The Genetic Revolution: Pregnant with New features

An Edited Transcript of an Informal Lunch Speech, delivered by

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Three days ago, on February 28, 2003, was the 50th Anniversary of one of the most important events in the history of science. On February 28, 1953 a very young American Biologist by the name of Jim Watson and a young British physicist by the name of Francis Crick discovered the structure of the DNA molecule. The importance of their achievement was not that they had solved a difficult scientific problem, although they did. In the same year, other scientists, even in the same laboratory and in the same building, solved problems, which were no less difficult. The great achievement was that they asked the right question. They understood that the secret of life is hidden in the structure of that particular molecule. That is why they wanted to understand how it worked and that is why their achievement would forever be a milestone in the history of science.

That was the beginning of the Genetic Revolution. We are now in the midst of it. It is evolving in all sorts of unexpected directions, which are changing our lives and will continue to do so, more and more, as time progresses. When our Chairman, discussed with me topics, which might provide mild scientific interest and entertainment, and would be suitable for an after lunch speech, I proposed to discuss some of the far-reaching implications of the Genetic Revolution for our life. In the spirit of full disclosure, I must remind you at the outset that I am "only" a Physicist. I am not a Biologist and I am not a Medical Doctor. This may actually be good news, since I will not be able to bore you with technical details and with long Latin words. I simply do not understand them myself.

Having agreed on the general topic, our Chairman then sent me an e-mail, asking: "Can you suggest a sexy title for your talk?" Faced with the challenge of finding a title, which combines Genetics and Sex, I came up with the obvious "Pregnant". Hence the title of this talk: "Pregnant with new features". It is actually a fact that the Genetic Revolution is

indeed pregnant with an enormous number of new features: technological, scientific, medical, ethical, moral, legal, economic, and many others.

Because of our time limitation, there are several crucial and fascinating topics, which I will not discuss at all. First among these is cloning. Almost all scientists and, definitely, all serious scientists, are against cloning people. But there is an important and non-trivial dispute concerning the application of cloning technology, not for the purpose of cloning people, but in order to produce elements of the human body, which might save lives ("spare parts"). This is a fascinating subject, but I will not discuss it today. Another topic of current public debate, which I will not discuss, relates to genetically modified organisms, used for agricultural purposes. This is a matter of fierce debate and of a substantial amount of disinformation in several countries.

The Genetic Revolution has to do with the understanding of the connection between genes and properties of organisms. Its simplest examples are cases in which a given disease, sometimes a deadly disease, is completely determined by one gene. If you have the "bad version" of the gene, you are sick. If you have the "good version" you are not sick. More often, if you inherit the bad gene both from your father and from your mother, then you have the disease. If you inherit it from one of them and not from the other, you are a carrier. You are healthy, but you may introduce the disease to your children, if your spouse is also a carrier. This is the "simple case" from the conceptual point of view. This type of situation has been understood for a long time. In certain cases, it did not require any deep understanding of the structure of DNA and did not have to wait for the gigantic effort of the Human Genome project. A disease like hemophilia has been understood for generations, in these terms, and there are many other genetic diseases of that category.

What is happening now – and that is a significant development- is that we are beginning to understand much more complex connections between certain genes and many other features. In most cases, it is statistical information rather than "yes or no". Certain features of an organism, be it a human being, an animal or a plant, are too complicated to be expressed in terms of one gene. So you face a new situation. If you have a certain gene, you may have a higher probability of getting a certain kind of cancer or perhaps a lower probability of getting a certain kind of heart disease. Even more complicated are correlations, either correlations among genes or correlations among a gene and another issue. Let me invent a few purely fictitious hypothetical examples. There may be a certain gene, such that, although smoking is extremely harmful, to the carrier of that particular gene, it may not be so harmful. Perhaps you may have a certain gene, which will make you react much better than average to a specific medication, allowing you to choose among several possible treatments. You may have a certain gene or several different genes, which may act in a probabilistic way on your medical situation. And we are only beginning to scratch the surface of other features of human beings. You may have a gene, which gives you a better memory, great musical talent, no arrogance, a combination of the above or even perhaps a gene which makes you very talented musically, but only if you are arrogant. Now obviously I am making up all of these examples, but the concept is correct.

All of this leads to a situation, which should attract the attention of every one of us. It will happen during the lives of most people in this room. Every one of us will probably have a card, like a credit card, on which our entire genetic information will be registered. This is, of course, significant bad news and significant good news, at the same time. The bad news is that, suddenly, you will be informed that you will have a high probability of getting a certain disease. The good news is that perhaps this will lead your doctor or your health insurance to have more frequent screening against this disease, increasing the probability of early diagnosis and successful treatment. If you have a higher probability of colon cancer, they might recommend that you undergo a colonoscopy every six months. This is not affordable for everybody, but may be a good investment for those who have a higher genetic probability for the disease. This is the rudimentary level of this particular possible genetic feature. But then, of course, it immediately leads to other things. Would anybody insure you, if you have a gene, which gives you a high probability of a certain deadly disease? Well, probably not if they know it. Should all of this remain secret? It can hardly remain secret, if you want to use it beneficially by allowing more frequent screening and preventive medicine to be applied to you, because you are more likely to get a certain disease. Would anyone offer you a job if you have a high probability of the certain disease? Certain countries are already passing laws, which require absolute confidentiality of all of this information. But in my humble opinion, no matter what laws you pass, this will not work, because of the probabilistic nature. If it would be a yes or no issue, it might be possible in many cases to protect the confidentiality of whether or not you have this particular gene. But when we are talking about such complex situations, so many different genes, so much probabilistic information, possible correlations, etc, it is almost impossible to protect the confidentiality.

Is all of this really new? When you think about it for a moment, you suddenly realize that there is nothing new in it. What is it that all of these genes are telling you? They are telling you that you have a higher or lower probability to have a certain disease. We are already facing this every day. You go to a doctor and he asks you: “Did your father have a heart-disease? Do you have high cholesterol? Do you have high blood pressure? Do you smoke?” He asks you five or six questions and immediately determines if you are or are not in a high-risk group. We have been living with this kind of information for ages. Nobody is keeping this kind of information too confidential. It is confidential in the sense of normal doctor/patient relation but the files are open to many different people and you have to fill in such forms when you apply for life insurance or health insurance. Conceptually, the difference between this contemporary daily experience and the full “genetic identity card” is not very fundamental, except that the entire panorama of problems, diseases, probabilities, and knowledge will be much more abundant with the new genetic information.

There is a new field of science called pharmaco-genetics. That is the study of the reaction of different people, depending on their different genes, to different pharmaceutical products. I already alluded to it a few minutes ago, when I mentioned that you might have a gene, which will make you react better to a specific medication. But, again, the possibilities are infinite and drug companies are very much interested in the subject. For

instance, there are certain very dangerous diseases, which have today only one or two treatments and those treatments are effective only for some patients. It is very important to find out who will benefit and who will not benefit from this treatment, especially if it is a very expensive one and if it has serious side effects. There is an enormous variety of such situations. Incidentally, just to confuse you, there is also now a different field of research called “pharmaco-genomics”, allowing us to design new types of drugs and new types of molecules, which may help treat diseases, using information derived from the genome project.

There is an important social issue here, which is caused by a lack of understanding of the concept of risk assessment. The subject of risk assessment, in general, is a neglected field, about which most of the population is shockingly ignorant. A high-quality logical risk assessment would decrease the circulation of newspapers and the rating of TV stations. Coal power stations kill many more people than nuclear stations, car accidents kill more people then terrorists, heavy smokers demonstrate against genetically modified organisms, dirty water kill more people than AIDS, and I could go on for hours, with such examples. But in the age of the Genetic Revolution, this subject becomes even more crucial. For instance, suppose you find that a certain ethnic group in the population has a chance of one in a million to have a certain bad gene and the general population has a chance of one in ten million. There are two ways to refer to this, both technically correct: the first is to say: “both probabilities are so small, that you might as well forget about the entire issue”; the second is to say: “this ethnic group is ten times more likely to have the bad gene than the rest of the population”. The first attitude is what we should follow. The second attitude, which is more likely to be advertised, immediately leads to ethnic discrimination, to rejection, to a variety of different negative situations and to stigmatization. This has already happened. There are certain groups that were found to be more likely to have a certain gene that is related to a specific type of cancer and, for some time, people from that group started to have difficulties in finding jobs. Only later it turned out that there is some other complicated genetic feature – which I will not get into – that actually made it less likely for that group to have the relevant cancer, even though its members had a higher probability to have the particular cancer-related gene.

I am not even touching upon the entire minefield of possible connections between genes and intelligence. Here, again, there seem to be good news and bad news. The good news is that so many genes must be involved, in so many ways, in various intellectual features, that it is not possible to make general claims about certain ethnic groups. The bad news is that it is almost certain that specific intellectual talents do relate to specific genes, which may be more frequent in certain populations. This may be a subject, which we would like to avoid, but it is not clear that it will be possible to avoid it, once we have the full genetic information of every person. There is an enormous variety of topics, which are related to these issues and there are fascinating combinations of medical, economic, ethical, moral and legal issues. They all relate to certain aspects of confidentiality. The problem is that certain positive features of knowing the genetic makeup of a person may be so great that confidentiality may become a death-sentence in certain cases. That is what makes the issue very, very difficult.

I wish to spend the rest of my talk, discussing an entirely different issue. I refer to the new fascinating technology of what is called in the trade PGD, for "Prenatal Genetic Determination". Let me clarify: I am not talking here about attempts to genetically modify anybody or anything. I am not talking about cloning. PGD is not related to cloning. It has nothing to do with any genetic modification. It also has nothing to do with another important subject that we have not mentioned here: gene therapy. This last topic (gene therapy) is, in principle, a very promising field, but it is at its infancy. The idea of gene therapy is to cure a deadly disease by "curing" your genes through a certain modification or replacement. PGD is none of the above.

What is Prenatal Genetic Determination? The world of medicine has been creating babies in a test tube, what is known as "in vitro fertilization", for quite some time. This is normally done in cases where this seems to be the only way to produce a baby, because of various fertility problems. In this process, you often fertilize several eggs of the mother. Often, there are more eggs than are needed to be implanted in the mother's womb. Sometimes these eggs are destroyed and sometimes they are frozen. But the fertilized egg, which is implanted in the womb, is normally unscreened for disease or any other genetic issue. Today there is a technology, which is difficult but possible, practiced only by very few research groups in the world, which allows you to do the following: you let the fertilized egg grow in the test tube, for 24 or 48 hours, until it becomes an object consisting of 8 cells. Now, such an object is on its way to becoming a fetus, but it is still microscopic, it certainly has no human features, it may still decide to divide into two identical twins, and I will avoid the theological issue if it is a living object. At this stage, it is now possible to take away one of the eight cells and to do a DNA analysis on it. At that moment you can screen the prenatal "fetus-candidate" for some deadly disease, if the parents are carriers of this disease. If you have two or more such fertilized eggs, which have grown to the 8-cell stage, you may select for implantation, the one of your choice, based on what you have learned about its genetic properties. You are not changing anything and you are not modifying the genetics. You are selecting which of several possible normal babies of a given couple is preferred.

Now you might say: "this is playing God", "this is killing babies". But we are already doing it routinely in the fourth or fifth month of pregnancy when we do the standard test of amniocentesis in order to abort a Down-Syndrome baby. Is it OK to eliminate a fifth-month pregnancy, but not an 8-cell object, which is 24-hour old, is not even a pregnancy and has not even began to develop any human features? As I mentioned earlier, it is a stage in which it may still be possible that this object may split into two and become identical twins. It is very difficult to argue that something, which still has the option of splitting into two human beings, is a human being. But, again, this is already an ethical and religious issue and different religions have different answers to it. It is a fascinating debate.

Now what good is Pre-natal Genetic Determination? Well, the most trivial application is when you want to choose a boy or a girl. Is it good or bad to allow parents to choose a boy or a girl? This is another ethical and moral question. It is already done in certain situations. But the use of PGD may also be a matter of saving lives. There are at least two

cases, known today, in which a child was born with a deadly genetic disease that would certainly kill the child by the age of five or six. The only cure to this disease is a bone marrow transplant from a sibling with a perfect genetic match. Not every sibling is guaranteed to have such a match. Some do and some do not. If the perfect match is not guaranteed, one has to produce siblings until one has the right genes to save the original baby. The solution is then to perform an in vitro fertilization, produce as many eggs as possible, fertilize all, let all grow to 8-cells and then select, among the fertilized eggs, a future brother or sister, which is healthy from the same disease and which is a perfect donor for the bone marrow transplant. In such a situation, when a pregnancy results and a sibling is born, there is no need to even touch the new baby. All you need to use is blood from the umbilical cord and transplant it into the sick child and save his or her life. This incredible scientific tour de force has happened at least twice in the last couple of years, creating healthy new siblings and saving the lives of the older ones, before it was too late. This is an esoteric example, which shows how PGD can save lives. It is esoteric in a lunch talk, but not to the family of the saved children.

Now, let us move a few decades forward with this subject. An infinite number of problems and opportunities emerge. Suppose that one discovers a certain gene, which is responsible for a great musical talent. You are going to have one child, and you want that child to have musical talent. You can easily become pregnant by what we shall define as "the normal procedure", but you might still want to do it in vitro, have several fertilized eggs and choose the one that has the gene for musical talent, applying PGD. I deliberately chose the feature of musical talent because that is the least controversial item of all the things I can think of. You can continue this line of thinking into all sorts of directions, some frightening and others that avoid diseases and birth defects, save lives and perform other positive functions. No one is asking me, personally, what I would allow and what I would forbid, in this case. But I will still share with you my opinion: at the two extremes there are issues, which are clear to me. Saving lives by PGD should be allowed and encouraged. Certain other things should definitely be forbidden. Where is the line?

This leads me to one dogma, which I would like to advocate. It is not my own contribution to the subject. It is the opinion of many enlightened people who spent years thinking about these issues. There are other opinions, but I am convinced that the one advocated here will prevail. The statement is the following: in all the ethical and moral issues related to the fascinating subjects of the Genetic Revolution, no technology should be absolutely allowed and no technology should be absolutely forbidden. Practically every technique has dangerous or unacceptable aspects, on one hand and life-saving aspects, on the other hand. The difficulty is always drawing the line. This is the reason for the existence of ethical committees in most countries, as well as international ethical committees with participants from many dozens of countries, including scientists, medical doctors, philosophers, religious leaders, jurists and politicians. Almost all committees are reaching similar conclusions: there is always a clear yes and a clear no at the two ends of the application spectrum of a given technology. The gray areas will occupy our attention for generations.

An example of such an issue, which we have not discussed here at all, is cloning. All committees and all scientists would like to ban the cloning of people. Incidentally, cloning would be essentially useless, because if you clone yourself, the clone is likely to be several centimeters taller (because of nutrition), afflicted with different medical problems (because of many external reasons), with a totally different kind of intelligence (based on life experience in a different era) and with a large variety of other human features. Your clone will certainly be less similar to you than two identical twins, which were separated at birth and these are, usually, very different. So I, personally, cannot even begin to see what the purpose of the exercise is. But never mind the purpose – there is unanimity that this should not be done. On the other hand, you can perhaps save people with certain deadly pancreas diseases, including severe forms of diabetes, by creating certain cells from a clone of that person which is discarded again after 24 hours or 48 hours and injecting these cells to the pancreas. This life-saving exercise is, morally, on a completely different level from cloning an entire person.

The above remarks regarding ethics are the tip of a fascinating iceberg of moral problems. These will accompany us for generations and we have not even scratched the surface. Again, I emphasize that I am not an authority on the subject. At best, I am a partly informed observer.

Almost everything, which I discussed here, is neither a standard existing technology nor is it science fiction. It is technology, which is one hundred percent sure to exist. No one can predict if it is a matter of three, five, ten or fifteen years. It is possible that in 30 or 50 years, parents in advanced countries, who wish to produce only one child and to do it relatively late in life, may say; “if we do it once, we might as well do it right”. In that case, they may wish to use in-vitro fertilization and PGD so that they can have a free choice of selecting certain things they would like to have. First and foremost, they would choose an absence of serious genetic diseases and absence of genes with high probability of dangerous medical problems. They might then add a mathematical talent or athletic ability or music success or good memory. Clearly, they will not have enough fertilized eggs to have so many choices. In addition, not all the relevant features will be available in the “gene pool” of the two parents. But perhaps all of this will be forbidden, so that no one will get into his sick mind the creation of only tall, blue-eyed, blond babies. This is, of course the nightmare vision, in this case. Will any babies in the affluent countries be conceived in the “old usual way”? Come back in 50 years and see.

Since this is such a heavy subject, I cannot resist telling a Jewish joke about Moishe coming to his mother and asking: “Where did I come from?” She tells him about the birds and the bees. He asks:”This is very interesting; and where did you come from?” She answers: “From the same place.” “And where did Grandma come from?” “The same place.” So he calls his friend Yossi and he says to him: “Yossi, can you believe it? in my family they didn’t have sex for three generations.” Will the joke become a reality, in a few decades?

Do we want to stop all of this? I hear you ask. My answer is: We don’t want to stop it but we don’t want to allow it to happen unchecked. It is a very complex issue. We will have

to live with it. We have to struggle with this question in different countries, in different cultures. We must understand that there is almost no issue here, which is one hundred percent black or one hundred percent white. I know that I am repeating myself here, but this is perhaps the most important message that I am trying to convey to you. There have to be guidelines and there have to be discussions and there have to be rules. The same applies to the subjects I did not discuss, such as genetically modified organisms, which are clearly fantastically beneficial in certain areas of agriculture and food production but on the other hand you can not ignore that there are certain problems with them. To ban them is completely crazy, in my opinion, but to allow them to go completely unchecked is equally bad. We could continue endlessly with examples.

It is a new world. It is a revolution, which may change the world more than the information technology revolution, because it touches us in a much more intimate way. Our person, our children, our family, our health – the older you get, the more important your health is to you and it is the older people who are making the decisions in this world. Last but not least, and this is an appropriate way to conclude our discussion, the Genetic Revolution may also lead to the possibility of very, very prolonged life span, due to the possibility of creating "spare parts" for the human body. In the same way that you can have an antique Mercedes, you may have an antique person by just replacing the spare parts. The question is: do we want to live that long? Do we want to live 150 years? Can society afford to support us, if we live that long? Will we be able to work all our life? This opens an entire new set of social and economic issues.

Now that you are pondering this issue of longevity, I must conclude with a story about a nice man, married to a wife who was always nagging him to exercise every day, to eat only healthy food, to lower his cholesterol level, not to drink too much, of course not to smoke, go to sleep early, and on and on and on. He always listened to his wife and obeyed her and they lived to be 97, at which time they passed away. Being good people, they reached heaven. Everything was wonderful in heaven: the food was good, the temperature was right, the accommodations superb, the service fantastic and, of course, the location was out of this world. So he looks at his wife and he says: "It is only because of you that we have not reached this wonderful place 20 years ago." Thank you very much.