Appendix E

List of Abbreviations and Glossary

Abbreviations

ADA — Adenosine deaminase, an enzyme whose absence leads to metabolic errors that in turn inhibit the bodies' immune defenses. ADA deficiency is a rare disorder caused by genetic mutation that is inherited as an autosomal recessive trait. It is not the same disorder as PNP deficiency, although there are some similarities.

cDNA — Complementary DNA, DNA made from a messenger RNA template (see Technical Notes).

DNA — Deoxyribonucleic Acid (see Technical Notes).

EAB — Ethics Advisory Board, established under the Secretary of Health and Human Services to advise the Secretary on ethical issues related to public policy. There can be one or more such boards (Code of Federal Regulations, 1983). None presently exist, despite Federal regulations.

HPRT – Hypoxanthine-guanine phosphoribosyl transferase (or hypoxanthine phosphoribosyl transferase), an enzyme whose complete deficiency leads to Lesch-Nyhan syndrome, and whose partial absence leads to gout. HPRT deficiencies are inherited as X-linked traits.

IBC — Institutional Biosafety Committee, established at a university hospital, private firm, or other research center. IBCs supervise research protocols to ensure compliance with Federal Guidelines for Research Involving Recombinant DNA Molecules. In the case of Human Gene Therapy, this will involve review also by the RAC and the NIH Director before approval to commence experiments.

IRB — Institutional Review Board, established at a university, hospital, private firm, or other research center. IRB's must be composed of 5 members, at least one of whose primary interests are in nonscientific areas and one member neither affiliated with the institution nor in the immediate family of anyone who is so affiliated. IRBs supervise research protocols to ensure compliance with Federal Human Subjects Protections, and report noncompliance with the Protections to appropriate institutional officials and the Secretary (Code of Federal Regulations, 1983).

mRNA — Messenger RNA (see Technical Notes).

NIH – National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services.

OCT – Ornithine carbamoyl transferase (or ornithine transcarbamylase), an enzyme that mediates metabolism in the urea cycle, and whose deficiency is inherited as an X-linked trait.

OSTP – Office of Science and Technology Policy, reporting directly to the President.

OTA – Office of Technology Assessment, U.S. Congress.

PKU – Phenylketonuria, a disorder caused by deficiency of an enzyme, phenylalanine hydroxylase, that metabolizes one amino acid (phenylalanine) to another (tyrosine). It is inherited as an autosomal recessive trait.

PNP – Purine Nucleoside Phosphorylase, an enzyme whose absence leads to metabolic errors that in turn inhibit the bodies' immune defenses. PNP deficiency is caused by a rare genetic mutation inherited as an autosomal recessive trait different from ADA deficiency.

RAC – Recombinant DNA Advisory Committee, constituted at the National Institutes of Health to advise the Director of NIH on experiments involving recombinant DNA and molecules derived from recombinant DNA.

RFLP – Restriction fragment length polymorphism, a phenomenon involving variation in the length of DNA cut by specific enzymes that permits location of genes of interest, including disease-related genes (see app. A).

RNA – Ribonucleic Acid (see Technical Notes).

tRNA — Transfer RNA (see Technical Notes).

TSD — Tay-Sachs disease, an autosomal recessive disorder caused by deficiency of the enzyme hexosaminidase A.

UCLA — The University of California at Los Angeles.

Glossary

Achondroplasia—a defect in the formation of cartilage at the ends of long bones (femur, humerus) that often produces a type of dwarfism. There are a number of hereditary forms, the most common of which is an autosomal dominant.

ADA deficiency—an autosomal dominant disorder caused by deficiency of the enzyme adenosine deaminase, and resulting in inhibition of the bodies' defenses.

Allele-one of several possible alternate forms of a given gene.

Alpha fetoprotein—a fetal protein found in amniotic fluid that indicates, by its presence and concentration, the presence of certain fetal defects (e.g. anencephaly; spina bifida).

Alpha globin mRNA deficiency—an insufficiency in the messenger RNA coding for the alpha chain of hemoglobin.

Alpha-1-antitrypsin deficiency—a recessive heritable disease due to the lack of a protein inhibiting enzyme, alpha-1-antitrypsin. Death is usually due to degenerative lung and liver disease.

Alpha thalassemia—an hereditary disease due to an insufficiency in the number of alpha hemoglobin molecules in the blood. It is usually caused by the deletion of a portion of the gene coding for the alpha hemoglobin molecule.

Alzheimer disease—a progressive brain disease marked by progressive dementia (loss of memory and higher mental functions) and associated with characteristic changes in and near nerve cells: senile plaques and neurofibrillary tangles. The evidence suggests the disease can be caused in several different ways: a hereditary form exists, but its prevalence is uncertain; slow acting infectious agents may play a role; the body's immune system may react against the brain; specific populations of nerve cells may die; and environmental toxins (ionic aluminum or silicon) may be involved; or some combination of factors.

Aminoaciduria (branched chain; and ketoaciduria)—any of a large class of diseases marked by the accumulation of various amino acids (branched chain or ketoacids) in the blood. Symptoms vary with the specific compounds involved, each presumably the result of different defective enzymes in the relevant metabolic pathways.

Amniocentesis—the process of withdrawing a sample of the amniotic fluid surrounding the fetus in utero through a needle into a syringe. The fluid taken (usually 2 to 8 milliliters, or cubic centimeters) contains cells shed by the developing embryo. These can be grown in cell culture and either analyzed biochemically or cytogenetically to detect a variety (over one hundred) of hereditary diseases.

Anencephaly-–a congenital defect characterized by the absence or extreme reduction in size of the brain and spinal cord. It is usually due to complex developmental malformations rather than a simple genetic defect.

Antibody molecule-protein molecules manufactured in the body that serve to recognize and destroy cells identified as foreign. The antibody molecule is a tetramer, composed of two large, heavy chain molecules and two light (kappa or lambda) chain molecules. The ability to bind to different antigens (molecules that stimulate the production of antibodies) resides in antibodies.

Antigen—a molecule, usually a large protein or carbohydrate, which when introduced into the body stimulates the production of an antibody that will react specifically with the antigen to remove it.

Aneuploidy—a defect of chromosome number. Normal sexual organisms are diploid; that is, they have two complete sets of chromosomes, one of paternal origin and one of maternal origin. Defects of ploidy can be either of individual chromosomes, where one more or one less is present than normal (trisomy; monosomy), or of entire chromosome sets (e.g., triploidy).

Argininemia—a recessive genetic defect marked by severe mental retardation and various neurological disorders. It is due to an excess of arginine in the blood and spinal fluid, this being caused by decreased activity of the enzyme (arginase) that normally degrades this molecule. It was suggested a decade ago that argininemia could be treated in humans by deliberate infection with the Shope rabbit papilloma virus, which had been shown to restore arginase activity of deficient cells in tissue culture.

Arginosuccinate synthetase deficiency—see Cit*rullinemia.*

Arteriosclerosis (hardening of the arteries)-–a condition in which the walls of blood vessels become thickened and hardened due to a number of different pathological conditions. The causes are multiple and complex, and often incompletely known. There is good evidence that genetic factors are sometimes involved.

Arylsulfatase B deficiency—an autosomal recessive disorder of lipid metabolism caused by a deficiency in the production of the enzyme arylsulfatase B. A form of metachromatic leukodystrophy, the symptoms are severe physical changes including hydrocephalus, with death usual by the late teens.

Atherosclerosis—the most common form of arterio-

sclerosis in which there are localized deposits of fatty material (lipids) in the walls or the chamber (lumen) of blood vessels. It can be the result of defects in lipid metabolism, many of which are genetic in nature.

Auto-immune disease—a disease in which the body's defenses fail to distinguish its own tissue from foreign matter ('(self" from "non-self") and attack it. The causes are probably errors in gene regulation, and there are clearly hereditary forms of this disease. A common form is lupus erythematosus, in which the connective tissues of the body (collagen especially) are progressively destroyed.

Autosomal dominant—a genetic trait (or a gene) carried on one of the autosomes that produces an observable phenotype even if present in only one copy (i.e., of the two alleles present for any given gene, if only one of them is a dominant it will be expressed regardless of whether the other is dominant or recessive).

Autosomal recessive—a genetic trait (or gene) carried on one of the autosomes that must be present in two copies (both of the alleles present must be of the same type) in order for the gene to be expressed and the trait seen in the phenotype.

Autosome—any chromosome other than the sex chromosome.

Azacytidine (5-azacytidine)-a drug used in cancer therapy that has also been used experimentally to promote expression of hemoglobin F genes (to replace defective Beta globin genes) in patients with thalassemia and sickle cell disease.

Bacteriophage (phage)—a virus that infects a bacterial cell. Phage consist of a core of genetic material (DNA or RNA) carrying the particle's genetic information which is surrounded by a protein coat or capsule. When a phage infects a host cell, the cell machinery that manufactures protein in response to genetically encoded instructions is commandeered by the phage and used to produce offspring phage. These are released when the bacterium dies, liberating from 100 to 10,000 new phage particles per infected bacterium.

Beta globin--one of the several types of hemoglobin molecules. In normal adult humans hemoglobin is a compound molecule formed of four protein subunits (globins) and a heme group. The four globins consist of two alpha and two beta molecules.

Beta thalassemia—a hereditary genetic defect caused by a deletion or alteration of a portion of the gene coding for the beta globin molecule. The result is an insufficiency in the number of beta globin molecules, which leads to abnormal hemoglobin,

Blastocyst—the developmental stage (in a mammalian embryo) immediately following the morula. It consists of an outer layer (the trophoblast) containing a cell mass attached to the inner wall of the interior cavity, or blastocoele. (See Technical Notes.)

Carcinogen—an agent or chemical that causes cancer.

Carrier (silent carrier)—an individual carrying a genetic defect and capable of transmitting it to offspring, but who does not show the defect him/herself. Most often, a carrier is heterozygous for a recessive allele, that is, carries only one of the two copies of a gene necessary for the trait to be manifest. It is possible, however, for an individual to carry a dominant allele that is not expressed and thus to transmit the trait to offspring while never showing it him/herself.

Chorionic villus biopsy—a technique of ante-natal diagnosis by which a sample of tissue is taken from the placenta (whose cells are of fetal origin) and analysed to detect the presence or absence of certain hereditary defects *in utero.*

Chromosomal disorders-any of a great variety of pathological conditions associated with abnormalities of the chromosomes, whether of number (aneuploidy) or structure (insertions, deletions, rearrangements).

Chromosome (colored body)--so named by early researchers because they stained very darkly when colored with certain dyes, chromosomes are the location of hereditary (genetic) material within the cell. This hereditary material is packaged in the form of a very long, double stranded molecule of DNA surrounded by and complexed with several different forms of protein. Genes are found arranged in a linear sequence along chromosomes, as is also a large amount of DNA of unknown function, but that may serve simply to help keep one gene separated from its neighbors.

Citrullinemia--an autosomal recessive defect whose clinical symptoms are associated with a deficiency in the enzyme argininosuccinate synthestase. Symptoms include ammonia intoxication, severe vomiting, and mental retardation.

Cleavage–the stage of cell multiplication immediately after fertilization of the egg. It lasts until the cells begin to segregate and differentiate, producing a blastula and then gastrula.

Complementary DNA-- (cDNA)–DNA synthesised from a messenger RNA template rather than the usual DNA template. cDNA is often used as a DNA probe to help locate a specific gene in an organism. The advantage of cDNA over mRNA as a probe is that the mRNA can be used to identify a specific gene product (e.g., an enzyme important to the

cause of a hereditary disease) and then to produce a DNA probe (more stable and more easily handled than RNA) to find the gene responsible for the hereditary disease.

Conceptus—a fertilized egg; an egg after conception.

Cystic fibrosis—an autosomal recessive disorder in which the glands do not function normally. Most often seen in children and young adults, it is usually lethal. Death is due to excess mucus in the lungs and pancreatic insufficiency.

Cytogenetics—the study of chromosomes and their behavior in the cell: what they look like, how many there are, how they are replicated and distributed to daughter cells (mitosis) or among gametes (meiosis).

Cytotoxic agents-chemicals, compounds or other agents that can cause cell death for any of a variety of reasons.

Dementia—loss of higher mental functions: memory, reasoning ability, speech, etc.

Diabetes mellitus—a disorder of carbohydrate metabolism marked by elevated blood sugar due to inadequate insulin production.

di-methyl adipimidate–an experimental compound used to prevent sickling in the red blood cells of patients with sickle cell anemia.

DNA (deoxyribonucleic acid)—the molecule containing hereditary information in all but the most primitive organisms (some viruses, that use RNA). The molecule is double stranded, with an external "backbone" formed by a chain of alternating phosphate and sugar (deoxyribose) units and an internal ladder-like structure formed by nucleotide base-pairs held together by hydrogen bonds. The nucleotide base pairs consist of the bases adenine (A), cytosine (C), guanine (G) and thymine (T) whose structures are such that A can hydrogen bond only with T, and C *only* with G. The sequence of each individual strand can be deduced by knowing that of its partner, This complementarily is the key to the information transmitting capabilities of DNA. (See Technical Notes.)

DNA probe–a molecule (usually a nucleic acid) of known structure and/or function that has been tagged with some tracer substance (a radioactive isotope or specific dye-absorbing compound) that is used to locate and identify a specific gene or region of a chromosome or portion of the genome.

Dominant--a gene that produces a visible effect even when present in heterozygous condition; each diploid cell contains two copies (alleles) of the gene at any specific locus. An allele that is expressed regardless of the nature of its companion allele is said to be dominant.

Down syndrome—a chromosomal disorder caused by the presence of all or part of an extra 21st chromosome. The symptoms are mental retardation, congenital heart defects, immune system abnormalities, various morphological abnormalities and a reduced life expectancy. Down syndrome is one of those diseases that has been most clearly shown to increase in frequency with advancing maternal age. (Down syndrome has been known by several equally inappropriate common names in different cultures, e.g. '(Mongolism" in the West and "round-eye" syndrome in the Orient.)

Drosophila—a genus of diptera, or two-winged insects, that has been extremely useful in genetic studies of nearly every sort. This is because of the unique collection of advantages afforded those working with the organism, which include a short generation time (so that many generations can be studied in a fairly short period of time) a high fecundity (thousands and even millions can be realistically studied in a reasonable length of time) and the extremely favorable giant polytene chromosomes in the salivary glands of the larvae, which make it possible to correlate genetic phenomena with morphological changes in the chromosomes, and follow these characters through numerous generations and experimental crosses. Also known as "fruit flies, " this genus is generally harmless, and not to be confused with the '(true fruit-flies" or tephritids, which are severe agricultural pests.

Duchenne Muscular Dystrophy—see *Muscular dsytrophy,* Duchenne type.

Dwarfism-a pathological condition of abnormally short stature. Some cases are known to be hereditary, while others result from disease or metabolic dysfunction.

Electrophoresis--a technique for separating different molecules based on their differential movement in an electric field. This differential movement is a complex function of molecule size, shape, and net electrical charge.

Embryogenesis—the process of cell growth that produces an embryo from the proper mixture of a zygote, nutrients, and time.

Expression—the process by which the blueprint contained in DNA is converted into the structures and biochemical mechanisms present and operating in a cell.

Expressivity—a term referring to the degree to which a gene is manifest in an individual. Genes for some traits (e.g., curliness of hair) may vary in the extent or severity to which they are seen in different individuals. Genes known to be manifest in different degrees in different individuals are said to show differential or variable expressivity.

Fabry disease—an X-linked (the gene is located on

the X chromosome) hereditary disease of lipid metabolism. Symptoms are a particular type of skin lesion, kidney disease (the usual cause of death) and a variety of neurological and biochemical abnormalities.

Fetoscopy--a procedure whereby the fetus is visually examined with a fiber optic instrument while still *in utero*.

Galactosemia--an inborn error of metabolism (genetic defect of an enzyme system) marked by the inability to digest galactose, a sugar produced (along with glucose) in the digestion of lactose, the common sugar in milk and dairy products. The symptoms of galactosemia are an accumulation of galactose and byproducts which leads to liver damage, cataracts, and mental retardation. Some relief can be achieved by limiting the dietary intake of milk and dairy products.

Gametes—mature male or female reproductive cells—sperm or ova. Gametes of the opposite sex, when fused, lead to the formation of a new, diploid organism.

Gamma globulin—a large protein molecule found in the blood that is very important to disease resistance. Individuals with a hereditary deficiency in the production of this molecule (gamma globulinemia) experience a decreased ability to withstand bacterial and viral infections.

Gaucher disease–an autosomal recessive defect of lipid metabolism found with higher frequency among Ashkenazic Jews of Eastern European origin and their descendants. Symptoms include enlarged spleen and liver and various neurological disorders. There are several different types, the two most common being a chronic adult form and an acute juvenile form that often leads to early death.

Gene—the portion of a DNA molecule that comprises the basic, functional hereditary unit; a sequence of DNA that produces a specific product. The fruit fly, *Drosophila melanogaster* probably has about 10,000 genes, whereas man may have as many as 100,000 genes.

Gene modification—a process of genetic therapy in which genes are altered in the living organism. It is not yet possible, but is expected in the future.

Gene supplementation—a technique of genetic therapy in which "new" or repaired genes are introduced into a cell by microinjection or a similar process.

Gene surgery—a procedure whereby a defective gene is excised and removed from a cell. A normal gene may be substituted.

Gene transplantation—a technique of moving an entire gene from one organism into another.

Genetic marker-any character that acts as a signpost or signal of the presence or location of a gene, chromosome, or hereditary characteristic in an individual, a population, chromosome or a DNA molecule. For example, the phenotype of male sex is a reliable indicator of the presence of the gene for H-Y antigen, a cell surface protein found in all genotypic males.

Genome—the total genetic information contained in an organism's genes. Also described as the total content of all the chromosomes in an organism.

Genotype—the total of the genetic information contained in the chromosomes of an organism. Compare to the phenotype, or external or morphological appearance of an organism. For example, an individual may have a heterozygous genotype for eye color consisting of an allele for brown eyes (which is dominant) and an allele for blue eyes (which is recessive) or a homozygous genotype, with two alleles (both dominant) for brown eyes. In either case, the phenotype is the same: brown eyes.

Germ line—also known as "germinal tissue, " it is the tissue or cell lineage that produces gametes and is used for reproductive purposes, as opposed to that tissue or those cell lineages (somatic tissue, or soma) producing the bodily structures and tissues used for functions other than reproduction.

Globin–a class of proteins most often associated with processes of oxygen or gas transport (e.g., hemoglobin or myoglobin).

Hemochromatosis—a pathological condition characterized by abnormal deposits of iron throughout the body; signs and symptoms include defects of the liver, glucose metabolism, and heart function.

Hemoglobin—a complex molecule that serves as the primary oxygen transport vehicle in vertebrates. It is composed of a single iron molecule surrounded by four globin molecules, two each of two different types (two alpha globins and two beta globins in normal adult humans).

Hemoglobinopathies—a collection of different, hereditary disorders of hemoglobin structure and/or function (e.g., thalassemia, sickle cell anemia).

Hemophilia–a hereditary disease distinguished by an abnormally long blood coagulation time. The important genes are recessive, and are found on the X-chromosome, making it X-linked; this means that it is most often seen in males, and most often transmitted to offspring by asymptomatic females.

Heterozygous--each normal cell in the body carries two copies of any given gene; if these two copies (alleles) are different one from another, or alternate forms of the same gene (e.g., blue v. brown eyes), then the individual is said to be heterozygous at that

locus. If they are identical, the individual is homozygous.

Homozygous--each normal cell in the body carries two copies of any given gene; if these two copies (alleles) are identical to each other (e.g., both coding for brown eyes) then the individual is said to be homozygous at that locus.

Huntington disease—''Huntington chorea"--a genetic disease that is not manifest until after birth (usually between the ages of 30 and 50) resulting in death due to progressive degeneration of specific brain tissues. The primary signs and symptoms are disorders of movement and dementia.

Hydrocephaly—a developmental defect marked by an unusual accumulation of spinal fluid in the ventricles of the brain. The malformation caused by this fluid buildup usually retards brain development, often resulting in mental retardation and, in severe cases, early death. The condition can now be treated if diagnosed soon after birth.

Hydroxyurea--an experimental drug used to promote expression of hemoglobin F genes (to replace defective Beta globin genes) in patients with thalassemia or sickle cell disease.

Hypercholesterolemia (familial)—a pathological condition of excess blood cholesterol that is inherited as an autosomal dominant trait,

Hyponatremia—a condition of low sodium concentrations in the blood.

Immune deficiencies—any of a number of conditions (e.g., adenosine deaminase deficiency, purine nucleoside phosphorylase deficiency, or AIDS) resulting from a failure or malfunction of the bodily defense mechanisms, or immune system.

Immunoglobins—a collection of complex protein molecules that play a vital role in the body's immune system.

Implantation—the process by which the fertilized egg (zygote) becomes attached to the wall of the uterus (endometrium) which then serves to nourish the embryo through growth and subsequent development.

in *utero* (in uterus) preferring to procedures that are performed or events that take place within the uterus .

in *vitro* (in glass) —meaning in the laboratory; in the test tube.

in vivo (in life) —meaning in the living, intact organism.

Klinefelter's syndrome—a chromosomal abnormality in human males. In contrast to the usual complement of sex chromosomes, one X and one Y (XY), Klinefelter males usually have two X's and one Y (XXY), although some have multiple Y's or more than two X's. Clinical symptoms are abnormal height, gonadal dysfunction (testicular atrophy; sterility), below average intelligence, and possibly some behavioral abnormalities (although this is still disputed by some).

Lesch-Nyhan syndrome-an X-linked recessive disorder characterised by compulsive self mutilation and other mental and behavioral symptoms. It is caused by a defect in the gene that produces a particular enzyme (hypoxanthine-guanine phosphoribosyl transferase) important in metabolism. In the absence of this enzyme large amounts of uric acid accumulate in the blood, leading to gout. The causal relationship to the behavioral disorder is not yet understood.

Linkage—the association, in inheritance, of different genes due to their physical proximity on chromosomes.

Lipid metabolism–the process by which lipid (fatty) molecules are broken down or synthesised in the body.

Liposome—a structure with a lipid membrane like that of a cell that can be filled with specific substances and then used as a delivery vehicle to transport those substances to the interior of a target cell by fusion with the cell's own membrane. It is one of several potential delivery vehicles for use in gene therapy.

Lysosomal storage diseases—lysosomes are intracellular organelles that contain enzymes capable of digesting proteins and some carbohydrates. Lysosomal storage diseases result from an accumulation of certain of these molecules caused by an insufficiency of a lysosomal enzyme. The symptoms and prognosis vary with the specific enzyme involved.

Marfan syndrome—arachnodacytly ("spider fingeredness")--a single gene defect of which the symptoms are abnormally long fingers and toes, abnormalities of the eye lenses and heart. (Abraham Lincoln is thought by some to have suffered from this disease).

Membrane fusion—a process by which the membranes (outer walls) of two cells merge, thus creating one daughter cell from two parents. In contrast to fertilization by gametes, membrane fusion describes the joining of somatic cells. One of the most productive results of membrane fusion technologies is the formation of hybridomas, wherein an antibody-producing white blood cell (leucocyte) is fused with a tumor cell to produce a daughter cell that can generate very large amounts of a specific antibody for use in diagnostic and therapeutic procedures (monoclinal antibodies).

Mendelian-–referring to a trait that is controlled by a single gene, and which therefore shows a simple pattern of inheritance (dominant or recessive). So

named because traits of this sort were first recognized by Gregor Mendel, the Austrian monk whose early researches laid the basis for modern genetics.

Messenger RNA (mRNA)—a ribonucleic acid molecule produced by transcribing a nucleotide base sequence from DNA into a complementary sequence of RNA. Messenger RNA molecules carry the instructions for assembling enzymes (protein molecules) from the chromosomes in the nucleus to the synthetic apparatus (ribosomes) in the cytoplasm, or cellular tissue outside the nucleus.

Metachromatic leukodystrophy (MLD)—several closely related disorders characterized by a degeneration of the protective sheath surrounding nerve cells (myelin) and an accumulation of certain metabolic compounds as a result of insufficient activity of the enzyme aryl sulfatase. Death is the result of progressive central nervous system degeneration accompanied by abnormalities of the peripheral nerves, kidney, and liver.

Metallothionein—a protein that binds metal ions. The promoter sequence that controls the production of metallothionein has been spliced to other genes and used to control their expression after gene transfer, as in, for example, the rat growth hormone transplanted into mice, resulting in "mighty" mice of larger than normal size.

Microinjection—the technique of introducing very small amounts of material (DNA or RNA molecules; enzymes; cytotoxic agents) into an intact cell through a microscopic needle penetrating the cell membrane.

Morula—the solid mass of cells resembling a mulberry ("morula" in Latin) formed by the cleavage of a zygote; the stage before blastocyst.

Mucopolysaccharidoses--a group of heritable diseases marked by defects in the metabolism of a class of molecule, the glycosaminoglycans (formerly called mucopolysaccharides). Symptoms usually include mental retardation (usually severe) and various skeletal abnormalities all accompanied by abnormal deposition of mucopolysaccharides in tissues or excretion in urine.

Muscular dystrophy (Duchenne type)—an X-linked recessive defect (therefore most affected individuals are male) of muscle metabolism that usually causes death by the age of twenty.

Multigenic disorder—(polygenic disorder)—a genetic defect resulting from the interaction of alleles of more than one gene. Although such disorders are heritable they depend on the simultaneous presence of several alleles and therefore the hereditary patterns are usually much more complicated than for simple, single-gene (Mendelian) traits, making prediction and diagnosis much more difficult.

Mutagen--any substance that can cause changes in the structure of hereditary nucleic acids (DNA, RNA) or the way the information they contain is transmitted to offspring.

Myopia (nearsightedness)--a defect in vision such that objects can be accurately resolved only when they are unusually close to the eyes. An autosomal dominant form is known, but many (perhaps most) cases are either non-Mendelian or complex in their mode of inheritance (i.e., polygenic, or involving variable expressivity or incomplete penetrance).

Neural tube defect-the neural tube is formed by the fusion of the neural folds, which are ridges of tissue that arise on either side of the primitive streak. The brain and spinal cord develop from the neural tube, and neural tube defects are any that affect their formation or development. Most such defects are developmental in origin; that is, though genetic factors may be involved these defects are more likely to be polygenic or complex rather than single gene, Mendelian traits.

Oligonucleotide–nucleic acid molecules formed by the joining of a small number of nucleotide bases (generally fewer than 10 or 20). A short sequence of DNA or RNA.

Oncogene--a gene of which one or more mutant forms is associated with cancer formation.

Ornithine carbamoyl transferase deficiency—(transcarbamylase deficiency)–an X-linked defect associated with a specific enzyme deficiency in the nitrogen cycle (transcarbamylase). Symptoms include chronic ammonia intoxication, mental deterioration, and liver failure.

Papilloma virus (Shope)—a DNA virus found in rabbits that is associated with elevated arginase activity levels in epithelial cells. (See argininemia).

Penetrance--refers to the frequency with which the effects of a gene (whether dominant or recessive) known to be present are seen in the individuals carrying it.

Peptide—a class of compounds formed by joining amino acids together by a chemical process that produces one molecule of water for each joining of one amino acid to another. Peptides are intermediate in size between amino acids and proteins.

Phage–see "bacteriophage."

Phenylketonuria (PKU)—an inborn error of metabolism, or genetic disease, caused by the inability to metabolize phenylalanine to tyrosine. The resulting accumulation of phenylalanine and derived products causes mental retardation. The disease is due to a defective enzyme (phenylalanine hydroxylase), and the symptoms can be treated and the condition ameliorated with a diet that eliminates phenylalanine. The disease can be diagnosed at birth by a sim-

ple test that detects the characteristic elevated levels of phenylpyruvic acid (a phenylalanine derivative) in the urine.

Plasmid—a circular piece of DNA found in the cytoplasm, outside the nucleus. Replication and segregation of plasmids to daughter cells is independent of the chromosomes, and plasmid transmission from parent to offspring is almost exclusively matrilineal (from mother to offspring), because while plasmids are common in ova they are generally absent from that portion of the sperm that fuses with the ovum to form a zygote.

PNP deficiency—an autosomal recessive disorder of immunity caused by deficiency of the enzyme purine nucleoside phosphorylase.

Polycystic kidney disease—a hereditary disease (single gene dominant) in which a progressive deterioration of kidney function is associated with the development of large numbers of cysts.

Polygenic—referring to a trait or characteristic that is controlled not by one gene but rather by two or more acting in concert.

Polymerization—the process of joining molecular subunits (e.g., nucleotide base pairs) together in sequence to form a larger molecule (e.g., a polynucleotide). primitive streak—the first visible sign of differentiation **in the developing embryo. It is a darkened longitudinal stripe that forms at the caudal (tailward) end of the embryo, and is composed of a layer of ectodermal cells (which develop into skin and nervous tissue) and it marks the future location of the longitudinal exis of the embryo.**

probes—molecules that make it possible to seek out and identify specific cellular features (see DNA probes).

Promoter—a region of a DNA molecule found in front of a gene (as the DNA molecule is "read" by the proper enzymes) that controls the expression of the gene.

Protoplasm (first formed)—a single cell or a mass of protoplasm (the substance of which cells are formed). The term usually refers to a bacterial cell or to an individual plant cell from which the cell wall has been removed preparatory to cell-fusion experiments.

Pyridoxine responsive hemocystinuria—a condition of excess cystine in the blood that can be treated with the drug pyridoxine.

Recessive—(contrast with *Dominant)* referring to an allele of a gene that will not be seen in the phenotype of the organism carrying it unless it is present in two copies (i.e., on both chromosomes), or homozygous. If present in only one copy, or heterozygous, its presence will be masked. (See *Carrier). X-***linked traits generally act as if they were recessive in females and dominant in males.**

Recombinant DNA (rDNA)—referring to DNA molecules that have been assembled with the use of restriction enzymes, usually (but not always) by splicing together fragments from different species.

Restriction enzyme—an enzyme that has the ability to recognize a specific nucleotide sequence in a nucleic acid (ranging from four to twelve base pairs in length) and cut, or cleave, the nucleic acid at the point. So called because, occurring naturally in bacteria, they recognize foreign nucleic acid (e.g. the DNA of a bacterial virus as it begins to infect and destroy its host) and destroy it, thus restricting the ability of the virus to prey upon certain potential host strains. Over four hundred different restriction enzymes are known, recognizing a great variety of different nucleotide base sequences. This has made possible the cutting and splicing together of nucleic acid within and between different organisms and species.

Ribosome—a cellular organelle which is the site of messenger RNA translation, the process of reading the instructions in an mRNA molecule and using them as the guide to constructing the specified protein. Ribosomes are composed of both RNA and protein, and they spontaneously assemble from the necessary constituents present in the cell.

RNA (Ribonucleic acid)—a polynucleotide consisting of a backbone of alternating phosphate and sugar (ribose) molecules to which are attached the nucleotide bases adenine (A), thymine (T), guanine (G) and uracil (U, which replaces the cytosine, C, of DNA). There are several classes of RNA that serve different purposes, including messenger RNA (mRNA), transfer RNA (tRNA), and ribosomal RNA (rRNA). (See Technical Notes.)

Sickle cell disease (anemia)—a hereditary hemoglobinopathy caused by the presence of a defective beta hemoglobin chain. Patients with sickle cell disease have red blood cells that tend to deform into a sickle-like shape when the abnormal hemoglobin crystallizes. The specific defect is caused by an abnormal gene resulting in the replacement of the usual amino acid, glutamic acid, with valine, in the sixth amino acid position in the beta-hemoglobin molecule. This alters the resulting beta globin molecule in such a way as to increase its propensity to crystallize, thus rupturing the red blood cell and causing the cells to lodge in small blood vessels.

Sickle cell trait—refers to a person who is heterozygous for the gene producing the abnormal form of the beta hemoglobin chain. People carrying the sickle cell gene in heterozygous form (carriers) are

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usually asymptomatic, and thus not afflicted by the disease. Under some conditions of extreme exertion that reduce the concentration of oxygen in the blood a small amount of sickling of red blood cells may be detected, but usually not enough to bring on any of the pathological conditions of the disease. The mutation is found with high frequency in some populations subject to malarial infections, such as African blacks. The defective gene is thought to be maintained in the population because it confers increased resistance to malaria upon heterozygotes.

Single gene disorder (Mendelian disorder)--a genetic disease caused by a single gene that shows a simple pattern of inheritance (e.g., dominant or recessive, autosomal, or X-linked).

Somatic—referring to body tissues apart from reproductive (germinal) tissues.

Tay-Sachs disease—an autosomal recessive genetic defect resulting in developmental retardation, paralysis, dementia, and blindness followed by death, usually before the end of the third year of life. The defective gene codes for hexosaminidase A, an enzyme that degrades certain chemicals in the brain. Symptoms are caused by an accumulation of cerebral gangliosides, fatty acid, and sugar molecules found in the brain and nervous tissue. The gene is found in highest frequency among Ashkenazic Jews of Eastern European origin.

Tetramer--a complex molecule consisting of four major portions (moieties) joined together in some reversible, non-structural manner (e.g., hemoglobin, in which two alpha chains and two beta chains are joined by electromagnetic attractions).

Thalassemia--any of several heritable hemoglobinopathies resulting from defective genes causing deletions or other alterations of different hemoglobin molecules.

Transcription—the process by which a complementary messenger RNA (mRNA) molecule is formed from a single stranded DNA template. The result of the process is that the information contained in DNA is transferred to mRNA which is then used as a template to direct the construction of protein molecules that function in cellular metabolism.

Transferrin—a protein molecule that carries iron in blood plasma. A number of different, genetically coded molecules are known.

tRNA (transfer RNA)--specialized RNA molecules that function to bring specific amino acids from the cellular environment to ribosomes that are translating mRNA into proteins (constructing proteins according to the information encoded in the parent DNA template from which the mRNA was copied).

Translation—the process of decoding the information in an mRNA molecule and using it to direct the construction of protein molecules specified in the messenger RNA.

Transposable elements—a class of DNA molecules capable of insertion into the chromosomes of the host organism at any or several of numerous positions, and of moving from one position to another. Speculation on the origin of these molecules suggests that they may be derived from virus-like ancestors. They have been called "parasitic" DNA.

Ultrasound—high frequency sound waves that can be focused and used to picture tissues, organs, structures, or tumors within the body. Ultrasound is particularly useful for in *utero* examinations of the fetus. It is often used to locate the fetus and the placenta prior to such procedures as amniocentesis or chorionic villus biopsy.

Urea-cycle defects—the urea cycle is the metabolic pathway in the body that moves nitrogen from one source to another, and takes it out of and puts it into the body chemistry when and where needed. Each different step is mediated by one or more enzymes, all of which are genetically controlled and which can, under the influence of abnormal genes, lead to different genetic diseases (inborn errors of metabolism) that are collectively known as urea-cycle defects.

Wernicke-Korsakoff encephalopathy—a genetic disease (probably autosomal recessive) of oxalate metabolism caused by a defective transketolase enzyme. It seems to become clinically important only when the diet is deficient in thiamine, can be exacerbated by alcohol and treated with vitamin B 1 supplements.

Wilson disease--an autosomal recessive disease of copper metabolism in which various abnormalities of the liver are accompanied by different neurological symptoms.

X-linked—referring to traits found on the X chromosome. X-linked recessive traits are seen far more often in males, who have only one X chromosome, than in females, who have two.

Zygote—a fertilised egg; a product of the fusion of sperm and egg.