
Chapter 2

Genetic Inheritance and Mutations

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Genetic Inheritance and Mutations

“Like begets like” is an expression that describes repeated observations in families. Except in rare instances, most children are normal and generally resemble their biological parents, brothers, and sisters. In these cases, the genetic information has been passed intact from the parents to their children.

This report is about the instances when something goes wrong, when a genetic mistake is made; a mutation in the DNA of the parents’ reproductive cells, both of whom are physiologically nor-

real, is passed to a child who may or may not appear normal, depending on the nature and severity of the mutation. All types of mutations, from the benign to the severe, are considered in this report. As an introduction to human genetics for non-specialists, this chapter summarizes some basic information about normal functions of DNA, the various kinds of mutations that can occur, and health effects of mutations. More complete information can be found in a general reference such as Vogel and Motulsky (165).

FUNCTION AND ORGANIZATION OF DNA

Deoxyribonucleic acid, DNA, is the carrier and transmitter of genetic information. Its functions require that it is relatively stable and that it is able to produce identical copies of itself. Certain agents, such as some forms of radiation, viruses, and certain chemicals, alter DNA’s ability to maintain these characteristics. Mutations, changes in the composition of DNA, can occur as a result of these agents acting on DNA or on the systems in place to repair DNA damage.

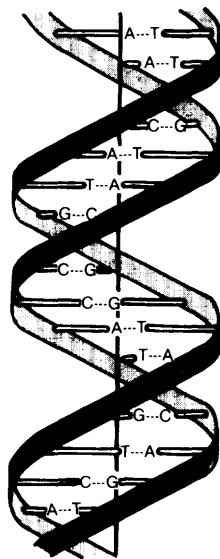
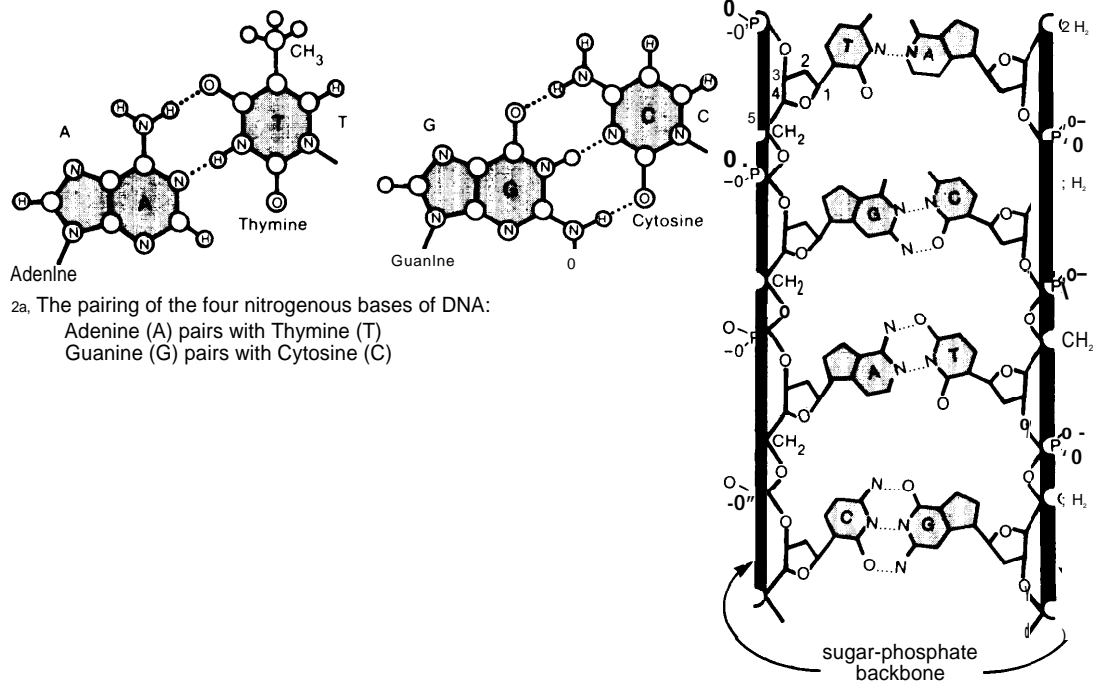
Human DNA can be thought of as an immense encyclopedia of genetic information; each person’s DNA contains a unique compilation of roughly 3 billion nucleotides in each of its two chains, the exact sequence shared by no other person except an identical twin. The genetic information encoded in DNA is contained in the nucleus of cells, and is packaged in units, or *chromosomes*, that consist of long twisted double strands of DNA surrounded by a complex of proteins. Each chromosome contains thousands of genes, the functional units of DNA, which are “read,” or transcribed, by the cell so that genetic information can be used to make proteins or to regulate cell functions. It is thought that only a small proportion, approximately 1 to 10 percent, of human DNA is translated into specific proteins. Functions of the non-translated majority of DNA are largely unknown. There are 23 pairs of chromosomes in all nucleated

human cells except human reproductive cells (germ cells). The latter contain one of each pair of chromosomes, since two germ cells (one egg and one sperm) fuse at conception and re-create a full set of DNA in the offspring.

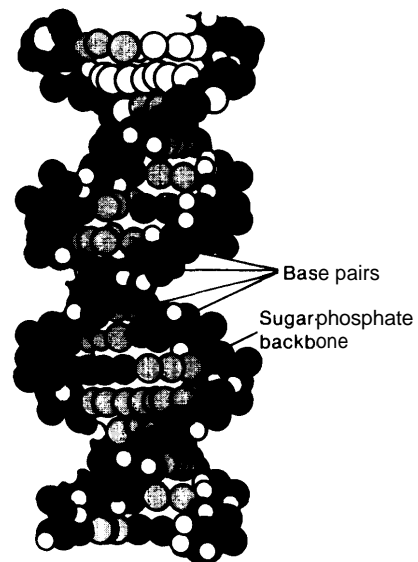
DNA is composed of two chains of nucleotides bound together in a double helical structure (fig. 2). The backbones of the two chains, formed by sugar (deoxyribose) and phosphate molecules, are held to each other by hydrogen-bonded *nitrogenous bases*: adenine, thymine, guanine, and cytosine, abbreviated A, T, G, and C, respectively. Each of the chains’ units, or *nucleotides*, consist of a sugar, phosphate, and nitrogenous base. The linear sequence of nucleotides repeated in various combinations thousands of times along the DNA determines the particular genetic instructions for the production of proteins and for the regulation of cell functions.

A change in even a single nucleotide, e.g., substituting G for T, among the 3 billion nucleotides in the DNA sequence, constitutes one type of mutation. Depending on where it occurs, such a mutation could be sufficient to cause significant pathological changes and dysfunction, or it could cause no impairment at all. In thalassemia, for example, a genetic disorder of hemoglobin synthesis, approximately 40 different “spelling er-

Figure 2.—The Structure of DNA



A schematic diagram of the DNA double helix.



A three-dimensional representation of the DNA double helix.

2c. The DbJA molecule is a double helix composed of two chains. The sugar-phosphate backbones twist around the outside, with the paired bases on the inside serving to hold the chains together.
 SOURCE: Office of Technology Assessment.

rors, " or (single or multiple) nucleotide changes, have been identified in a particular gene that specifies the production of globin, an essential constituent of hemoglobin. In complex diseases such as heart disease, susceptibility is thought to be influenced by the interaction of environmental factors such as diet, and genetic factors such as mutations in one or several genes.

During DNA replication, each chain is used as a template to synthesize copies of the original DNA (fig. 3). New mutations are transmissible to daughter cells. To replicate, the two chains of the DNA double helix separate between nucleotides, and each is copied by a series of enzymes that insert a complementary nitrogenous base opposite each base in the original strand, creating two identical copies of the original one. As a result of specific pairing between nitrogenous bases, each chain builds its complementary strand using the single chain as a guide.¹

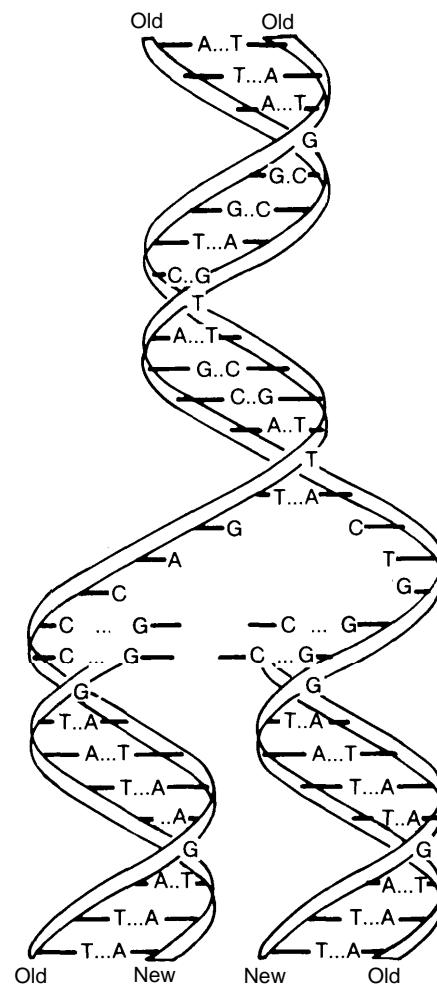
Protein Synthesis

The normal functioning of the human body—including the digestion of food; the production of muscle, hair, bone, and skin; and the functioning of the brain and nervous system—is dependent on a well-ordered series of chemical reactions. Proteins, especially the enzymes, promote the chemical reactions on which these processes are based. Each enzyme has a specific function; it recognizes a chemical, attaches to it, reacts with it, alters it, and leaves, ready to promote the same reaction again with another chemical.

To synthesize a protein, the genetic information contained in one or more genes along the DNA is transcribed to small pieces of ribonucleic acid (RNA), which are faithful replicas of one strand of DNA (see fig. 4). Each strand of RNA moves out of the nucleus to the cytoplasm of the cell, where it serves as a template for protein synthesis. Proteins are composed of hundreds of linked subunits called amino acids. At the ribosomes, RNA is used to gather and link amino acids in a specific sequence and length according to the design specified in the DNA to form the different proteins.

¹The molecular structure of the nitrogenous bases in DNA requires that A pairs only with T (or with U in RNA) and G pairs only with C.

Figure 3.—Replication of DNA



When DNA replicates, the original strands unwind and serve as templates for the building of new complementary strands. The daughter molecules are exact copies of the parent, with each having one of the parent strands.

SOURCE: Office of Technology Assessment

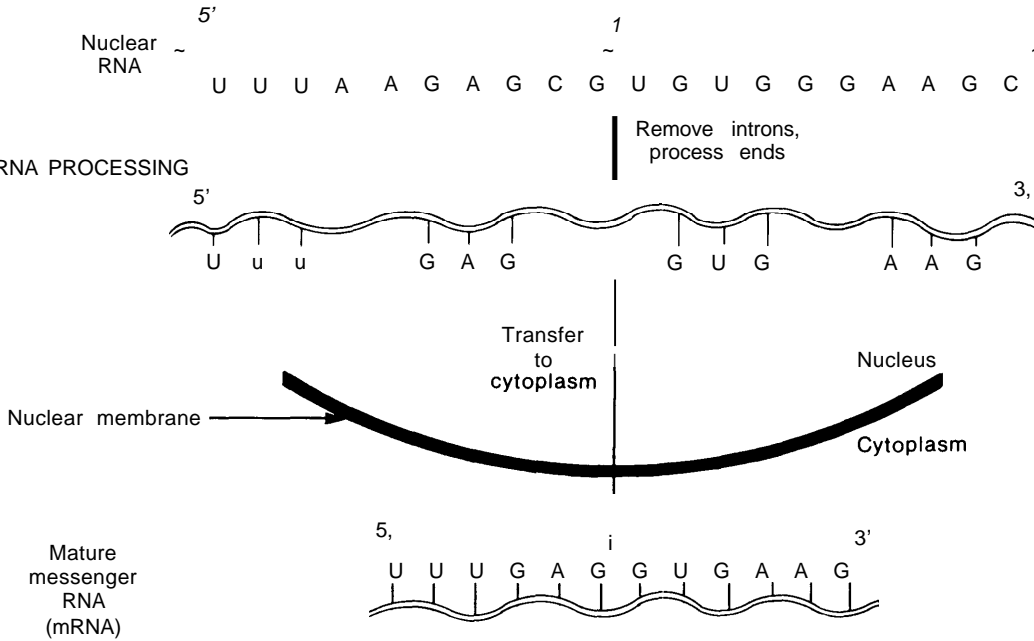
Genetic information in DNA is organized in a triplet code, or sequence of three nucleotides. Each triplet specifies a complementary codon in "messenger RNA" (mRNA) which, in turn, specifies a particular amino acid. The sequence of such triplets in a gene ultimately determines the amino acid sequence of the corresponding protein. Codons exist for each of the 20 amino acids that make up the myriad of different proteins in the body. Additional codons exist to signal "start" and

Figure 4.—Diagrammatic Representation of Protein Synthesis According to the Genetic Instructions in DNA

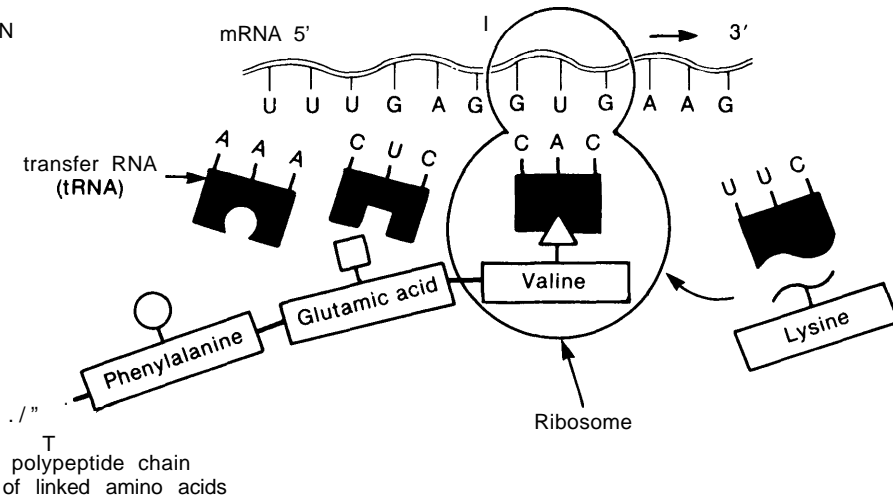
1. TRANSCRIPTION



2. RNA PROCESSING



3. TRANSLATION



SOURCE: Adapted from A.E. H. Emery, *An Introduction to Recombinant DNA* (Chichester: John Wiley & Sons, 1984)

Figure 5.—The Genetic Code

Codon	Amino Acid	Codon	Amino Acid	Codon	Amino Acid	Codon	Amino Acid
Uuu	Phenylalanine	Ucu	Serine	Uau	Tyrosine	Ugu	Cysteine
Uuc	Phenylalanine	Ucc	Serine	Uac	Tyrosine	Ugc	Cysteine
Uua	Leucine	Uca	Serine	Uaa	stop	Uga	stop
Uug	Leucine	Ucg	Serine	Uag	stop	Ugg	Tryptophan
Cuu	Leucine	Ccu	Proline	CAU	Histidine	CGU	Arginine
CuC	Leucine	CCC	Proline	CAC	Histidine	CGC	Arginine
CUA	Leucine	CCA	Proline	CAA	Glutamine	CGA	Arginine
CUG	Leucine	CCG	Proline	CAG	Glutamine	CGG	Arginine
AUU	Isoleucine	ACU	Threonine	AAU	Asparagine	AGU	Serine
AUC	Isoleucine	ACC	Threonine	AAC	Asparagine	AGC	Serine
AUA	Isoleucine	ACA	Threonine	AAA	Lysine	AGA	Arginine
AUG	Methionine (start)	ACG	Threonine	AAG	Lysine	AGG	Arginine
GUU	Valine	GCU	Alanine	GAU	Aspartic acid	GGU	Glycine
GUC	Valine	GCC	Alanine	GAC	Aspartic acid	GGC	Glycine
GUA	Valine	GCA	Alanine	GAA	Glutamic acid	GGA	Glycine
GUG	Valine	GCG	Alanine	GAG	Glutamic acid	GGG	Glycine

Each codon, or triplet of nucleotides in RNA, codes for an amino acid (AA). Twenty different amino acids are produced from a total of 64 different RNA codons, but some amino acids are specified by more than one codon (e.g., phenylalanine is specified by UUU and by UUC). In addition, one codon (AUG) specifies the 'start' of a protein, and 3 codons (UAA, UAG, and UGA) specify termination of a protein. Mutations in the nucleotide sequence can change the resulting protein structure if the mutation alters the amino acid specified by a triplet codon or if it alters the reading frame by deleting or adding a nucleotide.

U - uracil (thymine) A - adenine
C - cytosine G - guanine

SOURCE: Office of Technology Assessment and National Institute of General Medical Sciences

“stop” in the construction of a polypeptide (protein) chain. The triplet code provides more information, however, than is needed for 20 amino acids; all except 2 of the amino acids are specified by more than one codon (see fig. 5).

Inheritance of Genetic Traits

A child's entire genetic endowment comes from the DNA in a single sperm and egg that fuse at conception. The fertilized egg then divides, becoming a multicellular embryo, and the cells differentiate into specialized tissues and organs during embryonic development. In terms of genetic material, there are two general types of cells: somatic cells and germinal cells. Those that have a full set of DNA at some time in their development and do not participate in the transmission of genetic material to future generations are *somatic cells*, which include all cells in the body except the reproductive cells. Germ cells include the gametes (egg and sperm, each of which contains half of the total set of DNA) and the cell types from which the gametes arise.

A normal, full set of human DNA in somatic cells consists of 46 chromosomes, or 23 pairs of homologous chromosomes: 22 pairs of “autosomes” and 1 pair of sex-determining chromo-

somes. Females have 22 pairs of autosomes and two X chromosomes, while males have 22 pairs of autosomes and an X and a Y chromosome. Reproductive cells, with half the normal set of DNA, are produced by reduction division, or meiosis, from sex-cell progenitor cells in the female ovary or male testis. These progenitor cells are set aside early in fetal development and are destined to be the only source of germ cells. Each ovum or sperm has 23 single, unpaired chromosomes: ova have 22 autosomes and one X chromosome; sperm have 22 autosomes and one X or one Y chromosome.

Most genes are present in two copies, one on each member of a homologous pair of chromosomes. For instance, if gene A is found on chromosome 1 it will be present at the same location or *locus* on both copies of chromosome 1. The exact nature of the DNA sequence of gene A may differ between the two chromosomes, and the word *allele*, classified as either *normal* or *mutant*, is used to refer to different forms of the same gene. Many different mutant alleles are possible, each one defined by a particular change in the DNA sequence. A mutation that is not expressed when a normal gene is present at the same locus on the sister chromosome is called *recessive* and a mutation that is expressed even in the presence of a normal gene is called *dominant*.

A Normal Karyotype of 46 Human Chromosomes

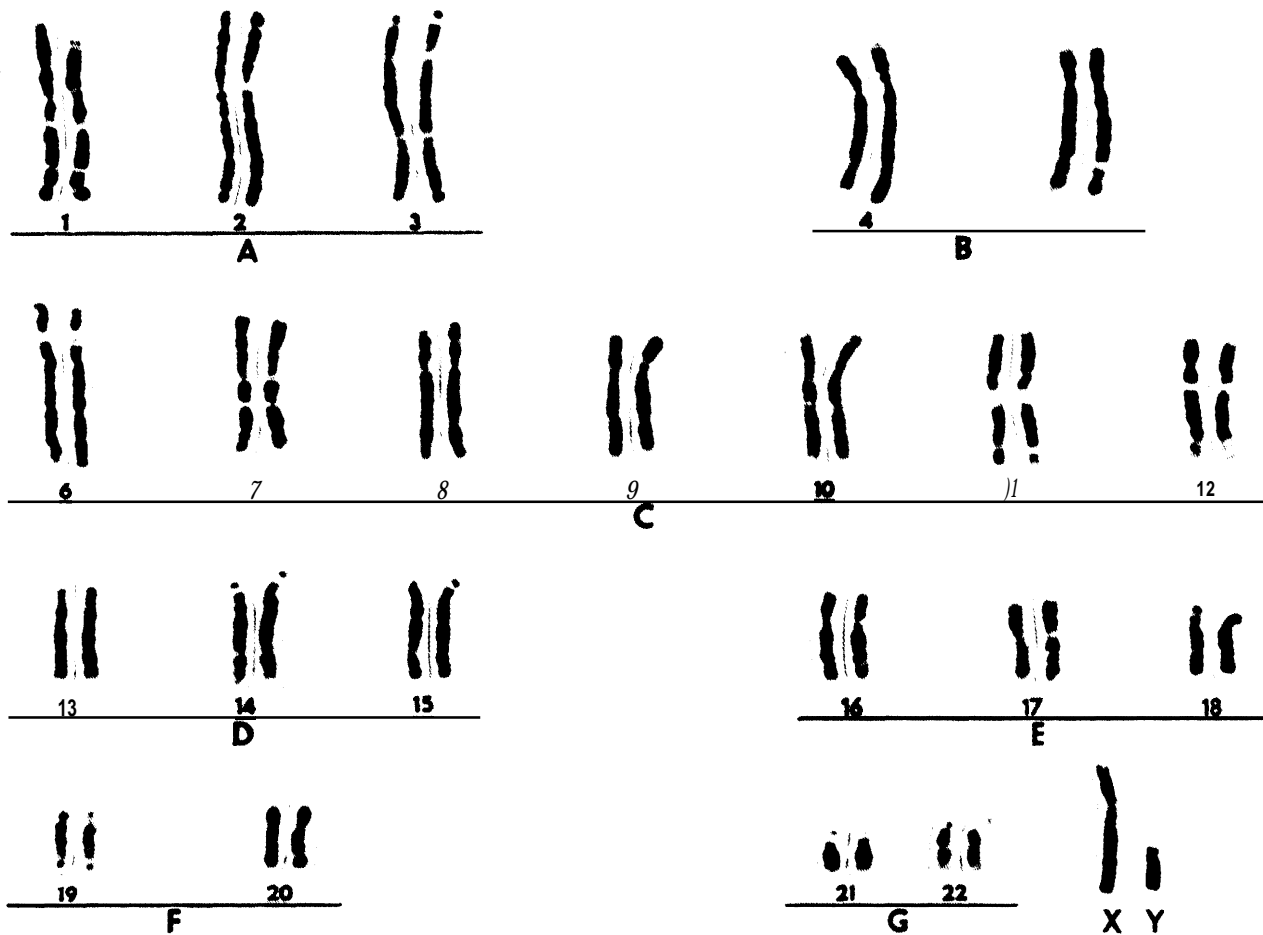


Photo credit: Gail Stetten, Johns Hopkins Hospital

Karyotypes typically show all the chromosomes of a single cell, and are used mainly to identify abnormalities in the number or structure of chromosomes. Chromosomes can be isolated from any nucleated cell type in the body, but are most often isolated from white blood cells derived from a sample of venous blood or from amniotic fluid cells obtained at amniocentesis. The cells are stimulated to grow and divide in the laboratory, yielding a large number of cells which contain a sufficient amount of DNA to isolate and examine. The cells are then blocked in their dividing phase by the addition of a chemical, such as colcemid, to their growth media. After harvesting the cells, they are treated with a hypotonic solution to cause them to swell, and then with a chemical fixative to maintain this fragile, swollen state. When small amounts of the cell suspension are carefully dropped onto microscope slides, the cells break open, spreading out their chromosomes. To visualize the chromosomes and to distinguish the different homologous pairs, the chromosomes are stained to produce a characteristic banding pattern for each of the 23 pairs of homologous chromosomes. The chromosomes can then be photographed under the microscope, cut out from the final print, and numbered and arranged in order of decreasing size as shown in this karyotype.

KINDS OF MUTATIONS

Mutations are changes in the composition of DNA. They may or may not be manifested in outward appearances. Some mutations, depending on where they occur in the DNA, have no apparent effects at all, and some cause changes that are detectable, but are without obvious impairment. Still other mutations lead to profound effects on human health and behavior: stillbirths, neonatal and early childhood deaths, various diseases, severe physical impairments, and mental deficiencies.

If mutations occur in genes that determine the structure or regulation of essential proteins, the results are often detrimental to health. Since most DNA in human cells is not expressed or used in any known way, mutations in these regions may or may not be clinically apparent, although it is possible that subtle physiological variations may occur. Interactions among several such mutations may result in unusual responses to environmental stimuli or they may influence susceptibility to various chronic diseases.

Mutations can be generally divided according to size into two groups: gene mutations and chromosome mutations. Chromosome mutations include numerical and structural abnormalities.

Gene Mutations

Gene *mutations* occur within or across a single gene, resulting from the substitution of one nucleotide for another or from the rearrangements (e.g., deletions) within the gene, or they may duplicate or delete the entire gene. The mutation responsible for sickle cell anemia, for example, is a point mutation: a single nucleotide in the gene coding for globin, a constituent of hemoglobin, is substituted for another nucleotide, resulting in the substitution of one amino acid (glutamic acid) for another (valine) at a certain position in the globin chain. One of the mutations responsible for a form of alpha-thalassemia, another form of anemia, involves the deletion of an entire alpha-globin gene, resulting in the absence of alpha-globin synthesis.

Since proteins are produced from the instructions in genes, a mutation in a gene that codes for a specific protein may affect the structure, regulation, or synthesis of the protein. A mutation that results in a different codon may or may not change the resulting protein, since different codons can code for the same amino acid. Alternatively, such a mutation may result in the substitution of one amino acid for another, and possibly change the charge distribution and structure of the protein. Another mutation in the same gene may result in gross reduction or complete loss of activity of the resulting protein. Detailed analysis of the mutations underlying thalassemia disease has shown that mutations occurring in the bordering areas, not within the translated parts of the gene, can also impair gene function (171).

Chromosome Mutations

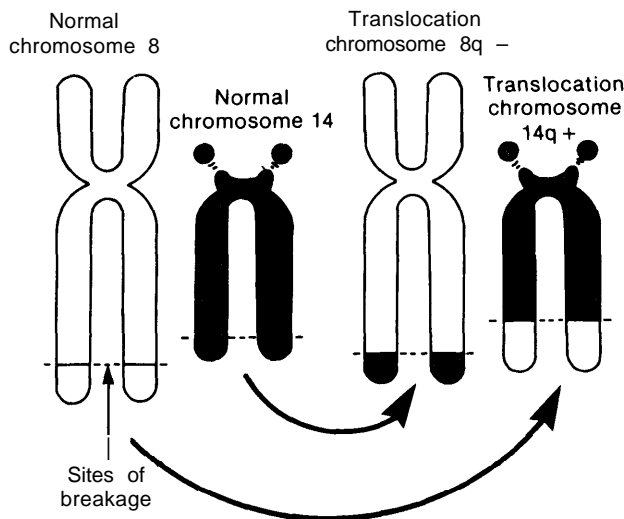
Major changes affecting more than one gene are called chromosome mutations. These involve the loss, addition, or displacement of major parts of a chromosome or chromosomes. They are often large enough to be visible under the light microscope as a change in the shape, size, or staining pattern (“banding”) of a chromosome. Major chromosome abnormalities are often lethal or result in conditions associated with reduced lifespan and infertility.

Structural Abnormalities

Structural mutations in the chromosomes change the arrangement of sets of genes along the chromosome. Sections of one chromosome, including many genes, may break and reattach to another chromosome (e.g., in a balanced translocation, shown in fig. 6) or another location on the same chromosome. Alternatively, sections of chromosomes can be deleted, inserted, duplicated, inverted.

Numerical Abnormalities

Numerical chromosomal mutations increase or decrease the number of whole chromosomes,

Figure 6.—Chromosomal Translocation

SOURCE: Office of Technology Assessment

without changing the structure of the individual chromosomes. Errors in the production of the germ cells can lead to abnormal numbers of chromosomes in the offspring. For example, Down syndrome can be caused by the presence of an extra chromosome (Trisomy 21); three copies of chromosome 21 are present while all other chromosomes are present in normal pairs, giving a total of 47 chromosomes in each cell. A similar, but opposite, error in production of the germ cells results in the lack of one chromosome. Turner syndrome (Monosomy X), in which affected females have 44 autosomes and only one sex chromosome, an X chromosome, results in abnormal development of the ovaries and in sterility. The effects of these mutations may result not from alteration in the nature of the gene products but from the abnormal amount of gene products present.

HEALTH EFFECTS OF MUTATIONS

In Western countries, genetic diseases are more visible now than in the earlier part of this century. Advances in medical care, public health measures, and living conditions have contributed to a gradual decline in the contribution of environmental factors to certain types of diseases, particularly, infectious diseases and nutritional deficiencies (32). Genetic disorders as a group now represent a significant fraction of chronic diseases and mortality in infancy and childhood, although each disorder is individually rare. Such disorders generally impose heavy burdens, expressed in mortality, morbidity, infertility, and physical and mental handicap. Approximately 90 percent of them become clinically apparent before puberty.

The incidence of genetic disease is not known precisely, but it is estimated that genetic disorders are manifested at birth in approximately 1 percent of liveborn infants, and are thought to account for about 7 percent of stillbirths and neonatal deaths and for about 8.5 percent of childhood deaths. Nearly 10 percent of admissions to pediatric hospitals in North America are reported for genetic causes. The majority of these genetic diseases lack effective treatment. A small, but increasing number are avoidable through prenatal diagnosis and selective abortion (21,32,40).

In most of these cases, the particular genetic disorder is passed along in families, or the asymptomatic carrier state for the disease is passed along for many generations, before it maybe expressed in a child with the disorder. In some of these cases, however, the disorder may suddenly appear in a child when no relatives have had the disorder. Not uncommonly, such an event can be explained by mistaken parentage or by one of the parents showing mild or almost unnoticeable signs of the disorder, so that this parent has a disease-causing gene that can be passed on to his or her children. However, the sudden, unexpected appearance of a new condition in a family can also result from a new mutation in the reproductive cells of the parents. Examples of conditions that result from new mutations in a large percentage of cases include Duchenne muscular dystrophy, osteogenesis imperfect (a condition resulting in brittle bones), and achondroplasia (dwarfism).

The exact causes of new heritable mutations are unknown. It is thought that the risk of some new heritable mutations increases with increasing age of the father. Certain rare disorders due to mutations occur at as much as four times the average rate when fathers are 40 years of age or older at the time of conception of their children. Such

disorders include achondroplasia, Apert's syndrome (a disorder with skull malformations and fusion of bones in the hands), and Marfan's syndrome (a complex syndrome including increased height). Advanced *maternal* age is a risk factor for some newly arising chromosome abnormalities, including Down syndrome.

Very small deletions of a particular chromosome have been found in children having certain cancers such as Wilm's tumor (chromosome number 11) and retinoblastoma (chromosome number 13). Some chromosome mutations are compatible with normal life, and others may be associated with increased morbidity and reproductive problems. For example, when a section of a chromosome breaks off and reattaches to another chromosome, both copies of all of the genes may still be present, but they are located abnormally. If no genetic material has been lost in the move, this type of rearrangement is called a balanced translocation. However, a gene that was previously "turned off" may, in its new location, be suddenly "turned on"; this explanation has been invoked to explain how cancer genes can be activated. Furthermore, in the production of germ cells, an abnormal complement of DNA could result, so that a parent with a balanced translocation may have offspring with unbalanced chromosomes, an outcome that usually has deleterious consequences for the child.

Early Mortality and Morbidity

Numerical and structural chromosome abnormalities have been detected in as many as 50 to 60 percent of spontaneous abortions, 5 to 6 percent of perinatal deaths, and 0.6 percent of live-born infants (43). Fetuses that survive to term with such abnormalities are apparently only a small percentage of the number of fetuses with chromosome abnormalities that have been conceived. Abnormalities such as trisomy 13 or trisomy 18 are among the more common disorders found in the liveborn group, whereas many numerical and structural abnormalities, most of which are not found in surviving infants, have been found in spontaneous abortions.

Some of the numerical chromosome abnormalities, such as trisomy 13 or trisomy 18, can be

compatible with a full-term pregnancy but may cause severe handicap in infancy and childhood and may be associated with a reduced lifespan. The health effects of structural chromosome aberrations (involving only parts of chromosomes) depend on the size and location of the aberration. However, features shared by many of these conditions include low birthweight; mental retardation; and abnormalities of the face, hands, feet, legs, arms, and internal organs, often necessitating medical care throughout an individual's life.

Diseases During Adult Life

Some genetic disorders, although present in an individual's DNA since his conception, do not manifest themselves until adult life. Huntington disease, a degenerative neurological disorder characterized by irregular movements of the limbs and facial muscles, mental deterioration, and death usually within 20 years of its first physiological appearance, is an example of a genetic disorder with adult onset.

Many disorders that develop during adulthood and that tend to cluster in families do not have classical patterns of genetic inheritance. Several genes may be involved in the development of these "multifactorial diseases," and environmental factors may also influence the manifestation and severity of these disorders. Susceptibilities to conditions such as diabetes mellitus, hypertension, ischemic heart disease, peptic ulcer, schizophrenia, bipolar affective (manic depressive) disorder, and cancer are thought to have genetic as well as environmental components.

Effects of Somatic Mutations

Mutations that occur in somatic cells may affect the individual, but they are not passed on to future generations. Somatic mutations may play a role in the development of some malignant tumors by removing normal inhibition to cell growth and regulation, producing cells with a selective growth advantage. A wide range of experiments in animals and observations in humans indicate that somatic mutation may be one step in the development of certain types of cancer, in-

cluding leukemia and cancers of the breast and thyroid. Mutations that cause deficiencies in the normal DNA repair system, such as in the genetic

disease xeroderma pigmentosum, can also lead to cancer following exposure to a mutagenic agent.

PERSISTENCE OF NEW MUTATIONS IN THE POPULATION

The “spontaneous mutation rate” represents the sum of “natural” error arising during the course of life and reproduction, and external influences, both natural and manmade. The mutation rates that have prevailed throughout recent human history may be in a state of relative equilibrium, although accurate information is lacking. Suppose, though, that mutagens are suddenly introduced heavily into the environment, and that there is an increase in mutation rates. It is impossible to accurately predict the number of people born with genetic diseases in future generations that will result from that increase, but some predictions can be made based on what is known about the effects of different types of mutations on subsequent generations. Two cases are considered below: 1) the effect of a doubling of the spontaneous mutation rate in one generation, and 2) the effect of a permanent doubling of the spontaneous mutation rate.

Assume that a population was exposed to a “pulse” of a mutagenic agent, such as radiation from an atomic bomb or from chemical agents in a toxic spill, and that the exposure caused a doubling of the heritable mutation rate. Overall, the number of extra cases of disease associated with mutation in the first generation after the pulse (the generation in which the effect would be greatest), will be comparatively small. One estimate (from a 1977 United Nations Scientific Committee on the Effects of Atomic Radiation report) is that 10.5 out of every 100 liveborn infants has some kind of genetic disorder (88). Almost all of those cases are from mutations already present in the gene pool, and not from new mutations. The National Research Council (NRC) estimates that one mutational pulse would add an extra 0.66 cases, so instead of 10.5 per 100, 11.16 cases would occur. The effects on subsequent generations would be smaller, but even after hundreds of generations, there might be some small increment of the mutational load as a result of the

pulse. To understand this phenomenon, it is useful to consider different kinds of mutations separately.

Chromosome mutations would be the shortest lived in the population, because in most cases they result in sterility, so they would not be passed on to the next generation. They would probably be eliminated completely after about 1.25 generations.

Dominant and X-linked (sex-linked) mutations are the next shortest lived. Many of these, because they often cause such severe disease, interfere with a normal lifespan and reproduction. After about four or five generations, on average, they would no longer be transmitted to future generations.

New recessive mutations will probably have the greatest chance of being maintained in the population. Virtually none would be eliminated in the first generation, because a single individual will have only one copy of the gene, and two would be needed to cause overt disease. Recessive mutations may take generations to surface as overt disease. There is much less certainty about the ultimate fate of recessive mutations than about dominant, X-linked, or chromosome mutations.

Many “common” or multifactorial diseases are partially influenced by genetic traits carried in families or arising anew. These include congenital malformations, and such common diseases as heart disease, diabetes mellitus, bipolar affective disorder, immunological disorders, and cancer. Since it is difficult to estimate the proportion of disease that is currently influenced by mutations, it is also difficult to estimate how long such mutations induced from a pulse of a mutagenic agent would persist in the population. However, the NRC report (88) estimates that these mutations would persist for an average of 10 generations.

These estimates suggest a surprisingly small increase over background rates of genetic disease

in the first few generations after intense exposure to mutagenic agents, which would decline slowly over many generations. The NRC report (88) suggests that about half of the total effect would occur in the first six generations. The most severe mutations would be more easily observable as dominant genetic diseases. These would be eliminated within one or two generations since they interfere with survival and fertility. Mutations with a less severe initial impact would persist in the population for a longer period of time.

A permanent doubling of the current mutation rate would, however, after perhaps hundreds of generations, lead to a new equilibrium, with the incidence of genetic disease at about twice its current level. One of the biggest unknowns about predicting future effects of mutations is the impact of an accumulation of recessive mutations in the population. There is also little information to bring to bear on the question of the impact of an increase in mutations to the prevalence of common diseases.