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GENETICS AND HEALTH
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I am grateful to the conference organizers from UNESCO and ICSU for the opportunity to present this talk and to Dr. Nicole Biros for her role as organizer of this session. Dr. Jorge Allende, our chairman, has been a colleague since our student days. He is a distinguished biochemist and citizen of Chile and it is an honor to share this occasion with him.

Now, as we look to a new century and millennium, biology is poised to effect profound changes in human lives. ~~And, because we are now the dominant species on our planet~~, this science gives us, as well, significant ability to influence the health of all other species and the integrity of the physical planet. ~~At the same time, our understanding of biology confers on us the responsibility to use our knowledge and in constructive and equitable ways.~~

This talk will review very briefly how we arrived at the current level of knowledge in biology. It will then describe some of the opportunities that this science provides. Finally I will ~~also~~ offer some brief thoughts on how we can assure that our opportunities are used for the benefit of future generations. I hope that these remarks can provide a context for the more specific talks that will follow during this session.

It was only a little more than 130 years ago, not so far from Budapest ~~in the~~ ~~neighboring~~ region of Moravia, that Gregor Mendel discovered the fundamental rules of genetics. Neither Mendel, nor those who revived his almost forgotten work at the beginning of this century, ~~could~~ imagined the developments that followed. One reason for this was that formal genetic analysis could not alone do more than describe outcomes. Then, Early in the twentieth century genetics was joined to cytology resulting in the chromosome theory of heredity. ~~Then~~, In 1941, genetics was joined to biochemistry resulting in the discovery that what a gene does is specify a protein. Not too many years later bacteria microbiology became a tool of genetics and revealed that genes of made of DNA. Soon after, the art of model building yielded

the DNA double-helix which has become, for some, the symbol of the 20th century. Less than a decade later, the genetic code was deciphered.

Through all these years, biologists of all kinds remained ~~primarily~~ observers and describers, motivated primarily by curiosity. In their dreams, though, they imagined that their science might eventually be put to use curing diseases and dealing with other human problems. Then, early in the 1970's, biologists became conscious manipulators of biological systems through the techniques that were collected under the terms recombinant DNA or DNA cloning. It was then apparent to many scientists and nonscientists too, that a revolution was underway. It was not very difficult to foresee, almost immediately, how the new techniques could advance biology and the understanding and treatment of a significant number of diseases. These opportunities became immediate when techniques were developed for rapid sequencing of DNA and thus the determination of the amino acid sequence of proteins. The alliance of genetics with modern cell biology and biochemistry began to illuminate the relation between genes, proteins, and function. There followed a level of research activity

and discovery that amounts to an explosion of knowledge about fundamental biological processes.

The various Genome Projects are the latest developments in the story. They aim to determine the entire DNA sequence of the genomes of humans, model experimental ~~organisms, both~~ plants and animals, and microorganisms. The Genome Projects are already contributing to strategies for treatment of human disease. They will continue to contribute, often in unanticipated ways, to the health of people worldwide. The vast genomic data bases by themselves would be difficult if not impossible to use. But concomitant with their construction, the computer revolution is generating sophisticated ways to ~~find our ways~~ maneuver through the data bases.

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I said earlier that the new biology allows us to manipulate biological systems consciously. What is new is the conscious aspect. ~~Unconsciously, even~~ unknowingly, our species has manipulated biological systems since our earliest days on the planet. Every time a fire was made, a hut or a house built, a field used for planting rather than gathering, or an animal or plant bred

for some useful trait, we were unwittingly altering an environment and affecting unknown ecologies. In this century of course the scale changed enormously, concomitant with technological developments and the growth of human populations.

Conscious future developments should be informed by the many profound generalizations that have emerged from this century of ~~biological~~ genetic research including that organisms are chemical, or if you prefer, molecular systems; that genetic information is stored and read out in virtually the same way by all living things; that organisms as distantly related as plants, fungi, invertebrates, and mammals have many almost identical genes that encode proteins with similar functions. This is why work with model experimental organisms such as yeast, worms, flies, fish, and mice, is essential to understanding human biology. Plants too share the common genetic mechanisms and research on plants is central to advancing the human condition.

Genetics has become the reference point for thinking about all biology and a compass for future research. It is also a partner to

other sciences such as chemistry and ecology. In our session today, we are stressing the collaboration between genetics and health.

As we consider how genetics can contribute to human health, it is important to have a broad view of that word, health. Certainly it refers to the absence of disease and injury in individuals. But to be healthy, people should also be well nourished, enjoy a good physical condition, have access to clean water, and live in a clean and comfortable environment. The definition of these conditions will differ from one community to another and with the age of the individual. To a remarkable extent, modern genetics can help achieve these goals for all.

Inherited diseases reflect mutations, that is nonfunctional or poorly functional alleles of important genes that are passed from one generation to another in germ cells and thus occur in all somatic cells of the resulting organism. Among the well known and relatively frequent examples of inherited diseases caused by defects in a single gene are muscular dystrophy, sickle disease, Tay-Sachs

disease, hemophilia, and cystic fibrosis. About 3-4000 such diseases are estimated to occur.

Other genetic diseases are not inherited but involve changes in somatic cell DNA during the life of the individual. Most of the many different diseases we call cancer fall in this group. ~~They~~ Cancers are associated with involve a series of mutations in different genes in a cell, leading to the acceleration of cell division and tumor formation.

Some cancers develop from a combination of an inherited mutation with additional mutations occuring in somatic cells; these situations can arise when an individual is born with a debilitating mutation in one of the two normal copies of a gene important for applying a brake on cell division....what is called a tumor suppressor gene. If, during the life of the individual, the remaining functional copy of the gene is damaged in a somatic cell, uncontrolled growth and cancer are initiated. Humans can inherit susceptibility to diseases other than cancer. Among these are cardiovascular diseases ~~resulting from~~ associated with excessive cholesterol levels. Susceptibility to Alzheimer's disease ~~to~~ is likely to be influenced by a group of particular alleles of certain genes. In many ~~such~~ other instances, too multiple genes and ~~probably~~ likely to be multiple alleles of those genes, are involved in disease susceptibility

Diagnosis of Genetic Diseases. The techniques and knowledge of molecular genetics make possible ~~informative and~~ of inherited and acquired genetic diseases, reliable diagnoses. Human alleles associated with disease and in some cases even with the likely severity of a disease can be detected. At present, these techniques are clinically feasible when the disease involves a mutation in a single gene. New methods promise to make such diagnostic procedures routine: in particular, there are automated techniques that use a variety of DNA 'chips' to screen thousands of sequences simultaneously, and are linked through computers to genomic data bases and the tools needed to use the data bases. Chips ~~They~~ are presently costly, and not available world-wide. However, we can anticipate that that will change. And with more research, they will be applicable to diseases and susceptibilities associated with multiple genomic loci. Presently, the rigorous study of inherited diseases is ~~now~~ concentrated in countries with well developed research enterprises in genetics. We need for such research to be developed in other parts of the world so that a wider range of inherited diseases will be defined and diagnosed.

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Treatment of Genetic Diseases. Molecular genetics has also provided new paths for the design and development of therapeutic agents. One such path, called gene therapy, would remove or inactivate or replace faulty genes. This has proved difficult and has not yet succeeded. What has succeeded is the use of cloned genes to synthesize therapeutically active proteins such as insulin, growth hormone, and erythropoeitin. Another approach that appears to be fruitful is to use knowledge about the structure of the proteins encoded by specific genes to design drugs.

This approach is illustrated by a recent paper in Science Magazine. A metalloproteinase called aggrecánase degrades aggrecan, a key component of cartilage. The enzyme appears to be important in the breakdown of cartilage in arthritis, a disease that is increasingly relevant as the world's population lives longer. The enzyme was purified and a partial amino acid sequence determined. From this, partial gene sequences were deduced and used to screen genomic data bases. A mouse protein of unknown function matched the DNA sequence and the mouse gene sequence was used to clone the corresponding human gene. To test the relation between this gene and arthritis, the mouse aggrecanase (-1) gene will be removed

(knocked out) from the animals and the effect on arthritis studied. If the relation holds true, the task will be to design drugs that specifically inhibit the enzyme, thereby perhaps ameliorating the loss of cartilege associated with arthritis (1).

This work was carried out in the research laboratories of the DuPont Corporation. Research of this kind, on probably hundreds of genes, occurs in laboratories of universities and small and large for-profit companies. The costs of the research and development are high. Even when the work is ~~carried out~~ initiated in universities, development and testing to produce an effective and safe drug is likely to involve corporate activity, sometimes in collaboration with universities. Organizations that make such investments expect to recover costs and return a profit. Thus the price of the drug will be high. The international community needs to explore new ways to assure drug availability in poor communities and countries without discouraging the development work. Research on this question can be as helpful as the basic scientific work itself.

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One of the most interesting prospects for genetic medicine is the possibility of individualizing treatments. Cancers, for example, differ from one another in the genes associated with tumor

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formation. We may be able to tailor drug regimes to the array of mutations in a particular cancer. Also, for diseases other than cancer, a screen of a set of gene alleles in patients may predict which of several drugs is likely to work best and cause fewest side effects in that individual. These are only a few examples of what the future may hold.

When we shift from considering the health of individuals to that of whole populations, research must focus on microorganisms. Infectious diseases have their roots in the genes of pathogenic bacteria, protists, fungi, and viruses. These genes are a leading cause of morbidity and mortality in the world. Also, the defense mechanisms of infected organisms depend on their own genes, be they humans or agriculturally important animals or plants.

By the 1950's, medical scientists believed that they could control many human and animal bacterial diseases with a combination of improved sanitation, vaccines, and antibiotics. That proved an optimistic illusion for three primary reasons. First, on the time scale of human life, microbes evolve rapidly and the changing environments brought about by human activities fosters

their evolution. We have, for example, seen many excellent antibiotics become useless as organisms evolve to resist their action. Tuberculosis, is thus once again a serious problem in the United States. Second, many microbes proved smarter than the scientists, and [illegible] their ability to alter their surface markers can render immune responses and vaccines less than fully successful. HIV (human immunodeficiency virus) and influenzae virus are two examples that remain serious challenges. Third, new or previously unrecognized pathogens have emerged. HIV is the most devastating of these. The HIV epidemic has also shown us that we do not understand the human immune system well enough to respond to new epidemics with effective vaccines. It has also shown dramatically that the spread of infectious diseases is a global problem. As we gather here in Budapest from all over the world, we don't arrive alone; we each carry microorganisms that are now mingling in every meeting room and restaurant. Research is urgently needed for the world-wide control and treatment of infectious diseases.

Organized, shared, world-wide public surveillance is the key to the early detection of infectious disease epidemics. This is one

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why scientists are needed
reason ~~to foster~~ scientific enterprises in all countries. Genetics gives us the ability to improve and enhance traditional surveillance techniques through screening for DNA sequences unique to particular organisms or their variants. DNA sequence identification is more reliable and can be faster than traditional methods. Internet networks for such data already exist (2).

Another advantage of DNA screening over traditional methods is the ability to recognize unsuspected, unknown, and newly emerging pathogens. ~~Genetics and genomics are also the best tools we have to identify organisms that resist the usual isolation methods~~. The genomes of more than 40 bacteria have been or are being sequenced. By comparing the gene sequences of pathogenic and nonpathogenic variants of microorganisms including ~~organisms~~ those that cannot be cultured, potential pathogenicity and virulence genes can be identified. One example is *Helicobacter pyloris,* which infects as many as 50% of us world-wide. It was recognized only since 1982 as an important factor in ulcers, gastritis, and gastric cancer (3). Already, thanks to modern genetics, various proteins that contribute to *Helicobacter*'s pathogenicity and virulence have been identified. It acquired, by horizontal gene transfer, a widespread DNA

pathogenicity cassette that encodes machinery ~~that facilitates~~ for the transfer of bacterial proteins into host cells.

The case of *Hemophilus influenzae* is also instructive. The lipopolysaccharides on its membrane play an important role in pathogenesis. Its 1.8 million base pair genome is completely sequenced. Screening of the genome and the proteins predicted to be encoded by it and comparison with proteins needed for lipopolysaccharide synthesis in other organisms allowed identification of 25 candidates for involvement in the biosynthetic pathways. ~~lipopolysaccharide synthesis~~. Genetic and biochemical analysis selected a subset of these as pertinent and began to show what elements of lipopolysaccharide structure influence virulence (4).

The convenience and precision of DNA screening is also useful for making sure that potential sources of infection are promptly identified. Blood and blood products can be the source of disease as well as part of a cure. Safer blood supplies are assured by routine screening for infectious agents and DNA screening is becoming an important technique (5).

Food increasingly travels long distances before it reaches our plates, sometimes halfway around the planet. Like human travelers, it comes with company. DNA testing can provide rapid, accurate and very sensitive screens for contamination. *Campylobacter jejuni,* for example, is a food-borne pathogen associated with severe gastrointestinal problems. It is difficult to culture but now that its genome sequence is known, it is possible to do research to understand and control its pathogenicity. It is noteworthy that it took less than 16 weeks to sequence the entire 1.64 million base pair genome (6).

The availability of potable water has been identified as a major and growing problem as the world's population outruns the planet's supply of fresh water. Many possible infectious contaminants can be identified by DNA screening using a single chip that includes sequences from all the usual suspects.

Unhappily, we are all now concerned about bioterrorism. This fear is to some extent exacerbated by the recent advances in biology and those same advances provide the best tool we have, DNA screening, for detecting such agents.

Improved nutrition Good nutrition and thus the provision of adequate and safe food supplies worldwide is an underlying prerequisite for good health. Conventional plant and animal breeding has, over many millennia, brought our species improved yields of essential foods. This kind of genetic manipulation has been especially fruitful for developing plants and animals that thrive in particular environments. The introduction of cell culture methods into plant breeding yielded greater efficiency and increased opportunities for desirable qualities. But some experts believe that these methods have achieved just about as much as they can. The new genetic engineering techniques offer great potential. To quote the agricultural ecologist Gordon Conway (7). who is widely credited with developing the notion of sustainable agriculture "*Genetic engineering has a special value for agricultural production in developing countries. It has the potential* (for)*...creating new plant varieties and animal breeds that not only deliver higher yields but contain the internal solutions to biotic and abiotic challenges, reducing the need for chemical inputs such as fungicides and pesticides, and increasing tolerance to drought, salinity, chemical toxicity, and other adverse circumstances. ..... It*

can be aimed not only at increasing productivity but at achieving higher levels of stability and sustainability."

The genetic manipulation of agricultural species is, at present, a matter of international debate fed by different evaluations of the scientific data and different cultural and economic conditions. The dispute about insect-resistant plants containing genes from *Bacillus thuringensis* , what are called Bt plants, is defining some of the issues. The underlying concern here is to protect the 30-40% of potential food estimated to be lost to pests of various kinds, worldwide (8). It is likely that different countries will come to different conclusions about where to strike an acceptable balance between the relative advantages and disadvantages of current agricultural practices including their environmental effects, the potential environmental effects of the new, genetically engineered varieties, and the need for producing more food. Conditions, cultures, and needs vary enormously from one nation to another. Every nation requires its own expert scientists if it is to make intelligent and productive choices.

The recent letter to Nature Magazine on the increased mortality of monarch butterfly larvae on milkweed plants dusted with pollen from Bt corn is a case in point (9). Monarchs should of course be protected. Assuming the experiment is reproducible, policy making will need to take into account the relative effects on Monarch mortality of chemical insecticide spraying compared to transgenic pollen as well as the crop yield and cost per acre of the as well as local conditions.
two methods. The authors of the paper recognize the need for such risk assessments. Media coverage, at least in the US, did not.

The most scientific approach to the whole issue at this time is to recognize that we are talking about a new technology and have a great deal to learn. There is enormous potential in genetically modified plants. They can help increase crop yields under conditions of poor soil and low water availability and water resources are fast becoming a limiting factor in some parts of the world. They can be used to improve the nutritional value (vitamin content) of common crops. Research is now directed at moving the relevant genes from naturally pest-resistant plants into crop plants. Vaccines against various diarrhea-producing organisms are being incorporated into edible, easy to ship plants like potatoes and

bananas, a development that could ameliorate distribution problems in many countries (10).

There are ways to formulate constructive governmental regulatory frameworks with which to deal effectively and scientifically with the important issues raised in each country. One is to focus on the risks that might be associated with the plant or plant product rather than whether the process used to develop the plant involved gene transfer by breeding or recombinant DNA. Another is to make the regulatory process open and transparent so that the public can judge for itself whether or not its interests are being served. Scientists need to be skeptical and outspoken about national and international policies that are based on misconceptions and bad science. And ideology is not a scientific response. Scientists should take the initiative in applying modern genetics to the challenge of providing adequate food supplies in all regions. We cannot simply turn our backs on useful genetic technology when faced with the moral imperative of feeding all people.

A second is to be sure that data used in policy making are sound.

The last element on my list of how modern genetics can contribute to health is a clean environment. Our species cannot

continue to thrive if we destroy the Earth environment on which we depend in complex and poorly understood ways. Some people think that we can solve that problem by colonizing Mars. Maybe. But not in the foreseeable future. Some people think we can solve the problem through conservation. Maybe. But not if population continues to increase and more and more people strive for an improved standard of living. There are enormous needs for new knowledge about known and unknown species and the nature of the interactions between species if biodiversity is to be preserved. New research is also required if we are to learn how to ameliorate the environmental degradations humans have already caused. And because biodiversity and environmental problems vary from one place to another, enhanced research efforts all over the world are essential. Genetics can help in many ways. DNA sequences can be used in constructing a census of existing organisms. Transgenic plants have the potential to limit dependence on the chemical pesticides and herbicides that pollute water and soil. They can reduce atmospheric pollution by becoming factories to produce commodities now made from fossil fuels. Transgenic plants may even one day provide useful fuels and lubricating oils for

automobiles. Green plants are of course a way to use, directly, the energy of the sun. By moving genes around, we can expect to develop plants with improved properties for phytoremediation....the cleansing of toxic wastes from soil. We may not need to clear so much forest land if transgenics improve agricultural productivity particularly on substandard farm land. Evolution has lead to intimate sometimes even essential relationships between plants, microorganisms, and insects. The more we learn about these, including those involving plant pathogens, the more intelligently we can decide about acceptable manipulation of environments and how to clean up after ourselves when we have mistreated the planet.

There are many challenges ahead of us if all the world's people are to experience improved health as a result of a century of genetic research. Fundamental to meeting those challenges is a need for all countries to strive to participate and to investigate those potentials that can best promote the general welfare of their own people. Such participation requires in all countries a vigorous, respected, and supported scientific research effort coupled to the education of new generations of scientists. It is through the research

experience that science is best taught. ~~And~~ new generations of educated scientists will include ~~can provide~~ ecologists, agricultural experts, physicians, public health experts, physicians, and others to work cooperatively with hospitals, farms, factories, and the policy making circles of governments. At the same time, the research effort can continue to produce the new knowledge that each nation needs to apply genetics to its own problems. Thus, for one investment, a nation can obtain new knowledge and scientifically trained people. Such an investment may seem a low priority for nations that lack essential health and social services and adequate food. But a scientific infrastructure and a community of scientists is essential to the future wellbeing of all countries. In those countries with large research communities, we can see that scientists help meet national challenges in disease, nutrition, and the environment. They are welcomed into the policy arena for their knowledge and their inclination to be problem solvers and innovative thinkers. They have taken important, even initiating roles in the consideration of the safety and ethical questions related to the new genetics.

The breathtaking pace of genetic research in the United States and Europe presents its own frustrations to those who have

followed its development but not as yet fully participated. In principle, the internet can assure that everyone all over the world, including students, has access to the latest research and the essential genetic data, wherever it is produced. At present, internet access is not readily available to all. Provision of internet access must be a goal of national and international science policy ~~in all countries~~.

Our species' view of the planet is a very brief window. We can only glimpse the many genetic changes that occurred in the almost 4 billion year span of life on Earth. We cannot foresee the future changes: neither those that will be brought about by natural causes nor those that will be brought about by human activity. We cannot know which of today's technologies may extend our species' lifetime in the face of an unexpected challenge. Scientists would do well to help all people value, with care and with caution, what a century of genetic research has taught.

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Beyond