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Genetics & Future

As Dr. Jacobs said I am a biochemist but I have the feeling and I really should state now that a topic such as this - to really do justice to it--one needs a guru of sorts--some wise man, and I am afraid that I can perhaps pose some questions but there are no pat answers to these questions--at least I have none. My only objective today will be to, at least, raise these questions so that they can be considered and perhaps you may have some answers.

Now, in considering the possibilities for genetics for the future this is really a question of evolution--biological evolution--and there are three broad areas that fall into this topic. The first is that a molecular supplementation, which is a very familiar area; that is, an individual, for example, has a deficiency disease and by simple supplementation, insulin, for example, for a diabetic, or vitamins, or what-have-you, it's possible to at least remedy this disease. Now, obviously a great deal more remains to be determined about the nature of the deficiencies, or the nature of the various diseases before it will be possible to supplement in any way.

Now the second broad area really is the topic of euthenics. This is a term coined by Joshua Letterberg in Stanford, some years ago. Euthenics means to simplify--to modify gene expression, not the genes themselves but the expression of the genes. It is a sort of engineering, human engineering and to alter either the embryonic development of the individual or the development of the adult. Included in this topic would be organ transplantations as well. The essential thing is that the genes are not modified. It is simply the individual.

The third topic, or obviously for euphantics one must again learn much more about the nature of embryonic differentiation. This is an area that extraordinarily topical and interesting to anyone who has worked in molecular biology today because most of the people in the field have the very, very strong feeling that many things can be attempted--that it is possible to do many studies now and that a great deal of information should be forthcoming related to embryonic development and the mechanisms involved.

The third broad area is that of eugenics and this is simply an attempt to improve the genetic quality of the genes by selective breeding and this, of course, has had wide application in agriculture and in certain societies as well--human societies--a voluntary type of eugenics has been applied. Also in this topic all the questions of population, population explosion, and the third aspect of eugenics, I think is a genetic manipulation; that is, to program cells with artificial genes, and it is really this last aspect that I would like to address myself to. It really would be impossible to do justice to the many exciting possibilities that can be envisioned for the future, so I would really like to focus on the possibility of using synthetic genes to program cells; where we stand today, what the problems are, and what the potential is, at least for the future, but before I can do that it is essential really to first point out the basic strategy that the cell employs in order to store the information, how it is stored and how the information is read. Now, may I have the first slide

FIRST SLIDE PLEASE: Now on this slide is shown very diagramatically a very simple protein. Each circle represents an amino acid. There are 20 varieties of amino acids and they are linked together in different sequences and essentially the protein is a linear sequence then composed of hundreds building blocks and there are 20 varieties of building blocks. Now the information that is passed on from generation to generation tells the cell how to build this protein. This particular protein is an enxyme and it's really a molecular machine--a beautifully designed machine. The ~~funcxxxx~~ function of this particular protein is to aid in digestion. It simply cuts a certain type of foodstuff into very small pieces which can easily be digested and then reused. The cell will reuse the building blocks to build new molecules. Now the secret of each amino acid is the all important thing because although one can make some changes in sequence without drastically effecting the function of the molecule, other changes--even removing a single amino acid, or substituting a single kind of amino acid for another variety of amino acid may completely inactivate the function of the protein.

NEXT SLIDE PLEASE--Now an essential cell will contain perhaps 3000 or 5,000 kinds of proteins and there may be many molecules of each kind of protein and each one will perform a different function so the information that specify about how to build this machine is encoded in DNA, and the top line shows DNA in a highly diagramatic fashion. Actually this particular slide came from that great scientific journal Fortune Magazine. It illustrates the point I think very well. It is a backbone and there are four kinds of letters, ~~CxAxUxG~~ C A and C G are the initials of each letter. Now it is a linear sequence--a very long linear sequence. In an average mammalian cell, for example, ~~a~~ single strand of DNA, a single cell may contain about three ~~billion cells~~ on the strand. That is enough information to specify something like ~~2 or~~ 3 million kinds of proteins. ~~Now~~ the sequence of the letters, ~~the all important thing~~ that specifies the sequence of amino acid in protein. First the DNA message is transcribed. It is rewritten in a different form--in the form of RNA, messenger RNA which is indicated diagramatically in the bottom and the important fact here is that there is a complementarity, that a C, the first letter in DNA corresponds to G in RNA; A in DNA corresponds to U, etc., as shown here, and it is the RNA that really is the message that is translated. Now how is the RNA message read? We will show this on the <u>NEXT SLIDE</u>

NEXT SLIDE PLEASE: The cell is filled with gray particles as illustrated here. The message--the long RNA message attaches to one of the particles as shown and the amino acid which is indicated in the upper, right-hand portion of the diagram are linked enzymatically to specific adaptors. The letters in the RNA message are not read directly by the amino acids but there is an RNA adaptor--that coil, hair-pin like structure with the red amino acid fastened to it at the top and three letters in RNA corresponding to one amino acid in protein as shown. You will see in the upper left hand corner of the slide is a growing peptide chain and amino acids are added on one by one starting from the left and proceeding toward the right, reading three bases at a time, three letters in RNA at a time.

The next slide shows this in a little more detail. The messenger RNA is starting there and the ribosome, the particles attach to it at one e and start reading down. One space will hold many translating units or many particles and as the particles proceed down the message the protein synthesis comes along and is finally released. Now the translating particle is in effect a robot. It can read any message if it is written in the correct form--in the correct molecular language and this is really how the code, which is really of the translation between the letters in a nucleic acid sequence and the sequence of amino acids in protein. It would prove to be relatively simple to decipher this language by simply adding to the robot particles of synthetic messages composed of one or two kinds of bases and then determining what kinds of proteins, what kinds of amino acids that were incorporated into proteins. One could even determine more by simply using three letters alone and just looking to see which adaptors carrying the particular amino acid associated with the ribosomes.

Now the next slide shows--this is the last slide-- and it simply summarizes the language. My intention is not to go into detail here, other than to make one or two points. That is, that the language is a very, very simple language--and a logical language. There are many synonyms and the words in nucleic acid are listed on the upper left hand; for example, one UUG is equal to phenylalanine, so is UUC. Now both are synonyms and synonyms differ only in the letter occupying the third position of the triplet and there are only certain kinds of letters of permissible combinations of letters so it is a very simple, logical kind of language and it has been translated, and there are also some words for start and other words for stop because it is a continuous message.

LIGHTS PLEASE: Now, it is not only a logical kind of language. All the available information now indicates that it is a universal language. That is, that all, or virtually all living forms on this planet at least uses essentially the same genetic language. There may be slight dialects or slight differences, but a considerable amount of evidence has been accumulated n , very recent evidence, which does indicate that the same language is used by all living things. There are a few general principals~~, I think, that one can~~ state. First, changes in the way the logic that the cell apparently uses the simple principal the cell uses. Use the principal of standardization. There are few kinds of parts and they are standardized. But great variety is achieved and great diversity also. By combining the part in different sequences and making many different kinds of sequences. Secondly, well, I mantioned the universality; but the important thing that I want to stress is that the particles will read any message that is given to them. Now this raises the possibility that synthetic messages could be inserted into the cells and the particles will follow the instructions. This is essentially what happened in viral infection. Virus by and large is simply a strand of information of genetic information with a code around it to protect it. The information goes--a simplified version obviously but in essence is correct--the information goes inside itself and is copied or translated, by the cell's machinery. Now, genetic surgery is a very sophisticated reality. In the late 20's it was discovered - and a truly spectacular discovery, that one colud prepare DNA from one strain of microorganism and simply add it in volume to another related strain of microorganism and under ideal conditions 10-15% of the individual's bacteria would take up the DNA and their enzymes inside the cell's other machines that will insert this DNA into the chromosome, genetic material of the host so that this organism is changed and it is changed genetically, the progeny then would have the inherited change. So this raises the question then that synthetic information could be used to program cells in much the same way as natural information has already been used to alter bacteria. Now I should say right now that this has not been done really with mammalian cells. That there are great technical difficulties in doing this. Although there have been some recent experiments that suggest that there are ways really of doing this. For example, it is possible and this already has been done, to prepare DNA from a virus added to mammalian cells and tissue culture. The DNA will get inside the cell and a virus is formed. Recently there have been techniques in which one can take chromasomes from one organism and two cells even from widely different species, fuse the cells together, the nuclei fuse and one has a mixture of chromasomes from two different organisms or 2 different species. The techniques are available for doing this kind of thing so I think it is really a matter of technical difficulty to find ways in which one could take a nucleic acid message and insert it into cells. Now the major difficulty really is in the synthesis of the information. The chemistry is quite difficult and complicated. Thus far techniques are available for synthesizing very simple messages. By synthesizing them, I don't mean simply copying preexisting messages because this can be done and has been done for 10 or 12 years and there are enzymes--molecular machines available that one can obtain from the cell that will copy a pre-existing strand of DNA with great stability. It is not a matter of copying but really a matter of composing synthetic messages. The chemistry, as I said, is still rather primitive, but it has been possible to synthesize long strands of DNA or RNA containing simple repeating known sequences and technology is bound to improve vastly in the near future. Now, it wouldn't surprise me, for example, if the synthetic messages that are available today even quite simple used to transform or to program bacteria and I think that this is potentially a reasonable experiment even to do today and surely it will be tried and as I said technology will almost surely improve greatly along these lines. So the main purpose of the talk this afternoon is to point out these possibilities and the current status of work along these lines, the probable future development of the experiments and ask questions because I think that when it becomes possible to do these things then man may be in a position to in some way control, alter or shape his own biologic evolution; i.e., to add information and to compose genes. Now this power I think could be used for great good. I think that eventually man stands to benefit greatly by techniques such as these. But I think it obvious that a great deal - an emense amount of basic information must be learned first before such information could be applied. I should emphasize again that it is not possible to do this today with synthetic information but I think that it will be possible. My rather conservative estimate is in bacteria it is virtually possible to at least try it today and it may be successful in 5-10 years. In mammalian cells a conservative estimate would be 25 years. I think if you were to ask a dozen knowledgeable molecular biologists their estimate of time you would get varying answers but my estimate would be in 10-25 years. I could be off very easily. Now it's necessary I think to formulate the possibilities, state these questions because of the many ethical considerations, moral considerations as well as the technical problems that are involved in this because if and when man becomes able to shape his own evolution by programming cells with synthetic information the question will arise "which way to go? What are the desirable goals. I think everybody will agree on certain goals but there are many others of which a great diversity of opinion obviously will arise, I think it very important to state this problem now, well in advance of the need to state the problem because it requires time to think the thing through to get reasonable answers to it and to begin to perhaps shape the institutional framework in which this kind of approach would be used. This essentially is the reasons that I've come here and tried to describe some of these developments and I can only say in closing that I think that this potential has great possibilities for good. I think that eventually man will benefit greatly by it but there are a great many facts and a gread deal of information that must be obtained first before it is applied.

Thank you very much.