Genetics Society of America August 31, 1967

Friends, colleagues, and disparate genotypes.

Marshall Nirenberg did me the favor of providing the very best possible introduction to the remarks I would like to make tonight in the form of an editorial that appears over his signature in the 11 August issue of Science, and I would like to ask you to hear me first read that editorial. It's entitled "Will Society Be Prepared?"

See front

All of the foregoing is a quotation from Marshall W. Nirenberg.

I have quoted Dr. Nirenberg's remarks because they make a good stalking horse for some criticisms which I would like to offer, and not in the spirit of any kind of personal criticism of Dr. Nirenberg himself. I must say that in self defense, because his own accomplishments in this particular field are so vast and so well known that I would hardly dare to stand up against him in his absence without some sort of reminder that I may be exaggerating the import of his remarks, ~~and his further comment, and that this was a very brief statement of them,~~ and that further elaboration on his part might give a different interpretation than for the sake of discussion I choose to put upon them at the present time. Nevertheless, I think ~~the~~ his language ~~that he has used~~ will evoke a familiar chord ~~with many of you~~. I think there is a reaction of fright about man's control of his own destiny, in particular about the use of genetic as compared to other forms of biological intervention, and I think it is important that we succeed in achieving a realistic point of view about what we can do, what we should do, what is likely to come about, the kinds of information that we need to find for ourselves to lead indeed to the wisest possible application of these new kinds of discovery. I will take a few of ~~the~~ my texts from these remarks, and comment on them.

The most awesome phrase, and I have heard it at least twice tonight, and hear it every day, and I use it myself on frequent occasions, is the reference to man's power to shape his own biological destiny. This is an awesome statement, and it is probably true, ~~We must consider what it means, and~~ but I'm not sure what it means. ~~I think the~~ Our central question about man's biological destiny is whether we will have a posterity able and willing to commend us for our foresight, intelligence and good will. Molecular genetics undoubtedly plays a role in the ultimate answer to this question. Even more do politics, military technology, and what we might call the religious aspects of human culture generally. The way that we deal with Indian famine and with Chinese nuclear power may be even more relevant to whether there is a biological destiny of man on earth. We also know that that destiny is finite in any absolute sense of the term, either with respect to catastrophic accidents of our own making, or with respect to the long term future of the solar system, and unless we, for example, ~~pollenize~~ colonize and propagandize the universe, we do have a finite, ultimate destiny. I say these remarks in hopes of achieving a certain re-focus about the nature of the problems that we should be concerned about; if we look too far in the future we may overlook the beam in our own eye.

The phrase "the betterment of mankind" also offers many difficulties of reference in any circumstances, and particularly when we're talking in evolutionary terms, which is the framework in which I choose to interpret Dr. Nirenberg's remarks. I could ask whether it was for the betterment of apekind when pre-hominids left the trees and moved on the ground, and had arms available for the acquisition and inspection of objects. Will any intelligent species stop evolution, in the conservative attitude that change is likely to destroy the existing framework of the species? Will it insist on having a completely rational view of the events that concern the existence of future generations many years, centuries, millenia hence, in the framework which we must judge any issues

that concern the evolution of our own kind. But if we do insist on that rational outlook, how can we possibly anticipate the unknown social and technological milieu of existence of such future generations? The one principle that we can probably find common ground on for all of us is to avoid rash irrevocability of the decisions that we make. Unless the very existence of scientific thinking is included in the irrevocable ~~that~~ we might wish to hold in order to avoid change, no isolated experiments can be regarded as globally irrevocable steps. In fact, they are indispensable for the wisdom needed to judge which institutions should be set up. When Nirenberg ~~refers~~ recommends that "when man becomes capable of instructing his own cells he must refrain from doing so", I believe we should translate that into "We should be very cautious about instituting social and political frameworks of change which constitute irrevocable steps for the entire species". But these remarks could very easily be misinterpreted, and some of us might be misled into adopting a point of view that suggests that we not undertake any isolated experiments whatsoever in an area so full of mystique. as the genetic programming of human cells, until we can understand all of the implications. How will we ever learn what these implications might be if we never do any such experiments? We must distinguish the rash irrevocability of isolated events in other spheres from those which would apply to experimentation with single organisms of our own species. History tells us that a nation infected with nuclear power has no choice but to use and develop it in the existing context of world affairs. A single nuclear detonation was an irrevocable event for the politics of our time. It is doubtful, but not certain, that any nation would make quite such a threatening use of genetic weapons, and they are likely to be less immediately impactful, and to have much longer time scales than the physical ones, which will permit some possibility of intervention in the premature social misapplication ~~in the premature social imposition~~ of ~~the~~ any single standard of biological control.

With respect to future developments, Dr. Nirenberg makes some remarks that I must characterize as imprecise. He refers to the "synthesis of messages," and their possible use in programming the cells. Whether the messages are synthetic or natural, so long as they are calculatedly used, would seem to me to make very little difference. I think when we talk about programming cells, and talk about messages, we should inquire for some greater precision into just what kinds of messages we are talking about, and what impact they will have on respective organisms. And the harm is that language of this kind read by laymen, read by political leaders, read by religous leaders, may be misunderstood, that very important distinctions may be blurred, and that we may end up with significant restrictions on our sense of freedom of action and experimentation, which in turn, as I have already remarked, is what we must have if we are ever to achieve the kind of wisdom that has been alluded to. Some of these distinctions are with respect to somatic, vs. germinal effects of these messages. Are we talking about the now conventional messages of the messenger RNA, (the means by which DNA transmits its information to the protein synthetic machinery) or are we talking about the message which is implicit in the DNA structure of the cell? And are we talking about somatic effects or germinal effects? In general somatic effects are highly personal, An RNA message that I may use for the repair of many of my own genetic defects is something that may help me live, but will surely die with me, and it is very difficult for me to distinguish the social relevance of the use of an RNA message for the remedy of such a defect in my own person from that of any other aspects of medicine, and in fact, many therapeutic agents are already involved in this kind of meddling with my somatic genetic programming. If, for example, according to most contemporary theories, I were to partake of the use of a hormone, its purpose is to elicit the calculated production of specific messages in certain of my cells in order to make protein synthesis occur in cells in which it otherwise would not. If I were a diabetic and could anti-

cipate the possibility of taking a single shot of the appropriate messenger RNA to reprogram the synthesis of insulin in some of my liver cells after my pancreas gave out, I think I might resent any blockage to my taking advantage of this on the vague grounds that this is in some general way a genetic message that we should refrain from using until we may know for sure whether it will ultimately be for the benefit of mankind. If we are to use that criterion, we should use the criterion with respect to every medical intervention for individual human betterment. ¶ In fact, I think it must be stressed that the point of view which is implied in the presentation of this editorial runs counter to the fundamental responsibilities of medicine. ~~The fundamental responsibility of medicine is~~ the care of the individual patient. It is certainly the concern of the rest of the social milieu that the sum of the care of individual patients works to the benefit of the entire community, but a literal following out of the prescription that Dr. Nirenberg has presented would be the total stoppage of medical practice. ¶ Now when we come to germinal effects, of course we must have some much clearer idea of what we're doing than might be the case with the personal intervention of somatic repair. If ~~the~~ my use of a medicament ~~on me~~ has an implication not only on my health and my survival and my longevity, and my ability to perform, but also that of my progeny, then of course we would insist, ~~and I think it would not require the comments of a molecular biologist to insist,~~ that we have a clearer idea of what we're up to. ¶ Here we are already guilty of some sins, I think most geneticists would deplore the sometimes careless use of anti-cancer agents, for example, that are known to cause chromosome breakage, and are known to cause mutations, sometimes possibly in patients who may still have progeny, and of course we have had a very necessary and very important furor about the indiscriminate use of radiation. If the reports about the breakage of chromosomes by LSD are correct, there might indeed be a very strong rationale for social control of the use of this agent, or for the compulsory

sterilization of individuals who insist on receiving LSD, because they may then be laying a basis for a very severe penalty that society as a whole must adopt with respect to the increased incidence of congenital malformation in the next generation. Here again, I don't think this is what Nirenberg was driving at; if he was concerned primarily about genetic messages with germinal effect, I don't believe that either he or I would be that greatly exercised about the possibility of some transgression in an experimental context. The occurrence of an occasional individual whose genotype is other than it might have been as a result of the use of genetic message of calculated composition at some point in its formation just does not have that kind of social impact. It is Something to be cautious about, but it is a caution already within the framework of medicine as it is now practiced. A more precise statement of what I trust are his concerns would be a caution against the imposed social control of those techniques, those apparent benefits, those advances that molecular biology may help to bring about. And in this we have a certain analogy with rational germinal choice, as has been advocated by by Huxley and Muller, for example, Muller was constantly being misquoted with respect to his advocacy of the use of the technique of artifical insemination of chosen donors. He had in mind individual choice of specific genotypes as sources of sperm for the production of what he hoped might oscasionally be superior kinds of individuals and he was constantly misinterpreted as advocating social imposition of such germinal choice on families that would have preferred to make their own mistakes rather than adopt those of the community in which they lived. ~~Now it is possible to argue, and sometimes I have argued myself that~~ that distinction isn't as easy as it might appear. The mere introduction of an attractive technique, of a technique which seems to confer a certain degree of social benefits, and which has unknown social hazards, may lead to its social adoption, If this is the problem, this is what ought to be stated, and this is what we should attack. I think, though,

that most of us would agree that while isolated modifications of existing genotypes in either a random way, or in a calculated way, can increase the range of variability and sometimes bias the range of candidates for natural selection to operate, the overwhelming source of man's biological destiny in the sense of the overwhelming basis of the changes in gene frequencies of the changes of the genotype of the human species come from our physical and cultural environment operating by natural selection; that differential reproduction is overwhelmingly a more important source of the definition of the next generation than any isolated changes in availability of individual genotypes.

Now Nirenberg says it has not yet been possible to program mammalian cells. That remark, strictly within the context of his statement, is correct. He was talking about the use of isolated DNA operating to replace mutant genes by other mutant genes or by normal alleles, by analogy with the well known pneumococcus transformation experiments (that possibility has been known for twenty-nine years. It did not require the development of synthetic DNA, to actually accomplish the fact. But as a matter of fact, I can't quarrel with Nirenberg's statement in the precise form in which he made it, but I believe we have to consider this in a somewhat larger context. Can we in fact program mammalian cells, in the sense of introducing genetic information of known import, calculated to produce an explicit purpose related to the genetic machinery? As a matter of fact we do, in this light, already practice biological engineering on a very large scale, and we are doing a rather sloppy job of it, and since this particular element of applied biology may indeed be a prototype for the way in which we may end up broadcasting favorable genes in other ways in the future, I would like to spend a little more time on it.

I am talking about viruses used for immunization. Polio virus particles, measles virus particles, any of a number of other agents have been developed in forms whihh have been attenuated in order to reduce their acute pathogenicity,

so as to make convenient the job of immunizing children so that they will not come down with frank disease. ~~Now~~, I don't want to rock the boat on this question; I still think immunization is a good thing ~~to do~~, and I don't deplore its development or its application at the present time. But I think I must speak out for a much more intense study than now exists of the human impact of these practices. It is very sloppy, it is unconscionably sloppy, considering the scope with which this form of biological engineering ;is carried out at the present time. The use of live virus is ~~as~~ sloppy first of all because ~~of~~ the techniques of production, monitoring, specification, characterization of live viral agents belongs to the dark ages. ~~I can give you empirical proof of that statement by the fact that~~ approximately ~~a third or~~ half ~~of~~ a billion doses of SV-40 virus were included in the polio virus immunization of the last decade! This was a passenger virus, originally, in fact constantly present in the monkey kidney cells that we used for growing both the Sabin and the Salk vaccines. It proved to be more resistant to formaldehyde than polio virus, and therefore was particularly prevalent in Salk vaccine preparations since these were used at a higher dose in terms of total virus particles. It was also present in the Sabin preparations. It may have been a subject of greater concern in the SAlk virus because this is administered parenterally, and the SV-40 would not have to face the barrier of penetrating the intestinal mucosa before it entered into the general circulation. SV-40 is a virus which seems to be a harmless passenger in the rhesus monkeys used as ~~a sources~~ the sources of tissue cultures for growing the polio ~~virus~~ virus - in fact, it is very difficult to demonstrate the virus in that species and very difficult to demonstrate it using human material, and one needs the green monkey to obtain good plaques with enough cytolytic action to demonstrate it. It's a notorious virus because it will induce cancer when injected into newborn hamsters, but after the hamster is a few days old, it has no known important effect on these organisms.

It is a little late in the day to raise any alarums about this particular subject. Nothing very catastrophic actually seems to have happened, in spite of the fact that many millions of children and adults have received rather large doses of this virus in past history. The Public Health Service thinks badly enough of the procedure that it now prohibits the presence of SV-40 virus in current batches of vaccine, so with one hand we have expert assurance that it can do no harm, but on the other, well, we'd better not have any more of it.

I deplore the fact that we have no way of knowing whether either of the SV-40 virus - let me say, particularly the SV-40 virus - or even the attenuated polio virus - have caused more subtle deleterious effects on mankind. We may never know whether the use of these vaccines was for the betterment of mankind, because we don't collect the kind of data that could enable us to reach this conclusion. It seems rather likely, judging from other characteristics of the present generation, that these viruses may have caused a reduction in IQ of the contemporary generation. If that were a matter of 20 points on the usual scales, we might have discovered it. If it were a matter of 2 points, we couldn't possibly have discovered it. And yet an average reduction of 2 points of IQ, whatever that means, but whatever is behind a statement like that, would surely be regarded as something most deleterious to mankind. Well, it could have happened. It could also have happened that the IQ's went up by 5 or 20 points, and our current generation may be too smart to want to bother with taking such IQ tests very aggressively!

One of the principle indictments that I would make in our contemporary exercises in genetic engineering is that we don't realize that we're doing it, and we're not following what's happening. One of the reasons for this is that we are looking too far in the future instead of at yesterday and today for the kind of wise outlook on what is happening right now in the species in the use of contemporary applied biology so that we can ask the right questions on a large enough population base that perhaps we could tell that what's going on

is for better or for worse. Now, it's not implausible that polio virus might get into some of the neurones of a developing child and have some specific morphogenetic effects, ~~in that contact, but we have no way of knowing it.~~ In fact, it's even possible that the neurone count of children who have received these viruses is larger than that of other individuals in the population, by 10 or 15%, and we would have no way of knowing it from our existing data. I can't stress this point too strongly, that we do not watch our populations closely enough to see even major movements taking place within them.

My second criticism has to do with the way that these agents are prepared, ~~while its really part of the previous one, that~~ we are not taking advantage of the kind of techniques that Nirenberg and Kornberg and I and others like to use daily in our own laboratories in a more rarified research context. There is no excuse for virus preparation being as contaminated as polio virus was, ~~part~~ quite apart from the difficulties of detection, the only way it could possibly happen is that we are content to use biological reagents of enormous potency without taking any real care to see that they are pure, homogeneous and what they are intended to be by physical chemical criteria. It was enough that the polio virus preparations produced the right kind of plaques on a selective group of tissue culture media for them to be authenticated as being pure polio virus.

~~on the usual media and therefore was disregarded completely. I don't know this as an explicit fact, but I would have to be surprised if it were difficult to distinguish polio virus from SV 40 by any of the physical-chemical criteria that we use every day of the week in our research laboratories.~~ But the virus agents used for this kind of genetic engineering applied on a large scale to our population are crude culture filtrates. They are subjected to no biological or chemical purification whatsoever before they are packaged in sugar cubes and passed out to the kids in school. And I don't see any excuse for it except the fact there is a myth that virus

immunization programs are mass medicine, ~~that they're not to be done under any circumstances with the kind of decision with which we will exercise ordinary medicine,~~ and of course they're not at all to be labelled as biological engineering having anything whatsoever to do with the new molecular biology. However, before we become to exercised about biological engineering and its hazards and a lack of decision in our understanding of the mechanisms that we're using on such a large scale, I think we ought also to remember that we practice psychological engineering also on a very, very large scale. ~~horrible example of it, is psychological engineering is certainly under very vehement social control.~~ It's compulsory. It's mostly pretty-well programmed from reasonably central authorities. It's equally unscientific, and we call it education. I think we should consider very literally that education shapes the child, shapes the character of the next generation in just as explicit a sense as any of the biological innovations that we have in mind and possibly if you believe some theories of the nature of learning, even from a morphological point of view, that is if you believe learning has something to do with the morphogenesis of the central nervous system as many people do. If we try to look beyond the specifications of what Dr. Nirenberg has laid out so conveniently for me to use as a point of exposure, might ask what else would I quarrel with him about. I've already quarrelled with him on the time scale. He says something twenty-five years in the future and I've tried to point out that we're talking about events that were well launched five years ago or ten years ago. The future events that he's talking about happened yesterday. ~~In more explicit terms I think again he's wrong in time scale that even within the frame work of what he was talking about, the twenty five years is much too long a time. However,~~ permit me to indulge in some of my own hypotheses of sources of evolutionary innovation. Let me begin with the most explicitly germinal changes, ~~or what we might draw as the eugenic~~

Here I would like to go back to viruses. Some of you may have been puzzled exactly why I called the virus immunization an example of genetic engineering. Well, let me illustrate what I meant by a hypothetical proposal that was put forward most explicitly recently by ~~Francis Rodgers.~~ Stanfield Rogers. He found that in tissue culture the Shope virus will, ~~as many viruses do, in fact~~ as all viruses do, induce the formation of certain special enzymes, many of which have a perceptible relationship to specific virus growth in the cells in question. Many viruses for example induce a unique thymidine kinase Most of the bacteriophages induce unique DNA polymerases that have properties somewhat different from the typical DNA polymerase of the bacteria that they previously infect, and so on. So, in fact, it is now regarded as commonplace to think that one of the special functions of the information in a virus particle is to impose a few special enzymes that are related to the unique replicability of the viral nucleic acid as compared to that of the host. In addition, the virus generates a capsid protein to protect itself outside of the infected cell, and that's what viruses are all about. Induced enzyme synthesis by viruses in a rather non-human context are very familiar now. Dr. Rodgers at Oak Ridge noted, and I believe others have as well, that the Shope virus in tissue culture would also in induce another enzyme, arginase, which has no obvious adaptive value to the virus, but we take it for granted that it's due to our own myppia that we areunable to see why it's there. That was a stepping-stone to another finding of his, namely, this was reported in Nature last December, that a considerable number of people who have used the Shope virus in the laboratory had very low serum agamy levels, arginine a pretty convincing case that they are statistically different from the

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rest of us, and though I do not believe he has definately demonstrated that this is the same phenomenon as has been demonstrated in tissue culture, it's indeed very plausible that virus workers in the laboratory have acquired infections with the Shoke virus which is known to have no effect in Man, but that they have indeed been cryptically infected so that some of their tissue cells have been induced to form a particularly active argenase ~~and this argenase has reduced serum level of argenase in them.~~ This has had no perceptual effect on the performance of these individuals unless their intellectual preoccupation with the Shoke virus is somehow a response related to their low serum argenase! ~~although we don't know how to make the kind of measurements in this types of man that can really make for phenomenon as well.~~ But you could not have told them apart by looking at them or by watching them, you had to measure their serum argenase to know that they'd had any previous experience of this kind. Well, this may have been the first understood example in Man of the appearance of a virus-induced enzyme as an augmentation of the genotype of these individuals, at least with respect to the somatic behavior, these individuals are not stigmatized by the fact that they have some additional genetic information than what they were born with, the information coded by the Shoke virus for the production of this specific protein. ~~And that is suggested why~~ we don't know of any use for argenase in Man, ~~I don't believe there are any argenase humans known or any genetic diseases that might be incorporated in this way~~, so we can't cure any known metabolic defect, If we could just find one it might make a very nice case for using Shoke viruses in a constructive sense. ~~The virus does not itself in these people by the way, and that it appears to grown in a cryptic form to leave at least some of its genetic information behind in the cell although not the entire virus genotype is present in any cell is an open question. It's an~~ whether or

~~equal open question for any virus infection that has long lasting effects.~~ Rodgers proposed ~~let's~~ to look for viruses that make more useful enzymes, for example, ~~let's look for viruses~~ that ~~make~~ will induce the formation of phenylalanine hydroxylase, ~~and~~ you all know that we could then cure PKU at a fundamental level, we might even want to get into the fetus and not wait for the birth of the recessive homozygote who might be impaired in his mental development because of his accumulation of phenylalanine on an ordinary diet. And if we can't find such viruses we really are just in the brink of being able to make them, that is a possibility of splicing a messenger RNA that codes for ordinary human phenylalanine hydroxalase to the viral RNA of one or another infectious virus seems like a very plausible ~~possible~~ possibility, both in the point of view of the chemical steps needed to fabricate such hybrids and from the point of view of the likely persistance of such ~~xxxxx~~ viruses themselves in much the same fashion as the original passenger viruses would have done. So this would have seemed to me the nearest thing on the horizon by way of the calculated ~~use~~ use of viruses for genetic engineering. ~~and so it occured to me it's~~ This is exactly what we are already doing for immunization purposes. The only difference is that the induced enzyme which Rodgers is calling for is, in fact, an induced antigenic protein, ~~which may indeed be an enzyme for all we know; but it is some specific protein~~ encoded by the viral nucleic acid, ~~who~~ we would like to see ~~xxxxx~~ this produced in the human being who receives this information ~~who would like to be produced~~ on a life-long basis (so we don't have to reimmunize) ~~xx and~~ the purpose of introducing that protein is to evoke an antibody that responds against it so that you will have immunity covering against infection by other virus ~~xxx~~ particles. But

it's fundamental biological operation is exactly the same as that of the late addition of the gene to the organism so the calculated production of the specific protein encoded by that genetic information.

This has come to the top of my list as a candidate phenomenon for human intervention because it's already here. It's hard to think of explicit ways in which ~~some of the~~ germinal changes, ~~but many of us are concerned as hope~~ might be brought about under calculated control. One wonders exactly how we are going to introduce nuclear ~~type~~ changes into germ cells so that they get into the zygote, ~~otherwise you are talking about somatic sex. I'm a little puzzled how we will ever be able to do that~~ without doing something else first, namely enabling the vegatative propagation of an existing organism. My argument is that we will somehow, if we are ever to get to the stage of the kind of genetic surgery that I think was in the back of Dr. Nirenberg's mind, have to be able to manipulate nuclei of specified origin to do something to them, and then put them into an egg so that they can operate in the normal development ~~hypothesis. And I would like to remind you that~~ if we can do that, even if we don't alter the genetic composition of that nucleus, we have already accomplished a major deviation in the reproductive habits of our species from an evolutionary standpoint, because we will have introduced vegatative copying of existing genotypes! ~~and that implys a necessity for recombination at every generation. We always do have to face up to the likelihood that the technology for this will be discovered.~~ As a matter of fact it's already been done long since, ~~but so many of these things have in some context,~~ but so far only in amphibia. I'm talking about Briggs and King's experiment on nuclear transplantation, ~~which I've usually thought of in this light because their emphasizing the congruous effects. They were not able to demonstrate that~~ in many examples they could ~~take nuclei from differentiated~~

tissues, put them into eggs and get normal development. They usually found very considerable restrictions on development. But they always do report a few cases of seemingly normal development from such transplantations, and Gurden working different species has had considerable different luck in this respect ,and what's outstanding about Gurden's repetitions of these experiments to my mind, is the frequency with which essentially normal development can be obtained from the nuclear transplantation of tissues of much later and sometimes even adult origin into enucleated eggs. So that vegetatively reproduced frogs are almost a commonplace, but how long will it be before they are commonplace in man, who can tell, but I don't think any of you can give me any fundamental biological reason why man should differ from amphibia in this particular respect; why nuclear transplantation should work any differently in man than it does in amphibia. This would be a prototype of the base-line experiment that would have to have been realized in order to exercise genetic surgery by any route I'm able to think of at the present time, and I think it'll be there first. Hopefully connected with this is a topic that has fascinated a few people in every biological generation. I'm reminded that Holdane referred to it and Mrs. Holdane, Helen Spurway, actually attempted a demographic survey to look for the possiblity of partheno_genesis in man. She found that there was a certain confusion about what birth actually ment. You may recall she advertised for examples of this over the BBC about 12 or 13 or so years ago. She did so not because ~~of the possiblity of~~ parthenogenesis was a new idea, but because a diagnosis of it ~~actually having happened appeared during this time. It~~ became possible by the development of our udderstanding of the genetic transplantation. ~~to be able to develop objective criteria of the genetic relationship of offspring to parent, one step better even than blood group comparisons would have done.~~ Her idea was that if any example of proported parthenogenesis

passed the other criteria ~~searchers~~, then she ought to try reciprocal skin transplantations, and if they worked in one direction at least, which is the expectation for parthenogenetic ~~p~~ occipitally, most any mechanism ~~of parthenogenesis~~, than it would be pretty good corroborative evidence that it actually happened. Her failure to find an un equivocal example, says nothing about the future, either on a random or a contrived basis. And I was really quite excited to see an article in last months *Genetics* by Olson ~~and I forget the name of his colleague at Perdue~~, on parthenogenesis in turkeys, where he remarks that the highest frequencyof parthenogenesis in these birds is a fundtion of the simultaneous presence of an appropriate genotype and of the Rous virus infecting these birds! Quite substantial yields of ~~several~~ turkey eggs parthenogenetically produced, are capable in quite a few cases of developing into normal male adults, ~~so you know what thehetogenetic con is, are already known~~. Well, again, if it can happen in turkeys, its going to happen in man, I'm quite sure. ~~I think~~ any evolutionist looking at what has happened particularly at plant species is likely to remark that experiments in vegetative propogation are likely to have a much more profound evolutionary impact on the further development of the species than is the occurrenceof any other sort of variability of genotypes present at any given time. These of course can work together, but the point about vegetative reproduction of course is that it is such a elegant answer to the eugenicists' ugenesis prayers. It the way of expanding an immediately adaptive genotype to the circumstances than existing, which is of course what the ugenesis are crying for, and well, you worry later about what happens when the environment changes or your ideals change. ~~I think also~~ a very reasonable predicate for future development besides the viruses that we may introduce for somatical manipulation, (we may have to generalize our concept of the virus in a couple of directions) ~~one for which there is already ample procedence~~, is that it takes very little

to turn a virus into a plasmogen. It's only necessary that the virus be very adherent to the embryo on its way through or be passed through the milk or be actually present within the cell of the egg as well as other cells of the body. There are any number of viruses which defacto are inherited as if they were plasmogens even though I believe in mammals there is no authentic example of actual intra-oval cytoplasmic transmission of a virus particle. I may be wrong about that and I'm not sure that pragmatically it matters very much from the point of view of its potential human impact. If it is in fact true that mothers who are infected with a virus accidentally introduced are going to pass that infection onto their offspring, it's hair-splitting to ask the question whether that was done through some external medium environment or internally as the plasmogen. Well we may find it desirable to incorporate immunizing viruses in this way, but as a matter of fact the odds are that we would prefer to avoid it. The reason we will want to avoid it is that by all odds we want to keep the next generation of infants from being builtin tolerant to polio virus antigen, which they are likely to be if that antigen is present before birth. But that also suggests the kinds of antigens that we might indeed want to be sure are pretty regularly transmitted, and I can imagine, for example, wanting to produce viruses that have a capability of coding the more common histocompatibity antigens so as to give these kids fresh kidneys when they are adults and their old kidneys have been worn out. But this kind of engineering does represent a very plausible way of getting around some of the other engineering problems of building genetic information into existing chromosomes. Another way to do that is to avoid using an existing whole chromosome and put in another one. And what I envisage as the next step along this line is building some very small chromosomes with just a few genes on them and transmitting these from cell to cell, for example by cell fusion which is already a very well

authenticated technique, and is able to produce, ~~I should like to remind you of this,~~ somatic cell hybrids between forms as distantly related as fish and man in tissue culture. These hybrid karyotypes do undergo very striking changes; once they are produced they eventually shake down to a number of somatic cell lines at the very beginning of understanding how to control this and what it takes to produce a balanced karyotype that is able to be well adapted to the circumstances of tissue culture like of any one kind. I think you can see what can lie behind that, by way of very detailed manipulations not of the molecular biological level, but at the level of chromosomes introduction for producing new genotypes. Combine that again with nuclear transplantation and we really do have germinal genetic engineering on a very large scale.

Up to a few years ago I think gametic selection would have been near the top of the list of anyone who wanted to look past the usual operation of contrived somatic selection that is the ordinaly forms of selection of somatic phenotypes. This is, in fact, turned out to be almost the least promising of all. It does look as if the gametes are expressing a very small proportion of all of their genes and if you manipulate a gameton being in such a way that it tells you what its existing genotype is, at the moment at least, you've removed the possibility of using that same gamete for any other purpose, for fertilization or whatever. But I think before we reach too rapidly at the very ineffective methods that are now being proposed, that would have been proposed in the last 40 years for eugenic manipulation in man we could give some consideration to the possibility of inducing or the processes and using somesort of somatic selection on those cells in order to find those genotypes which are appropriate for use as germ cells. This sounds so weak these days by comparison with the other kinds of engineering operations that are starting right before us that I almost hesitate to mention it.

And I'm sure that any of you to this kind of joint psychedelic exercise would be able to add some of your own experiences, many other ways in which we could contrive to do a considerable amount of genetic engineering in man if we just remember that man is an organism and not very different from your own typical subject of experimental investigation, except in his resistance to being experimented with. With Cell and tissue culture that resistance seems to dissapear and you can do a lot of your anticipatory work without running afoul of social interdiction. However I so far stress what I called eugenic effects, i.e. germinal modifications and I wonder about the long-term relevance of that distinction. Now it's a little hard for geneticist to play it down, our image, our unique distinctions from all the rest of the biologists is our ability to foist that distinction on all the rest of us. What is genetic and germinal is something very, very different from what is somatic developmental. There is something permanent about the germinal aspects of an organism. But I'm not sure whether this will not become obsolete in the framework of human affairs. the reasoning I would put forward is along the same lines that you would now regard certain genetic differences as already substantially irrelevant in man. I hope, for example, that the amount of hair on my head, which I do believe is under some genetic control, really is not very important because I can wear a cap. ~~and we can make much more sophisticated kinds of contrivances to take place of what our biological endowment was. Well that's the best example of what our concept I'm sure you're all very well acquainted with and I won't elaborate on. The extent to which~~ i.e., culture replaces biological endowment in the conduct of our own afairs. The more we learn about development the deeper that's going to be. The medical example of this are well known and are sometimes deplored. It's also less unfortunate as important now if I'm a diabetic because we know about insulin and better insulins have

come along, other kinds of drugs have come along, we sort of on the edge of thinking about using cell transplants to take the place of a failed lung and so on. And while this will entail a certain amount of extra cost it's just part of the cost of keeping civilization going that we become dependent on it in so many ways. ~~Well~~ this is ~~sort of~~ the lowest level of genotypic irrelevance, the technicological substitution of other kinds of artifices to the things we usually depend on. It isn't terribly important that we have great strength anymore, we have machines to take their place. We have automobiles to take the place of good legs, and so on and so forth. (There are some other aspects to good legs.*) ~~The point I would like to stress, and I don't think it's understood well enough or you wouldn't hear very much about eugenics at all in the contemporary context, is that~~ this kind of developmental intervention and ~~in order to stress~~ how firmly opposed it is to eugenics, I try to coin a sufficiently opposite name, so I thought "euphenics", but euphenics is really the same thing as medicine. Euphenics is beginning to acquire the kind of resources that make it relevant to the most fundamental aspects of human personality. Now here, or all things I've talked about so far, pale ~~fail~~ into insignificance by comparison with the one thing that distinguishes man from the other species, and that is his brain. We are just beginning to get the faintest ~~glimmer~~ inkling of what it is that controls the development of the brain. And the things we do as soon as we do understand that control, as soon as we know which hormones are involved in programming the development of the brain, what relevance will there be to the existing assortment of genes that control the count of neurons that we might have or the other much more complicated ways to determine what our performance on an IQ test is going to be. We so far just do not intervene at all, we don't even provide reasonable support for the most important of our developmental processes. Mostly because we don't

* i.e., leave our collective fantasies as is!

understand it at all. We are just beginning to investigate it, we have such findings as one nerve growth factor finally being gotten out in reasonably pure form, some understanding of its nature as a protein hormone. We are obliged to believe that a similar kind of programming is going to apply to the central nervous system generally. Not only will existing genotypes for the development of intelligence be irrelevent, it's to be expected that there will be paradoxical effects. We know calibrate our estimate of genotypic performance in terms of what happens in the relatively uncontrolled situation of a normal gestation with no external hormone control of brain development, and in fact, until reasonably recently it was rather important that the child not be born with too large a brain, because if he did he'd run into obstetrical difficulties. Well these are all points that we of course can get around to in considerable extent by medical and surgical intervention and there will be no relationship between the response of the endowgenous development of the organism, which is what is now measured, and what will happen when we are putting in an explicit program. We can use variations of genotype as a control of brain development to learn a great deal about the development of the brain, I mean to clue the phenylalanine in its mental development is one of the kind of things we can't afford to ignore. But I can see very little place for

intervention and there will be no relationship between the response of the endowgenous development or the autotomize development of an organism which is what is now measured and what will happen when we are putting in an explicit program. We can use variations of genotype as a control brain development to learn a great deal about the development of the brain. I mean to clue the phenylalanine

treasuring too much the existing genotypes for a month's intellectual performance in terms of their probable relevance to the control world of

brain development.

Now there are going to be some paradoxes and dilemmas in this field as there are anywhere else. There's a price to be paid for almost any kind of advance and here we're talking about something that sort of happened yesterday also. There are some fascinating reports from Dr. Money's laboratory, John Hopkins, about the impact of hormonal virilization on intellectual development. Though his data really are not very good, I'll pretend that they are, they are just hints; you really can't rely on them as being affirmative truths. For intellectual development the situtation is must too complicated for that to happen easily. But these are pointed at series of cases for which there has been either a natural accident, for example the idiopathic virilization syndrome in which girls with an excessive output of ~~antigens~~ androgens or, where in fact there has been a contrived euphenic intervention where little girls were exposed to ~~project their own~~ progesterone while in utero in order to have them be born at all. This is the ~~xxxx~~ treatment indicated as a ~~means~~ of sustaining a pregnancy in the face of a threatened abortion on the part of the mother. It has been known for some time that the administration of this hormone could lead to anatomical ~~mass immunization~~ masculinization or development of excessively large clitorides which could be ~~xxxxxxxxx~~ surgically diminished ~~and though denote~~ without important evidence that this resulted in any deleterious changes in later development. Well, ~~xxxxxxx~~ Money has found two things about some of these girls as they grew up to be young women. First of all, by the kinds of tests that as a psychologist he was able to administer, they were tomboys. They had adopted a masculine point-of-view about the world and if this an explicit influence of a hormone and the parts of the brain that are concerned with gender identification, it will of course be of extraordinary interest in that light alone. Now, life is too complicated to draw such a simple conclusion. Of course the parents of these girls knew something about their history, and they've learned something about it themselves, and we don't know to what extent the social milieu was the vehicle

for this psychological mass immunization. Together with that I think none of you might be too surprised to find that they also had an exaltation of their IQ's. The reason one shouldn't be surprised is that with the biological endowment of a complete set of X chromosomes and with some of the pagnacity of the male, how can you beat that kind of female! Well, there's already enough of a hint that this works that ~~I don't know~~ if there are any pregnant women here tonight, ~~but I'd be surprised~~ ~~that~~ some of you ~~didn't~~ might contemplate trying to masculinize your fetuses at the present time, particularly if you knew that they were girls! ~~That's why~~ we have a culture that recognizes male values very much more than it does female, and most of our eugenic efforts are dedicated to producing super man and the hell with the women. (Are you going to go along with that or not?) Until we can resolve that very simple issue of human values as to whether we have a bisexual society or a unisexual society in fact, I think we have to be very restrained about the other interventions that we want to make in human performance. And I should perhaps also remind you that everything by which we now calibrate human genotypes is in the framework of our existing culture, our existing educational system, and all of the rest of it, ~~and~~ one of these days we are going to find out something about education, and I wonder then if any of the ground rules of that calibration are going to be relevant at all, along the same lines of argument that I had with respect to euphenics.

I would like to revert to the main thrust of Dr. Nirenberg's concerns, and that is, should we wait to use genetic messages for the programming of human cells until we can understand all of the consequences and be able to make a final judgement about human betterment? I would reiterate my concern about rash irrevocability of any of the steps we take, and I would like to ask for the most sympathetic consideration and for the most savage

intellectural criticism of individual experiments that go to the roots of human nature. Unless, in fact, we do use genetic messages in an intelligent way to do these kinds of experiments, you will never learn anything about the man himself and we will have no future other than/endowment that we received at the time that intelligence first appeared in the species. I do not think we want to characterize ourselves as man, the uniquely conservative animal.

Thank you.