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Recombinant DNA Technology – its Prospects for Fundamental Research and for Biotechnological Applications**

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Recombinant DNA technology enables the investigator to insert any given gene into a vector DNA molecule which then can be propagated in an appropriate host cell. This makes it possible to efficiently study gene structure and function. The benefits from applications to fundamental as well as applied research are obvious. Attention is given here to ethical and environmental concerns with regard to such applications: 1) risks of introducing hybrid organisms with undesirable properties into the environment; 2) ethical barriers against attempts to transplant genes into human beings; 3) risks of abuse in the application of the methodology; 4) more general problems related to an undesirable increase in population density as a consequence of attempts to ameliorate human living conditions.

Long filamentous macromolecules of DNA are carriers of genetic message

Since the middle of this century it has been known that the carrier of genetic information is deoxyribonucleic acid (DNA). The alphabet of the genetic message contains four letters, and, as in a written language of man, the sequence of letters determines the information content. There is no need to explain here the chemical nature of the letters of the genetic alphabet. In accordance with common use, we will use the term «base pair» as a synonym of «genetic letter». Taking into account the polarity of the genetic message, double-stranded DNA molecules, the most common form of DNA, are composed of four distinct kinds of base pairs.

The total content of the genetic message of a living cell is called the genome. It is subdivided into a large number of individual chapters called genes. Genes can be considered as fundamental, functional units. When a given gene is expressed (read), a specific product is made. Most frequently, this is a protein which is synthesized following the universally valid rules of the «genetic code». Each gene product forms, in principle, a distinct molecule, although sometimes several gene products must assemble in order to acquire a specific biological function. In contrast, and this may be surprising, the genes are lined up on very large, filamentous DNA molecules. As a matter of fact, all of the genes of the bacterium *Escherichia coli*, the «guinea-pig» of microbial geneticists, are carried on one single, very large DNA molecule. The bacterial genome, or chromo-

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some, is composed of about 4 million base pairs, and the information of several thousand genes is contained in this single molecule. When we equate a base pair with one letter of our alphabet, the information content of the bacterial genome corresponds roughly to the information content of the Bible.

The genetic information of genomes of higher organisms also is contained in very large DNA molecules or chromosomes, although usually more than one. But their information content is considerably larger than that of bacteria. The human cell, e.g., has a haploid genome of about 3000 million base pairs. In its normal, diploid configuration, comprising 46 chromosomes, the human genome is twice as large and corresponds to a library of 1500 volumes of the size of the Bible. It should be mentioned that not all genes have the same size, and that a given gene may be the equivalent of a few lines or up to one or two pages of this very large library.

Specific fragmentation of DNA at the basis of studies on gene structure and function

The principles of molecular genetics were elucidated in studies of DNA molecules which are much smaller than the DNA molecules in chromosomes. The genetic information of many viruses is contained in DNA molecules with a size which varies from less than 10000 base pairs to somewhat more than 100000 base pairs. It has been observed that many bacterial strains contain in addition to their cellular genome small DNA molecules, called plasmids, which are of a size similar to viral DNA molecules. The genetic information of plasmids is often dispensable for normal cellular functions. Intensive studies using viruses and plasmids have allowed scientists to elaborate the technology to investigate both the structure and function of single genes.

In this analysis, restriction enzymes play an important role. Such enzymes can be isolated from bacteria, in which they serve to inactivate foreign DNA molecules which may invade a bacterial cell. This inactivation is brought about by a cleavage of the invading foreign DNA into short fragments. Some restriction enzymes cleave the DNA at very specific base pair sequences, so that the complete cleavage of a DNA molecule by a given enzyme yields a population of DNA fragments of distinct sizes and distinct information content. Fragments of each particular class can then easily be purified by gel electrophoresis. With a population of purified DNA fragments of uniform information content it is possible to read the genetic message from one end. This method of sequence analysis allows one to determine the precise structure of any studied gene. This represents an excellent basis for detailed functional studies of a gene, e.g. for studies on the regulation of gene expression.

Recombinant DNA technology inspired by natural hybridization mechanisms

Since cellular genomes are very large, it has not been possible to purify cellular DNA fragments to uniformity by the method described above. Often, two or more heterologous DNA fragments, which result from specific cleavage by a restriction enzyme, are of a very similar size. To circumvent this difficulty, molecular geneticists were inspired around 1970 by an older observation that viral DNA molecules sometimes pick up one or a few genes from the genome of their host cell. Depending on where in the viral genome such foreign genes are inserted, the hybrid DNA molecules may sometimes maintain all of their viral functions. If such a hybrid virus propagates, its inserted host genes are also propagated, and sometimes their functions are expressed. Depending on the host range of a particular virus, such propagation can sometimes occur in cells different from those in which the chromosomal genes were picked up.

Recombinant DNA technology produces an analogous hybridization in the test tube. In its most commonly applied form, DNA containing the gene to be studied is fragmented, and individual fragments are recombined in vitro into a so-called vector DNA molecule. This could be a viral DNA molecule or a plasmid. Products of this in vitro recombination are then introduced into an appropriate host cell by processes such as transformation or viral infection after packaging of the hybrid DNA molecule into complete viral particles. One of the often difficult, laborious steps in this procedure is the identification of the particular gene of interest for the scientist. But for an increasing number of genes it has been possible to achieve their integration into a vector DNA molecule and eventually to grow them up in host cells such as *Escherichia coli* bacteria, so that sufficient homogeneous material became available for structural and sometimes also for functional studies.

Biological knowledge benefits from recombinant DNA technology

Thanks to recombinant DNA technology major advances were achieved in fundamental research on a number of cellular genes from either bacteria, plants, animals or man. A few striking findings of the last few years follow:

First, it became apparent that many genes of higher organisms have a mosaic structure, i.e. their genetic message is fragmented and carried on the genome in a number of discrete segments. This implies that in the process of gene expression each distinct segment is specifically recognized, so that the complete genetic message can be assembled in a correct manner for the synthesis of the gene product.

Another interesting finding was the structure of genes for immunoglobulins, the antibodies found in the immune system of vertebrates. It was known for some time that the immune system of mice as well as that of man can produce about a million different antibodies, each of a distinct specificity. Molecular genetic analysis has now revealed that this large diversity is brought about by specific recombination of gene segments in the course of differentiation from stem cells to lymphocyte cells producing antibodies. Therefore, at least in this particular instance, the genetic information already present in embryonic cells is not yet found in its functional configuration, which only results from a recombination process during somatic cell proliferation.

In the last few years, cancer research has received a new perspective by the identification of a number of different genes involved in the development of cancer. Further studies with these so-called oncogenes are expected to yield new insights into the mechanisms of harmonious growth of normal cells and into the abnormal growth forms of malignancy. We must be aware, however, that many cellular functions are under the influence of more than one gene. We may expect, therefore, that a complete understanding of all the subtle mechanisms contributing to the normal growth of a cell may not be understood for many more years.

How strictly does genetic information determine life processes?

Since it has in principle become possible to investigate structure and functions of any given gene, it is of interest to raise the question whether all biological processes are fully determined by genetic information. In other words, would it be possible to predict the life of an organism shortly after its conception, if its content of genetic information were fully known? This question is equivalent to the old philosophical question of predetermination. Studies of individual reactions of biological macromolecules suggest that biological processes are often not fully predictable. The following example should illustrate this statement.

Some bacterial restriction enzymes do not cleave foreign DNA molecules at distinct sites, but more or less at random. However, we know that these enzymes still recognize the DNA as foreign by looking at very distinct sequences of base pairs. The enzymes also bind to these particular sequences. In this recognition process, they become activated and in some sense receive the signal to cleave this particular DNA molecule. Cleavage is brought about while the DNA filament is looping through the enzyme still bound at the particular recognition site, and in each individual cleavage reaction the cutting of the DNA filament occurs at a different site. In this particular molecular reaction, therefore, restriction enzymes follow exactly their instruction to behave as an enzyme, the function of which is to inactivate foreign DNA. However, the products of this reaction differ widely from one individual interaction

to another. Overall, the reaction yields a variety of different products, and since the products represent genetic material, which may still be preserved for further use, the nature of the products may be relevant for a future function.

Recombinant DNA methodology applied to biotechnology

Let us now turn our attention to applied research involving recombinant DNA technology. By definition, biotechnology makes use of the synthetic capacities of living cells. In biotechnological applications, cells are either used directly for a particular process, or a specific product is harvested to be used later for some particular purpose. An example of the former strategy is the microbial purification of sewage, while an example of the latter is the isolation of microbial antibiotics. In classical biotechnology the cells serving in a particular process were isolated from nature, where they already carried the particular gene of interest. This has now changed. Recombinant DNA technology adds a new dimension to biotechnology. In principle it has become possible to transfer any given gene into any chosen host cell. In large scale biotechnological procedures some cells can be propagated in culture much more easily than others. Thus, the ability to choose the host cell for the propagation and expression of a particular gene can be of major importance, both biologically and economically. In addition, the efficiency of expression of a particular gene may vary considerably depending on the host cell used. The functional properties and the stability of a gene product may also depend on the cell in which it was synthesized. Finally some host cells can secrete particular gene products efficiently, and this may represent an economical advantage in production and purification.

Recombinant DNA technology brings another, additional advantage to biotechnological applications. This is the possibility to mutate genetic information in a site-specific manner. Indeed, based on the knowledge of gene structure, it is possible to specifically alter a selected region of a gene, either in the part of the gene determining the precise structure of the protein product, or by changing the signals responsible for the control of the expression of the gene.

These advantages make it clear that recombinant DNA technology has opened a tremendous potential for future biotechnology. Applications can be envisioned in practically any field in which bioorganic molecules serve to exert a specific function. These fields include applications in diagnostic, therapeutic, and prophylactic medicine; food production for humans and for domestic animals; pest control; processing and degradation of waste materials; the catalysis of chemical processes; mining and recycling of minerals and other natural resources; energy production from renewable sources. A number of these interesting applications are already very close at hand and will soon influence our daily life.

Evaluation of benefits versus risks

Before discussing some caveats with regard to the application of gene technology, we should clearly state that great benefits reside in the application of this methodology. However, as in any other human activity, potential risks can also be seen in these applications and should be carefully evaluated. Risk assessments are as important in this particular field as in any other technological advance. Four separate categories of possible concerns shall be discussed.

Does recombinant DNA technology interfere with natural biological evolution?

The first category of risks relates to the question of whether a DNA molecule recombined in vitro may provide its host cell with new, undesirable properties, e.g. rendering the cell pathogenic. These possibilities were already widely discussed by scientists and the public at an early stage in the development of recombinant DNA technology. In order to minimize these kinds of risks, appropriate guidelines were introduced and now are followed by scientists working in the field.

In the meantime new information was obtained about natural «horizontal» gene transfer. It confirmed that in microorganisms individual genes sometimes cross species barriers by natural mechanisms of gene transfer. For example this can occur upon infection with viruses carrying genes picked up in a previous host cell, or upon cell-cell contact involving the transfer of a conjugative plasmid. In addition, molecular mechanisms are known which bring about the recombination of genetic information from various sources, even when such information is non-homologous. These recombination mechanisms, together with the means of horizontal gene transfer, have been identified as important elements in natural biological evolution. These studies made it clear that future biological evolution, at least as far as microorganisms are concerned, will again depend on horizontal gene exchange between living organisms not necessarily closely related with each other. Therefore, the entire gene pool, rather than the gene content of a particular species, is relevant for any future biological evolution of this particular species. For this reason, preserving the richness of the gene pool in nature is of primary importance in order to maintain the wide scope of future biological evolution.

In view of existing natural mechanisms of horizontal gene exchange it may appear unlikely that gene transfer brought about in the laboratory by recombinant DNA techniques may produce a new species of living organisms possessing ecologically undesirable properties. However, present scientific knowledge does not allow us to conclude that risks do not exist. Therefore, appropriate precautions must be taken in any investigation. Today, the guidelines followed in work with recombinant DNA are widely harmonized between different countries, thanks to an intensive collaboration between individual scientists on the one hand and various scientific-political organizations on the other. Thus, in most countries deliberate release of living organisms containing recombinant DNA molecules requires permission.

Recombinant DNA techniques applied to human beings

A second type of concern relates to transplantation of genes into human beings. Potentially, the transfer of a gene isolated from a healthy human being could provide the means to cure a particular inherited disease. However, this so-called gene therapy poses serious ethical problems. Accordingly, this kind of therapy can not be undertaken on the basis of purely medical and biological considerations. Instead, any decision in this area should conform with current ethical values.

In principle, it is possible to limit gene therapy to somatic cells of a person suffering from a genetic disease. In this case a successful treatment might cure the person for his lifetime. However, his decendents may still inherit the deficient gene. In contrast, one could transform germ line cells with the hope of curing all of the progeny of a person suffering from a genetic disease. The present attitude of society tends to allow for gene therapy at the somatic level in very well studied, particular cases. Gene therapy of germ line cells still encounters unresolved scientific problems, and it is considered by parts of our society to be a violation of our present ethical values.

In 1982, The Council of Europe recommended to its member countries a number of principles related to genetic engineering. Part of this recommendation states that it should be a Human Right for each human being to inherit a genetic pattern which has not been artificially changed. However, the recommendation foresees the possibility of gene transplantation in very serious cases of well studied inherited diseases. In the meantime the Council of Europe has charged an ad hoc committee of experts to elaborate more specific proposals keeping in mind the principles formulated in 1982. In its recent meetings this committee has concentrated on the application of modern genetic technologies to human beings. Besides gene therapy, these include in vitro fertilization and embryo transfer, experimentation on the human embryo, and possibilities for molecular screening for particular genetic defects. Both the moral and the legal aspects of such biomedical applications are given strong attention in this work. Let us hope that specific recommendations will soon be available to the member countries of the Council of Eu-

rope. Some non-European countries are heavily engaged in similar discussions, and harmonization is attempted to be reached between these different groups of countries. A full, world-wide harmony on moral grounds may be difficult to reach and, in view of the differences between various human cultures, perhaps not desirable. However, it is to be hoped that one can avoid extreme situations susceptible to exert an undesirable influence over the national borders and the continents.

Possible abuse of recombinant DNA technology

The third category of concern represents abuse. If we start to look for possible abuse in human gene therapy, both cosmetic applications and eugenically motivated modifications come to mind. However, any fear that genetic manipulation of human behaviour will occur still appears unjustified today. Indeed, no single gene is known to influence human behaviour in a specific way, and if many genes do so, the mechanism is likely to be complex. With the available technology, only well studied genes can be appropriately identified and consequently transferred into another genome. Nevertheless, strict ethical rules already are required in order to prevent this kind of abuse of recombinant DNA technology in the future.

Another potential abuse could occur in applications to biological warfare, although there is probably no great advantage to the use of recombinant DNA compared to classical approaches for the manufacture of the pathogens in biological warfare. Certainly, we have no means to construct a completely new pathogen. But one may envisage that variants of a given pathogen with new antigenic or host range properties could be constructed in the laboratory to be used as biological weapons. Existing treaties between different nations prohibit biological warfare. The role of biotechnology should be given special attention in these treaties and, as far as needed, new treaties should be negociated.

Long range consequences of technological applications are hard to predict

The forth matter of concern relates to our difficulty to predict long range consequences of technological applications, particularly with regard to their possible influence on ecological equilibria. What will be discussed here does not only relate to recombinant DNA technology, but is of a more general nature and relates to any kind of technological advance. Of course, the possibility of abuse for the purpose of warfare discussed above is also of general relevance. It seems to me that voluntary abuse of technological advance represents an exception rather than the rule in the application of scientific knowledge. Most often applications are based on a high ethical motivation, and often the goal of such applications is to improve the quality of human life. This is obvious for any project designed to ameliorate medical care or to improve nutritional conditions. The introduction of a new medication, the improvement of housing conditions or the improvement of an agricultural crop plant are generally considered as steps in the advance of our civilization. In the last few centuries, and in particular in most recent times, these and other improvements of the human condition have led to a steady increase not only of life expectation, but also of the human population. Improved sanitary conditions and medical care may be major causes for this development. With the improvement of the quality of life, each single member of the human population requires more living space, uses more natural resources and produces more waste than previously. Too often this destroys the environment. This unfortunate development is aggravated by the increase in the total human population and may represent a very serious obstacle to ever benefiting from such ethically motivated attempts to raise the quality of life of all human beings on this planet.

The space offered to living organisms on our planet is limited

The following simple calculations could help the reader to understand the problems raised here. Let us first estimate the approximate number of living cells in the biosphere of the planet Earth. The surface of our planet is about 5×10^{14} m^2. If we now assume all cells living on the surface of our planet, including those in the air, in the oceans, and in the soil to form a compact surface layer, we can calculate the volume of all living cells. It is somewhat difficult to know how thick this compact, theoretical layer of cells should be assumed to be. However, as we will see, the possible variations are almost neglectable. Let us then make the calculation assuming the layer of densely packed living cells to be 20 cm thick. The volume of the biosphere will then be 10^{14} m^3. Not all cells have the same cell volume. One bacterium is about 10^{-18} m^3, average plant or animal cells may be in the order of 10^{-15} m^3. Taking again an average, one can estimate the approximate number of living cells in the biosphere as 10^{30}. For those who like to assume the thickness of the densely packed biosphere to be 2 m, the total cell number would then be 10^{31}.

10^{30} is a large number. However, relative to the actual growth potential of living cells it is amazingly small. Living cells generally propagate exponentially. If one inoculates an appropriate growth medium with one single bacterial cell, after about half an hour the cell will divide into two. These two daughter cells will grow again, and after another 30 minutes each of them will again divide into two cells. This propagation continues as long as enough nutrition is available. If we study the increase in the number of bacteria in a very large vessel, one could theoretically obtain 10^{30} cells in only two days of exponential growth, beginning with a single cell. Cells of higher organisms generally also grow exponentially, although their generation times are longer than those of bacteria. If we assume these cells to divide every 15 hours in an appropriate growth environment, 10^{30} cells would theoretically be obtained in only two months of growth starting from an inoculum with one single cell.

The 10^{30} living cells in the biosphere do not belong to one single living species. It has been estimated that on our planet there are a few million different living species including microorganisms, plants, animals, and man. Obviously, growth conditions would not allow one single species of bacteria to propagate until it would have occupied the whole volume of our present biosphere. However, there is no doubt that maintenance of a complex ecological equilibrium in which many different living organisms live together in a complex situation of interdependence remains far from being explained scientifically. But the above, simple calculation can teach us that it would be wrong to consider the intrinsic cellular growth potential as limiting for expansion of life. Rather any living organism has a tremendous growth potential. However, this is used only during very brief phases in the life cycle. The normal condition of a living cell should rather be considered as a phase of active rest, in which most genes are silent, while only a few particular genes are expressed and furnish those functions required for the specific tasks to be exerted by the given cell.

The special condition of man as a member of the biosphere

Man is and will always remain part of the world-wide ecological community. He is and can only be a very minor part of this community, and any attempt to escape from this condition must end with a failure. The number of cells in a human being has been estimated to be a few times 10^{13}. If we multiply this number with the number of human beings on Earth, 4.8×10^9, one obtains approximatively 10^{23} living human cells to be present today in the biosphere. This is large in comparison with the maximal capacity of 10^{30} cells of the biosphere.

Man was, for a long time in his history, a stable part of the ecological equilibrium. Only in relatively recent times has man succeeded, thanks to his high intellectual capacities, to provide himself with some advantages, which other living organisms may not have. In this way man steadily improved his living conditions. This development has now reached a stage in which man cannot any longer be considered as a stable part of the world-wide ecological equilibrium. Large surfaces of the planet have been intentionally altered by man into areas tolerating only a very limited number of living organisms, e.g. in agricultural monocultures. In addition, human activities are increasingly spoiling the envi-

ronment, air, water, and soil. This again represents serious limitations to the natural proliferation of communities of wide varieties of living organisms.

In view of these considerations it appears urgent to find an answer to the question of the maximal world-wide population density which will permit us to attain living conditions of man which we consider desirable. In the past man has used his intellect to sort himself out from the community with other living organisms. He did this in order to offer himself better living conditions than were given to him by nature. Man will now have to use again his intellectual capacities and to motivate his will in order to be able to maintain his special position which we characterize as civilization. He can do so only if he understands that he will continue to depend stringently in the future on a very wide variety of other living organisms on this planet. Destruction of the rich variety in nature may represent a very serious obstacle not only to improve but also to maintain present living conditions of man. Science and technology can and shall help to master the problems which we face. This will require a steady sense of responsibility, and any applications of scientific advance should continue to be scrutinized repeatedly and very carefully for their eventual consequences.

I added these general remarks to my contribution on the prospects of recombinant DNA technology[1,2], since I know that many hopes and expectations are given to the potential benefits of its application. This is fully justified. However, a better prediction of possible long-range consequences of this and other technological improvements could avoid later deceptions, which could be caused by unexpected effects from the application of these techniques. This seems to me to be of particular relevance with regard to the hopes given to biotechnology in developing countries, where population growth continues to be excessive. It would be wrong to believe that biotechnology alone (including improvements in medical care and in agricultural practices) might solve the problems with which these countries are faced. Any improvement in their living conditions brought about by the application of modern technology can only reach its goal if population density remains limited, so that man can continue to form part of a rich ecological equilibrium in which a wide gene pool remains preserved. This is of major importance for any future, natural biological evolution.

Mankind is engaged to improve the human condition to reach a life with less suffering. New possibilities of great promise are at our disposition. We should be wise enough, however, to realize that our ambitious goal can only be reached if we do not ignore the real biological basis of life in our prospective planning of future technological and cultural developments.

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