⊗ (not published)

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Start Side 1 - Session I Colloquium

(Rodney Nichols, Moderator started) (Moderator: Lennart Philipson

Joshua Lederberg: Thank you. I have been speaking on this subject for 35 years and I have found almost without exception that my position has been misunderstood and when I give an enthusiastic account of what are the scientific possibilities on them lambasted immediately for being a nazi minded ageneses in interfering with the lives of people and so on and so forth so I hope you don't make that mistake. Maybe after 35 years, some people who know me may also be able to correct that kind of impression but I'm not joking, it's in print and it does illustrate a little bit about the level of discourse that we have seen on some of these matters.

Voice from audience: (inaudible) (Laughter after that).

JL: It's eternal. (laughter from audience).

Voice from Audience: (Inaudible).

JL: I've been given about 20 minutes to give you the full and detailed history of molecular biology in the last 50 years. I feel quite comfortable about doing that but I am going to have to read pretty fast. In fact, it's a particular slice of molecular biology, but I think it's the one that one had in mind and it focuses very much on the science and technology of DNA, how we know about it, what it does in the cell, what kinds of uses can be made for it. On several slides, I'm going to put gene discovery as the top element of the list and I think Len also made this point. The overriding progress that comes out of molecular biological research is analytical understanding. And from that, there flow many, many important consequences, some of which are technological applications of first order but far more deep seated and far reaching are the insights that we get on pathogenesis and ultimately even on human

nature. We have well developed technologies, now that DNA is rather well understood as a material substance, although I continue to marvel every day one sees more of the kinds of tricks that this incredible molecule is capable of undergoing, the kinds of chemical and secondary structural changes, its interactions with other material, the panoplay of enzymes and processing steps that occur within the cell so in a certain sense, we can say we have only scratched the surface of that. But we know enough now to know how to isolate DNA with extraordinary efficacy. From tiny amounts of material we have the PCR and related amplification procedures, whereby starting even with a single molecule of this material, we can make, I was going to say kilograms, I don't think anybody's quite done that, but you know, micrograms or even milligrams of genetically active material and using various kinds of tools. I call them semstering tools. That's the non-chauvinistic way of talking about what a seamstress does. And that's stitching together, cutting, splicing, tailoring, suiting to fit. We can do that with DNA molecules galore. And in simple organisms whose entire geno is readily accessible to us like most viruses and many bacteria, we can also move bits of DNA around from any source and put them roughly where we want them to be inside the target organisms. So the technical capacities for that level of gene engineering in microbes are completely available to us. I don't say they're aren't a few technical difficulties now and then, but the underlying techniques really are there and I daresay if you set your mind to it, that any post doc trained in the field with four or five years, if not less, could settle any task you gave about saying, I want to have this construct, I want this gene planted at such and such a location, in such and such a target micro-organism and with some luck, he can make it actually exercise some functions in that particular site. So that's really the short summary of that capability and it's already been put to vast use. Above all, again, for gene discovery. One of the best ways to find genes is to shotgun them and to target cells, be they bacteria, yeast or high organisms as a matter of

convenience isolate clones of those cells that contain the interesting pieces of DNA, even without having had much specific targeting, we can use expos facto selection on the vast scale. It is very easy to pull needles out of haystacks when you're dealing with microbial populations. They are very large to begin with, and we can apply a wide range of selective procedures to pull out essentially exactly what we want. So we have on a large commercial scale these billion dollar industries producing pharmaceutical, like TPA ethyropayote, various growth factors, and the list is very rapidly being extended to a variety of others. The pharmaceuticals have had the largest payoff quite understandably. These are products that are very precious, measured in thousands of dollars per milligram in certain instances and the life saving virtues that they have enables some possibility with people who are both very smart and very lucky of recovering the rather substantial development investment that's involved in trying to get there. So, a few lucky hits, like TPA ethyropayte, have kept the rest of the bio-technology afloat although most of those ships in fact have floundered. But the opportunities on average are indeed immense. And what is no longer now limited now to bacteria or yeast as those targets one can play similar tricks, not quite with the same facility, but using plants and animals, so with some qualification the remark I made about targeting genes and inserting them into microbial geneomes could be applied to making say transgenic mice. You can't apply selection on the million fold scale nearly as readily. but the basic principals are not that different and there are probably at this point several hundred, if not thousand, varieties of transgenic animals that have been produced mostly for research purposes as models of human disease or to try to elicit more information on the functionality of certain genes. A good deal of what we know of the workings of the immune system has been elaborated from those kinds of sources. And then again that can be put to technological application and instead of needing a fermentovat to produce large quantities, let's say of genetically

engineered immune globulins so that the people are very seriously going into the enterprise of using the cow as the producer instead inserting the appropriate genes into the proteant sequences that will be secreted into the milk and there you have it on large scale. You have some simplification of purification procedures and so on. And if that's not cheap enough for you then think about bananas or potatoes or seeds because one can extend that philosophy even to the use of plants as the target material for producing pharmaceutical on the tonnage scale if that should be required and there are applications where that indeed will come to the fore. When you consider how much of medicine and surgery today depends on the rather - what Carlton Gadeshek calls high tech cannibalism cause he's worked with low tech cannibalism with Kuru and the Foray Tribes in New Guinea. High tech cannibalism is using human blood as a source of pharmaceutical and we've already had opportunities both to congratulate and to rue that event considering some of the baggage that's come along with blood as a source. I'll be amazed if 20 or 30 years from now there is significant use of actual human blood as a source of the kinds of pharmaceutical. Not only the specific globulens with serum albumin and the whole array of materials that we now use cannibalistic sources for. We will have cannibalized one molecule of DNA at some point from some human cell and amplified that in order to accomplish that purpose. All of the DNA technology goes hand in hand with reproductive technologies if we're talking about generating new strains of mammals that's been long since foregone conclusion with plants. Certain artifices have been called for and there is the array of technologies that have become available and in principle, whatever could be done with a mouse might be applicable to the human. One used to say that about other vertebraes that may not be quite right but I'm not at this time aware of any fundamental issue in embryonic development, the role of sperm or egg, or modulation of the reproductive process, that would distinguish the mouse from the human in the basic biology of those

events. Without new discovery I think one should accept it is given that these technologies are technically and in principle transferable in the human situation. In fact, some of them were developed rather hastily for human application with what as far as I can tell was only a minimum of animal application. I have been quite alarmed at that and I am right now, when it comes to technologies like ICSI, the use of sperm and of other surrogates for sperm. Because I think the possibilities of some mishap and the generations of genetic abnormalities are not trivial and they should be investigated on a very substantial scale before one could proceed with great confidence that they are going to give you perfectly healthy human babies when they're applied there. But there's not the same kind of regulation for people just marching ahead and making a therapeutic trial of matters of this sort as there is elsewhere. I assume there is what might pass for informed consent on the part of the individuals, but not a lot has been published about the overall background of validation of those technology before they went in to the human. So in this case, some of it went from the human backwards. That's not the case with stem cells. This is an astounding discovery that it's been possible to get early cells from the mouse embryo and culture them and each of them behaves de facto as if it's another fertilized egg so there is a possibility of propagation of the zygote in culture. It is de facto cloning not of an existing adult organism but of that one fertilized egg. That's the origin of that particular embryo. That work has been done entirely in mammals. I think there are some taboos about jumping into doing that with the human. It was something that was de facto forbidden in the rules of engagement that were recommended in the last NIH study and it certainly is not something that would be countenance in any federally supported work in the United States. That's not the total domain of research in the world and it will not astonish me to find that some place, some where, there are individuals proceeding on that basis and that's going to open the door to a much wider range of the other application of the other

genetic technologies to the human situation. If we go now to more human applications, I have stressed so far the other mammals and plants and microbes. There's gene discovery again and it deserves to be highlighted. Of course as we find more genes that do various things and we extend the domain of our inquiry, no one has questioned the role of genetic factors and the physical structure of the human body, there seems to be inextricably some argument as to whether human behavior could be under some comparable degree of genetic control. I can't imagine how it could escape that. That function is embodied in structures that we're born with but there it is as a matter of some controversy and we have the whole bag about nature and nurture that we could spend quite a few hours on and I suspect we will. That's opened up by that kind of inquiry. Our factual knowledge on this subject is almost nil. We have had such primitive technologies until quite recently limited almost entirely to the study of monozygotic twins, some of them separated at birth and doing statistical comparisons as to what monozygotic twins separated at birth still have in common when they have been in presumably different environments. This has been the paradomatic experiment contaminated also by allegations of fraud in the actual conduct of some of them although I don't think that by itself has really made that much difference in the aggregate outcome. But the main point is such a crude methodology that you know it tells you this (sounds like) exheritability of a given trait. Genes do play some role in that trait. Nolan says that for the range of environments to which these monozygotic twins have been disbursed, then the apportionment of the genetic in the environmental component is it's almost always between 60 and 80% hereditary. But that's a very limited range of environment that these individuals have been exposed to. It's very easy to contrive situations where the environmental variance would be 100% of the story like whether they live or die and also imaginable to have such uniform environmental background that in those cases the hereditary variation accounts for all the difference that you see.

And above all, those experiments have zero, zero baring on the question of genetic components and racial difference. Because that simply has not been done. You have to disburse uniform gene types, color blind into a variety of environmental background such as those that characterize different racial situations before you (sounds like) taglamate any remark whatsoever about the role of genetic factors and differences and outcome by race. So, most of the evidence has been totally irrelevant to the controversy that;s then emerged but the underlining fact of the matter is we are going to find genes that affect behavior. It's not possible for that to have escaped the arena of genetic control, but we should not pretend that we know anything about it at the present time. We will be able to when we have genetic markers whose segregation can be followed in segregating kindreds and we can get specific correlation of the presence or absence of a particular DNA sequence.

End Side 1

Side 2

Carrying or not carrying that sequence and we are going to have important findings particularly in the arena of psychiatric disorder and a role of genetic factors on that matter I think in the fairly near future. When I talk about gene discovery I should generalize that to genetic discovery. Astounding new things have been found about how DNA behaves in the actual context of heredity in the human and these DNA molecules which were thought to be almost immutable when mutation was regarded as a rare stochastic event doesn't alter the uniform transmission of identical information from generation to generation and we find many circumstances where nothing of the kind operates and we have degrees of plasticity of the mutability of that DNA in generational transmission. They were undreamed of just a few years ago and these accordion genes that have sequences of repeats that are then found to either

decrease or increase in succeeding generations and cause quite significant pathologies when that happens and with very high frequencies from one generation to another are an exception to all we used to think about with regard to gene stability. We have only begun to discover the rules about those so called exceptions. And equally just to touch on one other amazing discovery are the role of the bits of DNA that are present at the ends of chromosomes, the so called (sounds like) tilameres. These would normally be nibbled away at every DNA replication, it's a detail that is just built into help DNA replication primed. There are enzymes that put back that's a DNA to the ends of chromosomes and so in the germ line this is more or less an equilibrium but in somatic cells it is not and one of the things that limits the life time of your somatic cells in the rest of your body is that DNA nibbling is progressing at every cell division and at some point it will limit the life of that cell. Though again, there is quite the contrary of absolute genetic stability from one generation to the next in that particular context. The human genome project was mentioned. I think we're beginning to see it in a reasonable prospective. It is a very important technological element in the pace with which new genes can be found in providing an encyclopedic reference work which provides a background in which to locate a new gene that's about to be discovered. As I have often said, if we had the entire encyclopedia given to us by Fiat on one day, the work would then just begin. We wouldn't know what to make of it and what Len said about the importance of our work moving towards function, what the significance is of the individual components of that genome would in fact come to the fore. That it does provide a very valuable tool and one that, yeah, let's congratulate the engineers for cranking it out and giving us the background makes life a lot easier for doing other kinds of scientific work is undeniable. What we've seen is a byproduct is that there are folks who think that cranking out the sequences are going to give them property rights to the further exploitation of that knowledge and that's a battle that's going to be fought

for some time to come but whether that's really enough by way of investment of innovation and so on to provide the basis for lock up on the further rights to that natural product which God made, not humans and who should share in it, so alot of issues come in under that particular heading. Polymorphism is one of the discoveries, one of the genetic discoveries that we get into as soon as we look closely at human beings and we find out how different we are. Well, it doesn't take much insight to see that, just look around the room and if they were identical twins here, you could spot them. They would look alike enough and the rest of us look different enough from one another that you'd really have no difficulty in getting a sense of the degree of heterogeneity that there is in the human population. Some important things to keep in mind about that are that the role of race in that matter has generally been grossly exaggerated that as soon as you go beyond the most superficial characteristics that the degrees of difference from one racial group to another, are not large. They are quite modest by comparison to the variability that we find within any racial group and on the other hand, taking the human species as a whole, it's variability is so large that it's within a factor of ten or twenty of the gene diversification that separates us from the other higher primates, and in fact there are quite a few polymorphisms within the human species, the AB of blood group, the rhesus blood factors, some of the HLA factors which undoubtedly precede the differentiation of the primates and to the human versus the other branches because we do see the same kinds of polymorphosms in those populations as we do in the human. And it reminds us it was not a single individual who branched off and became the first human. There were populations of nomineds who differentiated from one another and carried a lot of their evolutionary baggage along with them including many of the common polymorphisms. So I think those are some of the rather interesting insights that come out of polymorphism analysis. We have very important practical applications of these kinds of technology

and forensics and criminal identification. The FBI and the States are about to establish their legal basis for this exists and it's begun. A registry of certain classes of convicted felons, felons particularly of rape, but of other rather violent crimes that one of the penalties that can by law be imposed on them is that they leave behind a sample of their DNA so there's a library that can be consulted when DNA can be found at a crime scene to see if anybody who had been convicted before matches the DNA at the crime scene. So it becomes not only a tool for prosecution, it becomes an investigative tool and considering the degree of recidivism that there is in violent crimes of this kind and the even greater public outrage that there is at those circumstances, this is undoubtedly going to play a substantial part in law enforcement. It doesn't take much imagination to see some of the touchy issues about how far that's going to go. Some of the matters of privacy, and above all making sure that it's done right, and if they are of the appropriate quality standards and an appropriate understanding of what that technology can deliver by way of precision of identification of individuals. But, above all, I want to remind you that evolution is going on anyhow and in fact I don't think it's going to be greatly altered by our artificial interventions for quite a long time to come. I won't say that will never happen, but the drivers of evolution are natural selection on a very large scale. Sexual selection play some role and connect, and you might say is part of that, is the total uprooting of global lifestyle that we've seen just in the last century. The human species is a totally different creature from any ecological prospective today then it was 100 years ago. Above all, it is totally dispersed. Geographic barriers have all but disappeared. There are huge migrations of individuals and of course the family policies of all kinds that includes explicit family planning but it also includes sexual behavior and non reproductive behavior along a wide variety of axes. These are driving human evolution far more and on a much more profound scale than anything likely to come in terms of it's quantitative impact for many years to come from artificial

intervention. That could change. It could change if we face a great catastrophe if natural selection decimates us from some other source and if we then in turn adopt measures to try to cope with it. Today, the most important application of this insight is at the diagnostic level and is the diagnosis of heterozygous carriers of genetic disease and the opportunity for prenatal diagnosis of that disease where Tay-Sachs is an outstanding example of phenylketonuria (?) This can be applied to, could be applied in principal to a whole range of blood disorders including sickle cell disease and it would be possible to eliminate those disorders as a matter of practical consequence. We couldn't eradicate the genes but we could eliminate the disease with the broad exercise of these kinds of capabilities. You would pre-empt the embryos before they became fetuses. In order to do that, you would have to, the most efficient way is a preliminary screening of prospective parents to see if they are carriers. And the small minority of couples where both parents are carriers, would then be candidates for pre-natal diagnosis, during term and then pre-emptive abortion if that's the way they chose to go about it. Now as we go further and have the opportunities for deeper and deeper insight about genetic determination, predisposition to the disease and so forth, we have of course have important implications in other areas of social policy. The potential abuse of genetic information on the part of insurance companies and employers is very often mentioned. But there's another side to that coin and the quickest way I can summarize it is to say that if there is wide spread availability of access to knowing your own genotype and if that is kept private to you, life insurance is changed from a crap game to a poker game because you know your own hand and you will certainly exploit it to as far a degree as you wish. And now to cope with that, raises some very interesting issues but I just wanted to stress there are two sides to that particular concern. So let me just use very briefly the more aggressive interventions. I start with one of the milder ones because it does not on the face of it involve alterations of the target DNA although it

needs to be studied to see if that might happen as a side effect and that's the anti-sense RNA technology. Broadly speaking, this says, let's exploit our insight about the extraordinary specificity of the different bits of functional DNA within the human body and develop free agents that will target those particular bits of DNA. And that's what the anti sense RNA in principal, is capable of doing. So far, there's no one yet one clear cut case where it's come through. A lot of people are working on it. I really have no doubt at all that it will eventually have an important application. Somatic gene therapy goes a step further and says if there is a genetic defect or if we want to prime the activity of a given genotype so it will do even better than the normal make the right antibodies fight the right cancers and so forth. Let's move genes into the appropriate somatic cells of the human, within the body. And there are ways of doing that. Amazingly, raw DNA will work when inoculated in the muscle. There are viral vectors who will carry that DNA and will give you some degree of selectivity about what cells they target. Lots of problems still there about making sure that the entering DNA goes to just the right cells and to just the right places in the chromosomes where it is intended to do and asymptotic solutions may perhaps be found to that. The ethicacy is another issue for many diseases. Unless you can get a large proportion of the affected cells then we're stuck. I want to just make a point, finally, of very carefully distinguishing somatic gene therapy from germ line therapy. Until now, the interventions that I have in this chart would affect the somatic cells within the body of the existing individual ought not to have any effect whatever on the progeny of that individual. They are not genetic alterations in that sense of the term. The same principals that I've mentioned for other mammals, and which we are beginning to explore for somatic cells, might perhaps be applied in the germ line and that obviously raises a whole host of other conditions. Then, without a word, I'll just put a slide on. And I thank you very much.

MAPPING THE FRONTIERS OF MOLECULAR BIOLOGY

Emphasis on Technological Application

- **gene discovery**

- **gene splicing, transplantation in bacteria, yeast, plants, animals**
  - **Innumerable industrial production opportunities**
    - **TPA, erythropoietin from bacteria, yeast**
    - **Human antibody globulins in seed proteins, milk**

- **reproductive technologies (other mammals and human)**
  - **Artificial insemination**
  - **In vitro fertilization**
  - **Fertilized ova frozen and transplanted**
  - **Intra Cytoplasmic Sperm Inoculation ICSI; even spermatids**
  - **Embryonic stem cells**
    - **Cloning**
    - **Transgenic plants and animals**

Human applications -- diagnostic and analytical

- gene discovery
  - insights into pathogenesis -- esp. cancer, heart disease
  - Nature- Nurture controversy; entanglement with race
  - New insights: accordion genes, telomeres ...
    - transposable genes and viral mutagenesis
    - genetic hygiene wrt radiation, chemicals, inbreeding

- Human Genome Project

- reproductive technologies -- all as above
  - Contraception

- Polymorphism and its diagnosis
  - Forensics; convicted felons files; paternity; remains
  - Human evolution: primates as close relatives
    - Polymorphisms may be older than human species
  - Drivers of evolution:
    - Disease susceptibility (incl infectious)
    - Global life style: migration, family policy

- Carrier and Prenatal Diagnosis
  - preemptive abortion
  - relate to repro' technologies; blastomere diagnosis
  - implications for insurance: from craps to poker

Human applications -- interventions

- antisense RNA
  - potentials for cancer, restenosis, viral infection, immune disorders

- Somatic gene therapy
  - Compare to vaccination
  - Viral, retroviral vectors
  - DNA
  - Problematics -- context specific
    - targetting
    - efficacy
    - durability
  - Greatest Hazard -- we get what we want, as in pharmaceuticals
    - -- mitigation of natural selection

- Germ Line therapy
  - Dependence on Human embryonic stem cells
  - What would be sufficiently compelling reason?
    - eugenics as tabu
  - Counter: euphenic program

MAPPING THE FRONTIERS OF MOLECULAR BIOLOGY

Human applications -- interventions

Police in the bedroom

- **How far do we oversee parental choice in human reproduction**
  - **Fitness for parenting**
  - **Obligations and privileges of genetic vs bodily parents**
  - **Use of alleviating technology for sterility, genetic disorder**

- **What obligations do we have to next generation for rightful life?**

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Human applications -- interventions

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- **What obligations do we have to next generation for rightful life?**
  - **How enforced?**