideas necessary to serve industry, medicine and agriculture. The ideal theme-

oriented research unit should preferably consist of eight to twelve research groups each led by independent scientists with different backgrounds preferably focussing on a few topics.

If we want to be competitive with the rest of the world a substantial increase in European support of basic biology must be provided. Many more and longer-term fellowships for post-doctoral fellows, short-term fellowships, pre-doctoral fellowships, resources for moving research groups and ultimately a network of laboratories similar to EMBO around Europe must be introduced. Many of you will undoubtedly say that similar programmes are already available either through the European Community or through national programmes. But the counter argument is clearly that if we want to increase our economic and political coherence the furtherance of European basic science governed by scientific criteria is a prerequisite to provide the solid fundamental base from which to initiate new applied and industrial programmes. Science is by its very nature international and it is depressing to observe that many politicians use the scientific discoveries to claim national pride or esteem. In fact, the EMBO has proposed an extension of its role in fostering European molecular biology. Compared to many European projects in the EC or Eureka in the applied sector the costs are negligible. We, therefore, believe that a reasonable support to basic biology may rapidly unite European scientists in a supranational effort also involving the East European countries. After all, when the base of a skyscraper does not have the proper construction it may fall down."

APPENDIX

Organizing Committee

Honorary Chairman:	**Reimar Lüst** President of the Alexander von Humboldt Stiftung, Bonn
Chairman:	**Jozef Schell** Director at the Max Planck Institute for Plant Breeding Research, Cologne
Vice-Chairmen:	**Mutsuo Michael Yanase** Life Science Institute, Sophia University (former rector), Tokyo
	Wilhelm Stoffel Managing Director at the Institute of Biochemistry, University of Cologne
	Robert Huber Director at the Max Planck Institute of Biochemistry, Martinsried
	George Köhler Managing Director of the Max Planck Institute of Immunolobiology, Freiburg i.B.
	Peter Starlinger Institute of Genetics, University of Cologne
	Ernst-L. Winnacker Director of the Center of Gene Technology, University of Munich
Organizing Secretariat:	**Heinrich Pfeiffer** Managing Member of the Board of Trustees of the Alexander von Humboldt Foundation, Bonn
	Toshio Sasaki Managing Director of the Honda Foundation, Tokyo

List of Participants

Shuhei Aida
University of
Electro-Communication
Tokyo University
Japan

Kazuhiko Atsumi
Institute of Medical Electronics
Tokyo University
Japan

Eduardo R. Caianiello
Dept. of Theorsophical Physics
University of Salerno
Italy

Jean-Pierre Changeux
Institut Pasteur
Laboratoire de Neurobiologie
Moléculaire
Paris
France

Georges Cohen
Laboratory of Eucaryotic Gene
Expression
Pasteur Institute
Paris
France

Dreux de Nettancourt
Commission of the European
Communities
Head of the Biotechnology Division
Bruxelles
Belgium

Rainer Flöhl
Frankfurter Allgemeine Zeitung
Frankfurt
Germany

Toshiyuki Furukawa
President, Osaka National Hospital
Osaka
Japan

Hansgeorg Gareis
Bad Soden-Neuenhain
Germany

Yuri Gleba
Ukrainian Biotechnology Centre for
Agriculture
Kiev
USSR

Benno Hess
Max Planck Institute of Medical
Research
Heidelberg
Germany

Robert Huber
Max Planck Institute of
Biochemistry
Martinsried
Germany

Fotis C. Kafatos
Dept. of Cellular and
Developmental Biology
Harvard University
Cambridge, USA
and
Inst. of Molecular Biology and
Biotechnology
Crete, Greece

Hiromori Kawashima
Vice-President of the Honda
Foundation
Tokyo
Japan

Fumio Kodama
John-F.-Kennedy-School of
Government
Harvard University
Canbridge, MA
USA

Georges Köhler
Managing Director of the
Max Planck Institute of
Immunobiology
Freiburg i.Br.
Germany

José Llompart
Faculty of Law
Sophia University
Tokyo
Japan

Reimar Lüst
President of the Humboldt
Foundation
Bonn
Germany

Kenichi Matsubara
Institute of Molecular and Cellular
Biology
Osaka University
Japan

Fritz Melchers
Director of the Institute of
Immunology
Basel
Switzerland

Katsuhiko Mikoshiba
Institute for Protein Research
Osaka University
Japan

Yoichiro Murakami
Research Center for Advanced
Science and Technology
Tokyo University
Japan

Hirobumi Nakayama
Osaka National Hospital
Japan

H.J.J. Nijkamp
Department of Genetics
Free University of Amsterdam
Netherlands

Frei Otto
Atelier Frei Otto Warmbronn
Leonberg
Germany

Heinrich Pfeiffer
Managing Member of the Board of
Trustees
of the Alexander von Humboldt
Foundation
Bonn
Germany

Lennart Philipson
European Molecular Biology
Laboratory
Heidelberg
Germany

P.A. Reichard
Karolinska Institute
Stockholm
Sweden

Josef Rembser
Federal Ministry of Research and
Technology
Bonn
Germany

Helmut Ringsdorf
Institute of Organic Chemistry
University of Mainz
Germany

Rudolf Rott
Dept. of Veterinary Medicine
Justus Liebig University
Gießen
Germany

Toshio Sasaki
Managing Director of the Honda
Foundation
Tokyo
Japan

Jozef Schell
Max Planck Institute of Plant
Breeding Research
Cologne
Germany

Hans-Gerhard Schwick
Behring Werke AG
Marburg/Lahn
Germany

Hiroshi Shimizu
Faculty of Pharmaceutical Science
Tokyo University
Japan

Takeso Shimoda
President of the Honda Foundation
Tokyo
Japan

Reikichi Shirane
Institute of Management &
Information Sciences
Tama University, Tokyo
Tokyo
Japan

Jean-Claude Simon
Université Pierre et Marie Curie
Institut de Programmation
Paris
France

Peter Starlinger
Institute of Genetics
University of Cologne
Germany

Wilhelm Stoffel
Managing Director of the
Institute of Physiological Chemistry
University of Cologne
Germany

Tadatsugu Taniguchi
Division of Molecular Biology
Institute for Molecular and Cellular
Biology
Osaka University
Japan

Glauco Tocchini-Valentini
Institute of Cellular Biology
Rome
Italy

Erwin Wagner
Research Institute of Molecular Pathology
Vienna
Austria

Ernst-Ludwig Winnacker
Laboratory for Molecular Biology
Center of Gene Technology
University of Munich
Martinsried
Germany

Mutsuo Michael Yanase
Life Science Institute
Sophia University
Tokyo
Japan

Toru Yoshimura
Dean, Graduate School for Policy Science
Saitama University
Japan

Walther Ch. Zimmerli
Faculty of Philosophy
University of Bamberg
Germany

Harald zur Hausen
President of the German Cancer Research Institute
Heidelberg
Germany