Manuscript Draft

HUMAN MUTATION CAN SCRAMBLE THE CODED GENETIC MESSAGE OF DNA

In the normal cycle of generations, every individual receives his endowment of genetic information in equal portions of DNA from his two parents. Each portion of DNA is represented by a set of 23 chromosomes, allotted at random from the 23 pairs of the parent in the formation of an egg or a sperm. For better or worse, the DNA message is a faithful copy of what was inherent in the parent, except for the mishaps that we call genetic mutations.

Mutations are quite indiscriminately scattered over different genes and chromosomes. When a segment of the DNA is so altered, or if there should be an error in the distribution of a chromosome, the result may be a damaged cell or a diseased individual.

The kind of cell in which a mutation occurs is all-important. Every cell of the body is programmed by a copy of the individual's DNA and is subject to mutation. Only if the cell in question is a germ cell, leading to an egg or sperm, is there a possibility of transmitting the mutation to the offspring. And then it will have no effect on the person himself.

Alternatively, mutations may occur in body cells, which can have no effect on later generations. Their effect on the person is problematical; howeverm there is grave concern that some cancerlike diseases such as leukemia stem from mutations in blood-forming tissues. In addition, the disorganization of an increasing proportion of body cells by mutation is one of the plausible theories of aging.

Germ-cell mutations are what we commonly think of as genetic effects. (They must be distinguished from direct effects on the growing fetus, such as those of thalidomide. The deformations caused by this drug involved only the limbs, and not the germ cells, and will not be transmitted to further

generations.)

The function or organ affected by a mutation may range from color vision to thought, from toenail to scalp. The severity of effect may be a cosmetic nicety like a white forelock, a monstrosity incapable of surviving or, most tragic of all, a physical deformity or mental handicap. The mutation may be dominant, immediately expressed in one generation, or recessive, reshuffled through posterity until it appears simultaneously in a uniting egg and sperm.

Most of the genetic disease observed in any given cohort of births was presumably inherited from a series of prior generations; although a small proportion can be attributed to very recent, new mutations. In either event, we have a grave responsibility to minimize the level of preventable, new genetic damage that we in turn will transmit to our own posterity. While radiation has received the most extensive public attention as a genetic public health hazard, an enormous amount of laboratory work points to chemicals as potential culpits of equal or greater gravity. This problem merges with that of the prevention of chemically induced cancer; for many chemical agents will have both effects presumably due to similar underlying mechanisms. Nevertheless, many compounds are still widely used as drugs, and elsewhere in the human environment, that have not been systematically tested for this type of hazardous side-effects. Food additives have received more attention than a substance like the sweetener cyclamate was eventually disapproved for wide human consumption on the basis of evidence that it induced cancer in animals. Earlier data indicating that it might cause chromosome breaks were however disregarded, legal regulation not yet having caught up with scientific studies of this type of hazard.

Besides the responsible role that chemical science must have in the preventive sphere, advances in biochemistry also point to therapeutic applications for the relief of genetic disease already established in an individual.

Two kinds of strategies should be distinguished. One already used wherever we have the insight and capability is the replacement or compensation for genetic defects. For example, an important manifestation of diabetes (which is at least in part a genetic disease) is a failure on the part of pancreatic cells responsible for the secretion of insulin. We still know very little about the underlying pathways of pathological effect in this disease. Nevertheless, the availability of insulin, isolated and purified from animal sources, and eventually to become practically available from chemical synthesis, has been a life-saving intervention for many hundreds of thousands of people.

This kind of intervention, at a chemical level, is comparable to the surgical repair of a congenitally defective heart.

Many other genetic diseases are manifest by an abnormal sensitivity to dietary or other environmental constituents. For example, when children suffering from PKU, phenylketonuria, can be diagnosed by chemical tests of the new born, they can be placed on low phenylalanine diets which help assure normal growth and development.

These remedies however are still unavailable for the vast majority of genetic diseases, even the smaller portion of those about which we have biochemical insight into mechanism of development. It is a reasonable expectation however, but as we learn more about the pathway by which information coded in the DNA is transcribed into RNA and ultimately translated into protein, that more effective ways of managing genetic defects may emerge. Other approaches to the limitation of genetic disease are preventive or preemptive. For example, for certain diseases it is possible to apply biochemical tests that will identify prospective parents as symptom free carriers. For example, almost 10% of the black population of the United States carries a gene for sickle-hemoglobin. These heterozygotes individuals are, according to present knowledge, free of obvious disease, but when both parents are the carriers they have a one-in-four

that each of them carries a hereditary defect

risk ~~of having a~~ sickle cell-anemia ~~child,~~ a very serious defect. Biochemical tests are now available by which this carrier state can be recognized - information which may save a great deal of human misery if used voluntarily and intelligently by parents who know the prospects. While the sickle cell disease occurs at a high frequency in a particular ethnic group, a multitude of similar carrier-gene states occurs in every human population.

Chemical tests can also be applied to cells obtained from the fetus during the early weeks of pregnancy. In a number of cases it is possible to diagnose serious genetic disease at this stage of gestation. In many states, the laws of abortion have been liberalized during recent years so as to afford a lawful recourse to voluntary prevention of the birth of seriously damaged children diagnosed in this way. With this kind of help mothers who would otherwise have been in terror of additional pregnancies may now attempt, in high hope and good conscience, to produce a child free of evident handicap. The diseases for which this capability now exists are for the most part quite rare and the diagnostic tests now available too sophisticated for routine use. The biochemical knowledge needed to further this approach is being developed concomitantly with the social and legal context necessary for this type of application.

The ultimate aspiration for gene therapy would be a kind of atomic surgery which would permit the replacement of a single defective gene, within the chromosome, by a normal counterpart. This is a phantasy for which no plausible experimental approaches are now visible. However, it is conceivable that a near equivalent of such gene-replacement might be achieved by the use of new strains of viruses that have been bred, or perhaps enzymatically synthesized, so as to contain DNA sequences corresponding to normal functions of human cells. Without necessarily replacing their defective counterparts, such viruses could carry in supplemental genetic information that would override the defficiency. There are many obvious difficulties that must be overcome before such an

objective could be confidently applied before the treatment of genetic disease in man - not the least of which is an understanding of virus biology that would be invaluable in its own right. Many workers are, nevertheless, rightfully confident of ultimate success along these lines.

We have already reached the point where the limiting factor in designing approaches to gene therapy for many diseases is our understanding of their underlying biochemistry. This condition, while necessary for solving the problem will, however, not always be sufficient until such time as we develop some of the tools indicated earlier in this discussion.

Since the philosophical revolutions instigated by Darwin and Mendel some critics of the human condition have deplored the apparent suspension of creative biological evolution in man but is assumed to be a consequence of the supervention of culture and an altruistic morality ~~that may~~ appear for fends natural selection. The eugenic argument has emerged that we should be more attentive to the prospect of ultimate deterioration of the human species, for example if the "unfit" outbreed the rest of us. Such arguments have never had a very convincing technical foundation, for lack of rigorous evidence connecting economic success with genetic quality and in turn with reproductive prolificity. In addition, many serious ethical objections have been raised, on behalf of individual rights, as against the race- or species-quality demanded by the eugenic argument. Much of this disputation can now be set aside in the knowledge that our contemporary devices for assessing and for responding to the eugenic argument are ludicrously crude by comparison with reasonable expectations for the progress in knowledge of the next one or two generations. Alternatively stated, the pace of biological evolutionary change is so slow that even if we were to accept the worst assumptions of the eugenicists we could profitably set their fears aside for a period that would be very small in evolutionary terms, and very large in the span of scientific and technical advance. Meanwhile, we have an enormous challenge in perfecting and using the biochemical knowledge now

available for the alleviation of individual human disease and its accompanying heartbreak.