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Prospects for Genetic Bioengineering: Fact and Fantasy

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Describing two recent advances in the area of genetics – treatment of arginemia, and pre-conceptual sex determination – Dr. Wegmann calls for medical scrutiny of the field and for a responsible and wide ranging discussion of goals and consequences.

Prospects for Genetic Bioengineering: Fact and Fantasy

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The medical profession, in this country and elsewhere, has for a long time felt confident that it could ignore the field of genetics, and rightly so. What possible relevance could experiments on peas and fruitflies have to human problems? Also the overly eager and uncritical champions of eugenics, with their naive postulates about the mendelian heredity of such traits as violent temper, gave the field of human genetics an unsavory appearance. This early period culminated in the Nazi eugenic laws of 1933, with the apparent complicity of such leading human geneticists as F. Lenz and O. von Verschuer.[1,2] Ever since that time eugenics has been a word with nasty connotations. Even so, certain eminent and critical geneticists have proposed theoretically workable eugenic schemes for the improvement of whatever characteristics are decided on. The most notable plan is that of H. Brewer,[3] extended and advocated by H. J. Miller,[4] a pioneering geneticist who won the Nobel prize in 1945 for his work on X-ray mutagenesis. The scheme involves the use of sperm banks to store the genetic material of accomplished men. These sperm would be available to "enlightened" women who wanted to have offspring better than those that their husbands could furnish them with. First of all, it is clear that to make this plan workable would require a vast rearrangement of societal views and organization. Secondly, it is not clear which criteria would be used to select the eminent donors. Dunn has pointed out that Muller's first list (1935) included Marx and Lenin. A later list he compiled did not contain these names, but had

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added to it the names of Lincoln and Einstein.[1] The reason for this shift was made clear to me by a fascinating conversation I had with Muller in which he depicted his witnessing of the Stalinist purges of mendelian geneticists in Russia in December of 1936, and his subsequent narrow escape from the secret police across the Russian border. This episode merely illustrates the obvious problem of deciding what normal human traits are worth improving. This aspect of eugenics is labelled "positive", because the goal is the changing of the average man into a superior being. Many people, including G.K. Chesterton,[5] have challenged the validity of this goal.

On the other hand, few people would quarrel with the goal of negative eugenics. This involves performing some sort of genetic surgery on individuals afflicted with otherwise incurable debilitating genetic diseases, to allow them to lead normal lives. Recent explosive developments in the fields of cellular and molecular genetics have brought us closer to this goal, and it is my thesis that medicine can no longer afford the luxury of ignoring these areas. I would like to illustrate this thesis with two examples.

Arginemia is a disease similar to phenylketonuria. When two people who are heterozygous for this trait (i.e., have a gene for arginemia on a chromosome derived from one parent and a normal gene at the same place on the homologous or paired chromosome from the other parent) produce an offspring, the chance is one in four that this child will get both genes for the trait. If this happens, the person lacks the enzyme arginase, which is necessary for the metabolism of arginine, an amino acid found in the serum. The arginine builds up to high levels, and causes (after birth) progressive mental retardation and spasticity.[6] This of course is very typical pattern. Genes are specific sequences of nucleotides arranged along the macromolecule called DNA which is somehow integrated into the chromosome. The sequence of each gene is what constitutes the message of that gene, and for most genes this message is ultimately translated into a specific sequence of amino acids which then fold into an enzyme or subunit of an enzyme. If the gene message is altered or missing, so in general is the enzyme. Higher organisms accomodate for this by having two doses of each gene, and both have to be altered in order for the enzyme to be lacking. This is the case for arginemia, which is a recessive trait. The current prospect is that this disease is now potentially curable through genetic engineering. Dr. Stanfield Rogers and his colleagues at Oak Ridge have been working with the Shope papilloma Virus, which infects rabbits.[7] They found that rabbits so infected have a new arginase enzyme in their serum, biochemically distinct from their own liver arginase. Mutation in the virus leads to a detectable alteration of this arginase in the infected rabbits.[8] This almost conclusively proves that the virus is carrying into the rabbits a gene for arginase, which is then produced in the rabbits. Dr. Rogers and coworkers then made the exciting observation that about half of the people tested who had worked with the virus at some time in their careers had significantly lower levels of arginine in their serum when compared with control individuals. The most likely interpretation of this observation is that the virologists, like the rabbits, have had the arginase gene carried into them upon viral infection. Dr. Rogers informs me that a clinical trial is now being performed on infants with arginemia, before they develop the neurological disorders. The infants have been given the papilloma virus, in the hope that it will allow them to produce the arginase and lower their blood arginine levels, thus avoiding the disease.[8] If it succeeds, it will be the first case of bona fide genetic surgery in man.

One can reasonably question the general benefit of this, because arginemia is a rare trait. Recent work, however, may allow a more general application of this type of treatment. Dr. Har Gobind Khorana and his colleagues at the University of Wisconsin have announced the completion of the first total synthesis of a gene. This was done not by "copying" another gene, but by elegant organic chemical techniques. Once a single copy is made it can be replicated in the test tube ad infinitum, to build up a large pool. Since our knowledge of enzyme composition is also proceeding apace through the exploitation of automated sequence analysis, and since the genetic code is now well understood (partly through Dr. Khorana's efforts) a reasonable prediction is that sooner or later one will be able to manufacture genes at will that code for the enzymes missing in a wide variety of hereditary diseases. Dr. Rogers is anticipating these developments by finding ways to attach these genes onto the Shope papilloma virus.[9] We may one day adminster this specifically modified virus in the same way that we give Sabin polio vaccine, and prevent much more disease that was formerly considered incurable.

The second example of a recent advance worthy of medical attention (pun intended) involves sex determination. It has long been known that females have two X chromosomes, and males one X and one Y. Each ovum carries an X chromosome, and a given sperm carries either an X or a Y. Hence it is the father that determines the sex of the offspring. Up till now this has been an unconscious determination. A report in a recent issue of Nature describes how one can distinguish between X-bearing and Y-bearing sperm microscopically.[10] For reasons unknown the Y chromosomes in human sperm stain much more intensely with quinicrine dihydrochloride than do other chromosomes. Sperms carrying a Y chromosome can be shown to have a brightly staining body in them. This should greatly facilitate efforts to separate the two types of sperm, since formerly one would have had to rely on breeding experiments as an assay for the effectiveness of separation, which would be impossible in man. This method should allow a direct, immediate assay. If the separation succeeds and becomes available for general usage, it could do some good and lots of harm. Women who are known carriers of sex-linked hemophilia and other such diseases give rise to affected sons with a probablity of one in two. This method would allow them to have daughters exclusively. Although the disease would be avoided, the number of female carriers of the trait would be increased, since one half of the daughters of the above mentioned women would also be carriers. The daughters would in turn have to have similar treatment. If the method were applied to the population at large, it might cause significant uncontrolled shifts in the sex ratio, with much attendant unhappiness.

Other recent advances of equal consequence could be cited, but these two should suffice to support my thesis that the general area of human genetics is now worthy of medical and indeed societal scrutiny. My own opinion is that mankind will reap great benefits from recent work in this area. However, if the applications of this new knowledge are allowed to proceed without a responsible and wide-ranging discussion of goals and consequences, mankind may face problems that could make the Nazi era look like a

golden age. I therefore congratulate the organizers of this conference for providing such an excellent forum for this discussion to take place.

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