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Genes . . . The Nature of Human Development

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INTRODUCTION

"Where Mid I come from?" is not a question one hears very often today. With all the television coverage on childbirth and the emphasis on sex education, hardly a school age child is unaware of the facts. The baby is carried by the mother in her "stomach" (not delivered by the stork!). The questions that could be asked, however, are " *What* did I come from? and "How did I develop?". The answers here may be less than enlightened and knowledgeable.

This curriculum unit is designed to provide, in part, at least, some insights of the role of genes in the developing human. It is for those students who have had a basic introduction to genetics and a fair amount of information about the male and female reproductive systems. The data contained here is for students in courses of Health, Human Physiology and Human Biology and others who may wish to increase their knowledge about the factors, particularly genetic, that influence the development of a human.

The unit will present first a review of the process of gametogenesis, the preparation of egg and sperm. It is important to know how during meiosis the genes can be separated, scrambled and perhaps become disordered and finally passed on in the egg or sperm. A new view of meiosis is shown in oogenesis.

Having established the "What and How" of the genes, the next step will be to discuss the chemical nature and arrangement of the DNA that makes up the genes.

Then two basic and general types of patterns of inheritance involving autosomal and X-linked genes will be presented.

With a background then of the mechanism by which genes are sorted, made up and paired up, the student will explore some of the disorders and defects that can occur when nature's plan becomes imperfect.

It would be most despairing however, to conclude on such a note. Therefore, methods of prevention (prenatal screening) and treatment for the disorders will be noted.

Objectives for lessons, activities for each part as well as review and test items will be included. It is hoped that this presentation will provide a good basis for sound and informed choices that students may elect in the future.

With new advances in technology, a pregnancy may not be a question of doing what comes naturally. Nature may receive an assist in the way of amniocentesis and ultrasound and karyotyping and more. These procedures may require some heavy decision-making.

I. GAMETOGENESIS

Objectives **:**

A. Detail orally and in writing, the process of oogenesis noting the fate of the chromosomes.
B. Detail orally and in writing, the process of spermatogenesis noting the fate of the chromosomes.
C. Compare these two processes and cite their importance in human development.

Approximate time: one week.

The story of human development begins long before egg and sperm unite in fertilization. The earliest form of these gametes is seen in the primordial germ cells of the early embryo. These primordial cells grow by a series of mitoses to form oogonia in the fetal ovaries and spermatogonia in the fetal seminiferous tubules. The oogonial cells and the spermatogonial cells, which are the precursors of the egg and sperm, however, follow different paths of maturation.

The oogonia continue to divide by mitosis to produce more oogonia or begin to divide by meiosis and undergo the first meiotic division to form primary oocytes. (see Figure 1 Oogenesis). During the first meiotic division the full set of chromosomes, ^{46}, called diploid (2N) pair up or synapse as matching pairs or homologues and align themselves gene by gene. While the chromosomes are paired up they undergo crossing over whereby parts are exchanged between the chromatids (a half chromosome) that results in genes changing from one homologous chromosome to the other. The chromosomes at this stage are a tetrad, a four-stranded structure connected by an X-shaped chiasmata. This is prophase I.

OOGENESIS
(figure available in print form)
Figure 1 (NOTE: The fate of only one pair of chromosomes is shown.)
By the time a female is born, the primary oocytes have progressed to this point. Some of the oogonial cells have degenerated from " . . . 6.8 million, found in the five month fetus . . . to 2 million and by puberty less than 200,000 . . . " [1] primary oocytes are present. This suspended prophase or dictyotene stage lasts for several years until puberty or beyond when ovulation occurs. Then meiotic division resumes and the first meiotic division (reduction) is completed at the time of ovulation.

When the primary oocyte completes the first meiotic division a secondary oocyte and a polar body are formed each receiving 23 chromosomes, half (haploid) (N). The second meiotic division begins and stops at

metaphase as the secondary oocyte passes down the Fallopian tube. If fertilization occurs, the second division is completed and the sperm penetrates the egg with its 23 chromosomes. The act of fertilization activates the ovum to complete meiosis and also restores the diploid number to the zygote. There is only one ovum produced and another polar body. “By this time, the first polar body might also have divided into two tiny cells.” [2]

The male spermatogonia remain in the fetal seminiferous tubules until puberty when they undergo the process of meiosis with regard to the nuclear material and chromosomes. However, the events proceed without interruption once they are started. At about 13-16 years of age, the spermatogonia (which come from the primordial germ cells) in the walls of the seminiferous tubules in the testes enter meiosis as primary spermatocytes with the diploid number (2N). (see Figure 2 Spermatogenesis). These undergo the first meiotic division to form 2 secondary spermatocytes with the haploid number (N). Each of the secondary spermatocytes forms 2 spermatids with a total of four from the original spermatocyte. The four spermatids become changed in the process of spermiogenesis where much of the cytoplasm is lost and sperm emerge with a head and tail. There are 4 functional sperm formed as compared to the production of one functional egg. Another contrasting feature is that males, as far as can be determined, continue to produce sperm for life; females cease ovulating at about 45 years of age. It is noteworthy that the long time that the primary oocyte remains in “suspended prophase,” (can be almost 40 years) may account for some of the birth defects (because of meiotic nondisjunction: i.e. failure of paired chromosomes to separate) occurring in mothers over the age of 40 or in later years of life. In addition, the fact that the sperm undergo so many DNA duplications, since millions of sperm are produced, may account for the mutants discovered in late paternal age.

SPERMATOGENESIS
(figure available in print form)
Figure 2

II. CHROMOSOMES AND GENES

Objectives:

A. Relate the structure of DNA and RNA to chromosomes and genes.
B. Make models of the structure of DNA and RNA.

Approximate time: one week.

Before proceeding further with any discussion of how development is affected by the genes on chromosomes, it might be appropriate to pause and examine the structure of the chromosome.

Chromosomes are made up of a substance called Deoxyribonucleic acid (DNA). The function of DNA is to encode genetic information that will be transcribed to Ribonucleic acid (RNA) and then on to proteins from amino acids. This DNA is a large molecule of sugar, phosphates, 2 purine bases, adenine (A) ana guanine (G), and 2 pyrimidine bases, thymine (T) and cytosine (C). In RNA uracil (U) replaces thymine and the sugar is

ribose instead of deoxyribose. The structure of DNA as proposed by Watson and Crick in 1953 suggests a ladderlike or double helix configuration. Figure 3 details a procedure for making models of DNA and RNA that can be used most effectively in the classroom. These instructions by this author were published in the *Connecticut Journal of Science Teaching,* March 1974. The base A always pairs with T and G with C. The bases are attached to the sugar molecule like the rungs of a ladder. The sugar is attached alternately with the phosphate on the sides of the "ladder". The structures of DNA and RNA can be checked in any biology textbook. Three bases constitute a codon, a unit of genetic code which determines what amino acid will be added to a nascent protein chain. For example the codon GUG (and its complementary CAC) is for valine which can be part of a protein molecule. The genes are therefore composed of codons. If the genetic material is abnormal, incorrect coding of proteins will occur; e.g. sickle cell anemia which will be discussed later.

MAKING MODELS OF DNA AND RNA

To make *Models* of DNA and RNA:

a. cut a piece of 12 mm wide Scotch tape, 15 cm long. cut another piece of the same length and attach the two pieces lengthwise making the piece of tape about 2.5 cm wide and 15 cm long. If Scotch tape 2.5 cm wide is available, omit this step.

Tack one end of the tape down so you will be able to attach the following parts.

b. The following color scheme will be used to represent the different parts of DNA and RNA: yellow=deoxyribose sugar; white= phosphate; blue=adenine; red=thymine; green=guanine; orange = cytosine; red with dots= uracil; yellow with dots = ribose. Color strips of paper will be used.

c. Make the outer edges alike by attaching vertically on the tape, alternating strips, no more than 12 mm long of yellow and white on both of the outer edges. Check text for the appropriate arrangement.

d. Attach as the rungs of the ladder the appropriate pairs of chemical bases for DNA and RNA. Check text for the appropriate combinations and attachment of these pairs. Note: pieces of 6 mm should be sufficient.

e. When all the parts have been attached, cover the entire strip with another strip of tape to make a cover of 2.5 cn. Note: see Rig. below. This strip may now be twisted to form the double helix or creased down the middle.

f. Attach the entire model to a piece of white paper. Title DNA and RNA and explain the color scheme at the bottom of the paper.

(figure available in print form)

Figure 3

The full complement of human chromosomes is 46. Many genes for inherited traits have been "mapped" to one or another of them. Figure 4 Human Chromosomes exhibits the 23 types (with matching halves) of chromosomes. Some of the location for genes has been noted. Also the 23 chromosomes have a long arm (q) and a short arm (p) and can be classified in three groups based on the location of the centromere (constriction): metacentric with the centromere central; submetacentric with the centromere off center; and acrocentric with the centromere near one end.

III. INHERITANCE PATTERNS: AUTOSOMAL AND X-LINKED

Objectives **:**

A. Describe and illustrate autosomal inheritance.
B. Describe and illustrate X-linked inheritance.
C. Define and illustrate co-dominance, dominant, recessive, phenotype and genotype.
D. Use Punnett square to determine offspring from a variety of matings.

Approximate time: one week.

Just how the information coded in chromosomes is passed on to dictate the traits to appear in a new human is the subject matter of heredity.

Two patterns of inheritance can be described: *autosomal inheritance* , the traits associated with the twenty-two chromosomes other than the sex chromosomes, and *X-linked inheritance* , the traits associated with the X chromosome.

Several terms that are used to describe genes and chromosomes are as follows. The corresponding forms of a gene pair are called a *alleles* ; i.e. the gene for tasting PTC (phenylthiocarbamide (T) and the gene for non-tasters (t). For some characteristics there can be multiple alleles or factors. *Genotype* refers to the genetic composition of the organism or cell; i.e. Tt or tt. *Phenotype* refers to what is actually seen; i.e. taster or non-taster. A *homozygous* genotype is one in which the two alleles are the same; i.e. TT or tt; *heterozygous* is one in which the two alleles are different; i.e. Tt.

HUMAN CHROMOSOMES

(figure available in print form)

Figure 4

AUTOSOMAL INHERITANCE

(figure available in print form)

Figure 5

Genes are present on chromosomes in the nucleus. Chromosomes are paired just as the alleles are paired. The two members of a pair of chromosomes are known as *homologues* . The two alleles of the same gene are found on a particular spot or *locus* (location) on the chromosome; i.e. in a heterozygote (Tt) the allele T is found on a particular locus on a particular chromosome; at a corresponding locus on the homologous chromosome is found its allele for non-taster.

In regard to traits or characteristics such as tasting, the pattern of inheritance falls into two main categories. Those traits or genes for them that are fully or almost fully expressed, phenotypically that is, are known as *dominant* ; i.e. taster (T). The dominant gene has the same expression in the heterozygous or homozygous state. Those genes carried on the autosomal chromosomes are classed with autosomal dominant inheritance.

Criteria for Autosomal Dominant Inheritance

1. The trait is transmitted by an affected person to half his children on the average, though in an individual family wide discrepancy from the 1:1 ratio may be seen.
2. The trait appears in every generation, with no skipping.
3. Unaffected persons do not transmit the trait to their children.
4. The occurrence and transmission of the trait are not influenced by sex; i.e. males and females are likely to have the trait and equally likely to transmit it. [3]

A trait that is transmitted as autosomal *recessive* is expressed only in persons who have the gene in a homozygous state; i.e. non-taster (tt).

Criteria for Autosomal Recessive Inheritance

1. The trait characteristically appears only in sibs, not in their parents, offspring or other relatives.
2. On the average, one-fourth of the sibs of the propositus are affected; in other words, the recurrence risk is one in four for each birth.
3. The parents of the affected child may be consanguineous.
4. Males and females are equally likely to be affected. [4]

Figure 5 illustrates the transmission of the gene for PTC tasting in the dominant and recessive conditions.

So far the discussion has concerned only the genes that are expressed as fully dominant or fully recessive. When both alleles are fully expressed in the heterozygote the genes are said to be *co-dominant* . Such an example is shown in the blood groups. A person of blood group AB has both A and B antigens on his red cells.

The allelic genes A and B are therefore co-dominant. There are more than two alternative alleles in blood groups. Another allele exists for persons with type O blood and the gene 0 is recessive to genes A and B. This means that type 0 blood has a genotype of OO, type A blood is AA or AO, Type B can be BB or BO and type AB is AB. Figure 6 shows the possible combinations resulting from the mating of blood types. This information can sometimes be used to exclude paternity.

Genes on the X-chromosome are classed as *X-linked* and genes on the Y chromosome as Y-linked. There is only one suggested trait, “hairy ears”, linked to the Y chromosome; it is found in adult males in India, Ceylon, Israel and aboriginal Australia. For practical purposes only the X-linked genes have any significance in expression.

Classical Hemophilia or Hemophilia A is an X-linked recessive, in which blood fails to clot normally because of an abnormality in the anti-hemophilic globulin or loss of factor VIII. A person with this disease shows a secondary severe arthritic condition as a result of bleeding into the joints. It occurs about 1 in 10,000 male births. The classic case is described among the descendants of Queen Victoria who was a carrier. There are many possibilities in the matings of persons with various genotypes. Two such matings are described in Figure 7. Other matings can be worked out and described in the classroom with a similar chart. It is interesting to note there is another form of hemophilia called Christmas disease or Hemophilia B that is controlled by another gene on the X-chromosome; in Hemophilia B there is a lack of factor IX in blood clotting.

Criteria for X-linked recessive inheritance

1. The incidence of the trait is much higher in males than in females.
2. The trait is passed from an affected man through all his daughters to half their sons.
3. The trait is never transmitted directly from father to son.
4. The trait may be transmitted through a series of carrier females, if so, the affected males in a kindred are related to one another through females. [5]

BLOOD GROUPS ABO
(figure available in print form)
Figure 6
X-LINKED INHERITANCE
(figure available in print form)
Figure 7

There are a few X-linked genes that are expressed as dominant; for example Vitamin D resistant rickets.

Criteria for X-linked Dominant Inheritance

1. Affected males have no normal daughters and no affected sons.
2. Affected females who are heterozygous transmit the condition to half their children of either sex. Affected females who are homozygous transmit the trait to all their children. Transmission by

females follows the same pattern as an autosomal dominant. In other words, X-linked dominant inheritance cannot be distinguished from autosomal dominant inheritance by the progeny of affected males.
3. Affected females are more common than affected males (twice as common if the disorder is rare. [6]

These are some general types of inheritance. There are other traits and disorders that can be caused by many factors known or unknown; diabetes is an example as well as spina bifida or anencephaly. How intelligence is affected by genetic factors and how it is affected by environmental influences is an age old debate. Certainly there are cases of mental retardation that can be traced back to genetic causes (as will be discussed later) but when one speaks about intelligence in general it has been stated " . . . intelligence is a complex phenotype that develops under the influence of genes and the experiences of a lifetime." [6]

One tool used by geneticists to study the inheritance of traits or characteristics is what is known as the pedigree chart in which family data can be summarized. This consists of designated symbols with connecting lines to show the transmission of traits. Examples of such charts are available in many biology textbooks and can be used to trace family traits with students in the classroom.

Table I summarizes some of the inherited human characteristics and the patterns of inheritance. Crosses of matings showing these traits can be worked out in the classroom using a chart similar to the one used to illustrate autosomal inheritance and X-linked inheritance etc. (see Appendix 1).

TABLE I SOME HUMAN INHERITED CHARACTERISTICS

Autosomal	
DOMINANT	*recessive*
1. Black hair	all other colors
2. Curly hair	straight
3. Normal skin color	albinism
4. Tongue curling	lack of ability to curl tongue
5. Cleft palate (rare type)	normal palate
6. Astigmatism	normal vision
7. Brown eyes	blue eyes
8. Free ear lobes	attached ear lobes
9. Taster PTC	non-taster
10. Blood types A,B	Type 0 (co-dominance)
X-linked	
Vitamin D resistant rickets	Hemophilia Color-blindness

Sex-limited
Baldness in males Baldness in females
Multi-factorial

Diabetes

Spina bifida

Anencephaly

IV. COMMON DISORDERS AND BIRTH DEFECTS

Objectives : A. Discuss the genetics and occurrence of some common disorders: Huntington Chorea, neurofibromatosis, sickle cell anemia, Thalassemia, PKU, Tay-Sachs, Cystic Fibrosis, Down syndrome, Klinefelter syndrome, Turner syndrome, Cat-cry syndrome, retinoblastoma, Leukemia and the Philadelphia chromosome.

Approximate time: one week.

With the foregoing background information dealing with the genetic factors and patterns of inheritance, one can look at some of the disorders and birth defects that occur as a result of unusual or abnormal behavior of chromosomes or genes.

“Many genetic traits are determined by genes at a single locus, in either homozygous or heterozygous state. There are 2786 such conditions, most of which are abnormalities rather than normal variants; catalogued in a most useful reference: *Mendelian Inheritance in Man* by V.A. McKusick (5th ed., 1978). This is an appreciable amount of the estimated 30,000 human structural genes. Of the total, 1473 are autosomal dominant, 1108 are autosomal recessive and 205 X-linked.” [8]

Huntington Chorea described by Huntington in 1872 in Americans of English descent, is caused by an autosomal dominant gene. The disease is characterized by chorea (spasmodic movements and incoordination) and progressive mental deterioration. It occurs in 1 in 25,000 and can occur between 15-65 years of age. Anyone who is heterozygous will develop the disease if they live long enough.

Since carriers of the allele may reproduce before the allele reveals itself, their children live with the knowledge that they too may some day be stricken. This may be the situation with the children and grandchildren of the folk singer and composer Woodie Guthrie, who died of Huntington disease in 1967, as had his mother in 1930. However, the older the persons at risk become without showing the symptoms, the less likely they are to possess the gene.

Neurofibromatosis can be traced to an autosomal dominant gene. It is characterized by “ . . . multiple fibrous tumors of the skin and nervous tissue; scattered areas of brownish pigment in skin (known as cafe-au-lait spots). Biochemical defect unknown.” [9]

Several blood disorders, in addition to Hemophilia previously cited, are commonly found. Sickle cell anemia and beta-Thalassemia (Mediterranean anemia; Cooley anemia) are two such diseases. Both of these diseases

are described in connection with hemoglobin defects and with certain ethnic groups of people.

Before proceeding with each of these blood disorders, a brief description of the structure and function of hemoglobin seems necessary. Hemoglobin is found in red blood cells and has the ability to combine with oxygen and transport it throughout the body. It is a molecule of 4 subunits; each has two parts-a polypeptide chain, globin, and a heme group which is an iron-containing pigment. The heme portion is the same in all hemoglobins but the globin portion is affected by genetic variation. There are two different types of polypeptide chains; in normal adult hemoglobin (HbA) these chains are designated as alpha a and beta b. The four chains are folded and each is attached to the heme portion. The alpha chain has 141 amino acids and the beta chain has 146 amino acids. Two separate genes code for the alpha and beta chains. Other genes code for the heme portion.

Looking at sickle cell anemia, the cause appears to be a mutant gene that substitutes the amino acid valine for glutamic acid in the sixth position of the beta chain. The valine distorts the shape of the molecules so that they tend to stack into narrow crystals thereby changing the shape of the red cells to form the sickling phenomenon. This happens only in venous blood after oxygen is lost to the capillaries. When re-oxygenated in the lungs, the sickled cells return to their normal rounded shape.

Because of this irregular shape of red blood cells, blood flow is impeded which lengthens the time of return to the lungs and increases sickling. This slows the blood even further and the cells are irreversibly distorted and have a life span of only a few weeks rather than the normal three months. Also, sickled cells block small vessels anywhere in the body reducing oxygen, causing tissue damage and painful crises. Death can result from damage to a vital organ.

The disease can be treated in that pain can be relieved, the frequency and duration of crises can be lessened by rest, and transfusions and drugs and antibiotics can be administered. Sickle cell anemia can be diagnosed with a blood test.

The disorder occurs predominantly in African blacks and American blacks with a frequency of about 1 in 500. The heterozygous state, known as sickle cell trait, is present in approximately 8% American blacks. Sickle cell trait is not a disease and causes no health problems. The sickle cell disease results from the homozygous state (recessive) of the mutant gene. Persons who are heterozygous for sickle cell are protected against malaria. Figure 8 illustrates some of the possibilities resulting from two types of matings. Other matings can be demonstrated in the classroom using a similar chart (see Appendix 1).

In the Thalassemias, the amino acid sequence of hemoglobin chains are normal, but their rate of synthesis is not. In alpha (a) Thalassemia, the alpha polypeptide is either absent or produced in much reduced quantity. Hemoglobin is produced by other chains during embryonic life or out of four beta chains later in fetal life; but these chains are not suitable as oxygen carriers. When alpha chain synthesis is totally suppressed, death occurs in utero with miscarriage late in pregnancy.

The beta (b) Thalassemias account for 100,000 childhood deaths per year. The disease state is known as Cooley or Mediterranean anemia. The synthesis of beta chains is very much reduced. Homozygotes with beta Thalassemia major (Cooley anemia) often die before age 10; heterozygotes who have Thalassemia minor usually have only a mild anemia. The alpha chains lacking a beta partner precipitate inside the red blood cells and shorten their life span.

The nature of the mutations responsible for the Thalassemia syndromes is complex and only partially

understood. Some are simple deletions of the Hb or Hb ; others appear to be mutations of nearby control genes. The Thalassemias occur in Canada and United States, Mediterranean, Middle East and parts of Africa. Like sickle cell, the heterozygote is resistant to malaria.

Three other disorders that are produced as autosomal recessives are PKU (phenylketonuria), Tay-Sachs and Cystic Fibrosis.

In PKU, "The metabolic defect is an inability to convert the amino acid phenylalanine to tyrosine, owing to the absence of a liver enzyme called phenylalanine hydrogen; ase." [10] Some of the phenylalanine is converted to phenylpyruvic acid which is changed to several other compounds. Since there is a deficiency of tyrosine so too is its derivative pigment melanin deficient and people tend to be fair-skinned with blond hair and blue eyes.

SICKLE CELL ANEMIA
(figure available in print form)
Figure 8
Infants show motor and mental retardation when untreated. Babies are hyperactive but uncoordinated and have nervous system disorders. Dietary restrictions of phenylalanine and providing a protein substitute are used in treating the disorder. The child can eat almost all fruits and vegetables. Infants must be identified in the first few weeks of life and probably must continue the diet throughout their lives in some way or other.

Pregnant women with PKU, who have high levels of serum phenylalanine as adults but were treated as children may produce children of their own with brain damage even though the children are heterozygous. Their brains can be harmed by the high phenylalanine during fetal life. These mothers should go back on a more restricted diet during pregnancy.

Tay-Sachs is caused by a missing hexosaminidase enzyme (Hex A) that assists in the synthesis of a ganglioside, a lipid-sugar molecule in the brain.

The disorder is common among the Ashkenazi Jews from Eastern and Central Europe. Among American and Canadian Jews the occurrence is 1 in 4000, in non-Jews 1 in 550,000. One in 30 Jews is heterozygous, 1 in 300-400 non-Jews.

The disease is recognized about four months of age. Affected children become blind and regress mentally and physically with enlargement of the head. A "cherry-red" spot in the fundus of the eye is a striking diagnostic sign. The disease is usually fatal in early childhood.

"The most frequent autosomal recessive disorder in white (Caucasian) children is cystic fibrosis a condition in which there are abnormalities of several exocrine secretions, including pancreatic and duodenal enzymes, sweat chlorides and bronchial secretions." [11] The Tel-Med tape listed in the bibliography describes the incidence in the United States and symptoms and treatment.

Males are infertile as a secondary consequence of abnormal mucous secretion in the vas deferens. Loss of salt in sweat can cause heat prostration. In whites it affects 1 in 2000 births; about 1 in 22 is a heterozygous carrier. The disease is much less common in Orientals.

Down syndrome can usually be diagnosed at birth or shortly thereafter by its phenotypic features. The eyes may be close set with narrow slanting eyelids. Also, all parts of the body are shortened. Defects of major organs are common and moderate retardation is present. Almost all cases are recognized within a few weeks

of birth. The risk of having a Down syndrome child appears to increase with the mother's age.

Sex chromosome abnormalities include Klinefelter syndrome and Turner syndrome. Klinefelter syndrome produces an XXY male with Barr bodies (sex chromatin seen only in female somatic cells) in his cells. Maternal age is advanced in XXY patients. There are some variants of this condition: XXYY, XXXY, XXXXY. The chief characteristics are defects in sexual development and subnormal mentality.

An early observation that males with a second Y chromosome, XYY were found in excess numbers in a maximum security prison was greatly overinterpreted. Most boys and men with a second Y are normal. The origin of the XYY is paternal nondisjunction at the second meiotic division which produces YY sperm.

In Turner syndrome, the XO condition exixts. This is a female with lack of sexual development. Physical features include webbed neck and short stature. The chromosome loss may occur during early cleavage of the zygote.

Females with XXX have been reported. Generally they are normal although a few show some degree of mental retardation or mental illness.

"Homosexuality, transvestitism and other sexual psychological variations do not as a rule have their basis in either chromosomal aberrations or single gene defects." [12]

Deletions or the loss of part of a chromosome may also be responsible for abnormal development. One such example is the deletion of the short arm of chromosome 5 (5p) which causes among newborns a high-mewing cry like a kitten known as the cat-cry syndrome. Other characteristics include a small head with round face and slow growth. Most survive beyond childhood, albeit with severe mental retardation.

Deletion in the long arm of chromosome 13 (13q) are found in some cases of retinoblastoma (tumor of the retina of the eye).

The Philadelphia chromosome, a deleted chromosome 22 with translocation of the deleted part to Chromosome 9 is seen in marrow cells of patients with chronic myelogenous leukemia. Other chromosomal changes occur as the disease progresses.

"Although most malignant cancers have abnormal karyotypes, the relation between cancer karyotypes and phenotypes is poorly understood. Most cancers probably develop from a single mutant cell, followed by clonal evolution and selection for the cell line that grows most successfully. The process is usually irreversible." [13]

Researchers are now at work on what causes cells to become cancers. One study has demonstrated that there are genes with two components, one called "onc" and the other a control element working in tandem" [14] that could turn normal DNA into cancerous cells.

The table below summarizes all of these disorders and defects and the genetic factors for each.

TABLE 2 COMMON DISORDERS AND BIRTH DEFECTS

Disorder or Defect	*Genetics*
Huntington Chorea	autosomal dominant
Neurofibromatosis	autosomal dominant
Sickle cell anemia	autosomal recessive
Thalassemia	autosomal recessive
PKU	autosomal recessive
Tay-Sachs	autosomal recessive
Cystic Fibrosis	autosomal recessive
Down syndrome	trisomy 21
Klinefelter syndrome	XXY or variant
Turner syndrome	XO
Cat-cry syndrome	Deletion chromosome 5p
Retinoblastoma	Deletion chromosome 13q
Philadelphia chromosome in leukemia	Deleted chromosome 22

V. SCREENING, TREATMENT AND THE FUTURE

Objectives **:**

A. Describe the AFP (alpha-fetoprotein test as a screening test.
B. Discuss karyotyping in pre-natal diagnosis. Prepare karyotypes.
C. Discuss fetal transfusions for Rh incompatability.
D. Discuss the use of genetic counseling.
E. Cite the implications of genetic engineering.

There are several methods for screening and pre-natal diagnosis. One of these can detect the presence of alphafetoprotein (AFP), a substance produced by the baby and passed into the mother’s blood and the amniotic fluid.

A blood test is offered between the 15th and 20th weeks of pregnancy. It can tell a woman: 1) that she may be carrying twins; 2) that the pregnancy is further along then she thought and she could deliver earlier and 3) that she may have a baby with a neural tube defect such as spina bifida (open spine) or anencephaly (lack of cover of brain).

If the test is positive a second test, ultrasound (obtaining a picture of the fetus by using sound waves) is used to determine how long is the pregnancy or whether there are twins. If ultrasound does not explain the abnormal AFP, amniocentesis (withdrawal of amniotic fluid) is performed. One in 15 at this point will prove to have spina bifida or anencephaly.

The AFP test is not perfect and a negative test is not conclusive. It detects most cases of anencephaly but only 80% of open spina bifida.

Recently, a test has been developed to find out if a fetus has normal or abnormal chromosomes. The test consists of a special analysis of amniotic fluid obtained by an established medical procedure called amniocentesis. The amniotic fluid contains cells shed by the fetus. These cells are allowed to grow and multiply in cultures in a laboratory until there are enough for analysis. The cells are analyzed to determine the chromosomal pattern of the fetus This is done by karyotyping which is the photographing and grouping of the chromosomes obtained from the cultured cells. For a more detailed explanation see Appendix 3.

If the results of the test show normal chromosomes, some of the worry of the expectant parents can be eliminated. If the results show abnormal chromosomes indicating severe birth defects, the option of elective abortion is available. Amniocentesis is best performed during the 16th to 18th week after the first day of the mother's last menstrual period.

There are many birth defects for which pre-natal testing is not available. Examples of these include cleft lip and palate, congenital heart defects and cystic fibrosis. Consequently, a normal result from pre-natal chromosome and AFP testing will not guarantee a normal baby.

Fetal transfusions are used to treat cases of Rh incompatability. Rh incompatability exists if the mother is Rh negative (-) and the fetus is Rh positive (+). Small amounts of the fetal blood can cross the placental barrier and reach the mother's blood which is stimulated to build anti-Rh antibodies if she has previously been sensitized to Rh + cells. These antibodies then travel back into the baby and attach to its cell destroying them. The baby can be transfused in utero or immediately at birth. A first pregnancy with a Rh + fetus rarely leads to this blood problem. The probability increases with subsequent Rh + pregnancies. The Rh-mother can now be treated with anti-Rh globulin when she delivers an Rh+ baby to prevent sensitization.

Genetic counseling is available and a useful tool to deal with genetic disorders. The aim of genetic counseling is to convey to an affected or potentially affected family the medical and genetic facts and to explain the medical options that may be available. It requires a person or a team of persons skilled in genetics and medicine. They will be dealing with persons who may show anger, shock, despair and guilt. The procedures may include medical diagnosis, including karyotype analysis, pedigree analysis, estimating risks, options and follow-up and supportive services. It may also involve examining the couples own values with the most information and support.

Genetic engineering that involves the manipulation of genes or gametes, i.e., recombinant DNA techniques, in vitro fertilization and cloning is still in its formative stages. How useful it can be will depend on how much it can improve the quality of human life.

The tools and the technology are here; and so is the knowledge to use them. There is still much to be learned. How all of this will be handled in the future may involve some serious medical, philosophical and ethical decisions.

LESSON PLANS

I. GAMETOGENESIS

A. *Suggested Activities*

1. Lecture on oogenesis and spermatogenesis pointing out the special features of each. Note especially the second meiotic division in oogenesis. Use Figure I and Figure 2.
2. Have students diagram both processes and explain using their own words. Compare both.
3. Use the Vocabulary Review and Concepts which follow as preview material or review or tests. The tests can self-tests or post tests.
4. Make copies or transparencies of illustrations (Figures I and 2).

B. *Vocabulary Review*

Match the words on the left with the descriptions on

the right. Each letter may be used once only.

a. primordial germ cells	1. earliest egg cell
b. oogenesis	2. female cell from first
c. oogonium	meiotic division
d. primary oocyte	3. male gamete
e. secondary oocyte	4. when human chromosomes
f. ovum	become 23
g. reduction division	5. special division to
h. polar body	form gametes
i. fertilization	6. male cell resulting from
j. spermatogenesis	earliest cell
k. spermatogonium	7. cell resulting from first
1. primary spermatocyte	meiotic division in male
m. secondary spermatocyte	8. second cell formed along
n. spermiogenesis	with functional egg.
o. sperm	9. the process of producing
p. meiosis	mature sperm.
	10. union of egg and sperm

11. earliest gametes
12. female gamete
13. the process of producing the mature egg
14. female cell resulting from earliest cell
15. earliest sperm cell
16. formation of sperm with head and tail

C. *Concepts* Fill in the blanks below.

1. There are ___ chromosomes in human cells.
2. When a female is born there are only ___ oocytes.
3. The second meiotic division is completed only if occurs.
4. During meiosis, chromosomes pair up during the division.
5. 6. When chromosomes form a tetrad celled (5) parts are (6) .
7. 8. Each oogonium forms no.) mature egg(s), whereas each spermatogonium forms no.) mature sperm(s).
9. The long time that primary oocytes remain in suspended ___ may account for some birth defects.
10. Because sperm undergo many DNA ___ ,some mutants may occur when the father is older.

ANSWERS:
Vocabulary Review: 1.c 2. e 3.o 4.g 5.p 6. 1 7. m 8. h 9. j 10. i 11. a 12. f 13.b 14 d 15 16. n

Concepts:
1.46

2. primary

3. fertilization

4. first

5.

6. chiasmata, exchanged

7.

8. one, four

9. prophase

10. duplications.

II. CHROMOSOMES AND GENES

A. *Suggested Activities*

1. Make models of DNA and RNA using instructions in Figure 3 (make copies or transparency)
2. Discuss the models and their relationship to genes and chromosomes. Use Figure 4 to illustrate the full complement of human chromosomes. Note the chromosomes that show mapping of genes. Make copies or transparency of Figure 4.
3. Use Vocabulary Review and Concepts as noted in part I.

II. CHROMOSOMES AND GENES (continued)

B. *Vocabulary Review*

Match the words on the left with the descriptions on the right. Each letter may be used once only.

a. helix	1. base paired with guanine
b. DNA	2. sugar in RNA
c. RNA	3. base paired with adenine
d. genes	4. base in RNA replaces thymine
e. chromosomes	5. short arm p, long arm q
f. mapping	6. lined up between sugar group
g. thymine	7. ribonucleic acid
h. adenine	8. functional unit of heredity
i. guanine	9. base paired with cytosine
j. cytosine	10. unit which determines amino
k. uracil	acid

1. phosphate	11. deoxyribonucleic acid
m. ribose	12. sugar in DNA
n. deoxyribose	13. coil nature of DNA
o. codon	14. locating genes on chromosomes
	15. base paired with thymine

C. *Concepts*

Fill in the blanks below.

1. Chromosomes can be classified by location of the
2. A codon of CAC will be paired with ___.
3. The sugar and phosphate are the ___ of the helix.
4. The paired bases form the ___ of the helix.
5. Genetic information is encoded by DNA and transcribed to ___ .

ANSWERS:.
Vocabulary Review

1.j 2.m 3.g 4.k 5.e 6.1 7.c 8.d 9.i 10.o 11.b 12.n 13.a 14.f 15.h

Concepts
1. centromere

2. GTG

3. sides

4. middle

5. RNA

III. INHERITANCE PATTERNS: AUTOSOMAL AND X-LINKED

A. Suggested Activities

1. Using Table I and Figures 5,6 and 7 (make copies or transparencies), discuss autosomal, X-linked inheritance and co-dominance.

2. Practice using the Punnett Square (see Appendix 1) with data from Table 1.
3. Use Vocabulary Review and Concepts and Applying as noted in part I.

B. *Vocabulary Review*

Match the words on the left with the descriptions on the right. Each letter may be used once only.

a. autosomal	1. corresponding forms of a gene
b. X-linked	2. two members of a pair of chrom-
c. phenotype	osomes
d. genotype	3. summarizes family data
e. homozygous	4. two alleles are different
f. heterozygous	5. both genes expressed in heter-
g. homologues	ozygote
h. locus	6. trait as expressed
i. dominant	7. gene expressed only in homo-
j. recessive	zygote
k. co-dominant	8. chromosomes other than sex
1. alleles	chromosome
m. pedigree chart	9. location of a gene
	10. two alleles the same
	11. associated with sex chromosome
	12. genetic make-up
	13. traits or genes fully expressed

C. *Concepts*

Fill in the blanks

1. The blood groups illustrate ___ inheritance.

2. In the pair Tt, the T is a ___ gene.

3. Hemophilia is an X;linked ___ trait.

4. A genotype, TT is ___.

5. Blue eyes express the ___.

6. Tongue-curling illustrates ___ inheritance.

7. “Hairy ears” is a trait linked to the ___ chromosome.

D. *Applying*

If a mother is type A and a father type B, can the child be type C? Explain.

ANSWERS:
Vocabulary Review: 1.1 2.g 3.m 4.f 5.k 6.c 7.j 8.a 9.h 10.e 11.b 12.d 13.i

Concepts:

1. co-dominant 2. dominant 3. recessive
4. homozygous 5. phenotype 6. autosomal

Applying:

Yes. Type A can be AO and B can be BO; when crossed type 00 can result.

IV. COMMON DISORDERS AND BIRTH DEFECTS

A. Suggested Activities

1.Using Table 2 (copy), discuss the disorders listed. Note Figure 8 (copy).
2. Assign a library or research paper on some other birth defects to be selected by the student. (see Mange and Thompson for suggestions).
3. Use Tel-Med tapes; report in writing.
4. Dramatize one or more of the disorders; e.g. Huntington Chorea.
5. Use Vocabulary Review and Concepts as noted in Part I.

B. *Vocabulary Review*

Match the words on the left with the descriptions on the right. Each letter may be used once only.

a. Huntington chorea	1. fleshy tumors; brownish
b. neurofibromatosis	pigment of skin
c. sickle cell anemia	2. tumor of retina of eye
d. PKU	3. 141 amino acids
e. Tay-Sachs	4. abnormal rate of synthesis
f. cystic fibrosis	of hemoglobin
g. Down syndrome	5. missing hexosaminodase
h. Turner syndrome	enzyme
i. cat-cry syndrome	6. 146 amino acids
j. retinoblastoma	7. crescent shape of red cells
k. Philadelphia chromosome	8. spasmodic movements
1. alpha globin	9. inability to convert phenyl-

m. beta globin	alanine to tyrosine
n. Thalassemia; Cooley anemia	10. male with X chromosome(s)
o. Klinefelter syndrome	11. abnormal secretions of certain glands
	12. kitten cry in baby
	13. found in leukemia
	14. underdeveloped female
	15. trisomy 21

C. Concepts

Fill in the blanks.

1. There are about ___ abnormalities.
2. Down syndrome is genetically known as ___.
3. Turner syndrome shows ___ genotype.
4. Cat-cry syndrome shows deletion of ___.
5. The Philadelphia chromosome shows a deletion of chromosome ___.
6. Retinoblastoma shows a deletion in the long arm of chromosome ___.
7. Huntington chorea illustrates autosomal ___
8. Sickle cell anemia and Thalassemia are autosomal ___.
9. PKU and Tay Sachs illustrate autosomal ___.
10. Cystic Fibrosis illustrates autosomal ___.

ANSWERS:

Vocabulary Review: 1.b 2.j 3.1 4.n 5.e 6.m 7.c 8.a 9.d 10.o 11.f 12.i 13.k 14.h 15.g

Concepts:

1. 3000

2.trisomy 21

3. XO

4. 5p

5.22

6. 13

7. dominant

8. recessive

9. recessive

10. recessive.

V. SCREENING, TREATMENT AND THE FUTURE

A. *Suggested Activities*

1. Bring in a speaker-counselor etc. to discuss screening or pre-natal diagnosis and treatment. (Dr. Mahoney for example.)
2. Work with copies of chromosomes and attempt to classify them. (See Appendix 2). Refer to chart of Human Chromosomes Figure 4.
   This is an exercise in karyotyping.
3. Use Vocabulary Review, Concepts and Applying as previously noted.

B. *Vocabulary Review*

Match the words on the left with the descriptions on the right. Each letter may be used once only.

a. AFP	1. changing genetic make-up
b. fetal transfusion	2. alpha-fetoprotein
c. genetic counseling	3. giving blood to a fetus
d. genetic engineering	4. advising couples about choices
e. amniocentesis	regarding unborn child
f. ultrasound	5. chromosome study
g. karyotyping	6. withdrawal of amniotic fluid
	7. obtaining a picture of the fetus

V. SCREENING, TREATMENT AND THE FUTURE

C *Concepts* Fill in the blank

1.2.3. The AFP test can diagnose (1) (2) and (3).
4. Ultrasound gives one a view of the ___.
5. Amniocentesis is used to draw fluid for cell ___ .
6. By typing chromosomes, they can be ___.
7. Fetal transfusions are necessary when there is Rh ___.
8. Genetic counseling requires persons skilled in genetics and ___.
9. Genetic engineering may involve the techniques of recombinant ___.

D. *Applying*

If you were told that you were carrying a baby with Down syndrome, what options would be open to you?

ANSWERS:
Vocabulary Review:

1.d 2.a 3.b 4.c 5.g 6.e 7.f

Concepts:
1.2.3. twins/length of pregnancy/neural tube defects

4.fetus

5.culture

6. catalogued/ classified

7.incompatability

8. medicine

9. DNA

Applying:
Abortion; giving birth to a child with severe malfunctions and retardation.

Puzzle (Appendix 4) summarizes this unit.

Answers:

Across:

1. chromosomes

6. RNA

9. Meiosis

10.AFP

12. PKU

13. Cooley

15. Down

16. Tay Sachs

18. Allele.

Down:

2.ovum

3. sperm

4. map

5. sex

6. recessive

7. amniocentesis

8. Locus

10. autosome

11. sickle

14. DNA

17. CF

Notes

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3. Thompson . . . p. 61
4. Ibid . . . p. 67
5. Ibid . . . p. 72
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9. Mange . . . p. 495
10. Ibid . . . p. 356
11. Thompson . . . p. 62
12. Ibid . . . p. 178
13. Mange . . . p. 181
14. “Found: Cancer Genes” *Discover,* Vol. 3, No. 6, June 1982, p. 77.

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Greendale, Karen; Kelly, Kim; Panyon, Peter; “Human Genetics: Educational Resources for the Classroom”. *The American Biology Teacher* , Feb. 1982; Vol. 44, No. 2, pp. 128-130.

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This is a comprehensive text in genetics as applied to humans. An excellent reference.

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The cellular and molecular foundations of development from bacteria to humans is covered. It is written for the student with a modest background in Chemistry and Biology but ends with some complex matters.

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A good introduction to genetics as related to man.

READING LIST FOR STUDENTS

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Parker, Gary; Reynolds, W.; and Reynolds, R., *Heredity* , Educational Methods, Chicago, 1977.

This is a programmed text on the basics of genetics.

Milunsky, A., *Know Your Genes,* Avon, N.Y. 1979. Good for the layman.

"Genetic Diseases and Birth Defects: What every family Should Know", *Better Homes and Gardens* , March 1980, pp. 66-82.

A familiar everyday discussion of genetic diseases and birth defects.

"Found: Cancer Genes", *Discover* , Vol. 3., No. 6, June 1982. pp. 76-79.

Research linking the normal DNA to cancer is described.

"Pregnancy and Childbirth 1982. New Options", *Family Circle* , March 16, 1982.

An interesting article that discusses many common concerns about pregnancy.

MATERIALS FOR CLASSROOM USE

March of Dimes Birth Defects Foundation, 1275 Mamaroneck Ave., White Plains, N.Y. 10605. (check local chapter). Pamphlets, reading materials and films may be obtained.

National Clearinghouse for Human Genetic Diseases, P.O. Box 28612, Washington, D.C., 20005, (202) 842-7617. Resources include printed materials, educational packages filmstrips, audiovisual presentations and patient education packages. Also includes activities of programs and services. Excellent source.

Parco Scientific So., Po. Box 595, Vienna, OH 44473, (216) 856-2368.

Laboratory Experiences material available.

Tel-Med, Hospital of Saint Raphael, 789-3333. Many tapes available; e.g. 236-Cystic Fibrosis, and 566-Sickle cell anemia.

Yale University School of Medicine, Department of Human Genetics, 436-3654.

For information relating to facilities and services available.

Appendix 1

(figure available in print form)

Appendix 2

(figure available in print form)
Human Chromosomes from a cell culture.

This photograph obtained from the laboratory of M.J. Mahoney and C. Smith, Human Genetics, Yale University School of Medicine.

Appendix 3

*Procedure for Harvesting Cells to Karyotype **

Amniotic fluids are centrifuged and cells suspended in medium, placed in 3 culture flasks. If initial amniotic fluid volume was low (8 ml or less), the cells would be split into 2 flasks and the supernatant amniotic fluid would be placed in a 3rd flask with an additional 1-2 ml of culture medium. This 3rd flask would be left undisturbed for 1 week. Three or more colonies are expected in each culture flask.

Cultures are fed twice a week. They are always fed the day before planned harvest. RPMI medium with 18-20% fetal bovine serum is used as culture medium.

On the morning of harvest Colcimid is added at a ratio of 0.1 ml Colcimid to 5 ml medium. The medium is not changed on the morning of harvest. Colcimid is left with the cells from 4 hours (active culture) to 7 hours (slow culture). The medium is poured off and saved, and 1 ml of trypsin-EDTA is added. That also is taken off and saved and then another ml of Trypsin EDTA is added to the cell layer. The flask is returned to the incubator for about 2 min. and when the cells come off the surface they and the fluid are added to the previous media and rinse. This mixture is centrifuged and the cell pellet is resuspended in hypo. The cells are fixed with two changes of fixative and then the cell suspension is dropped onto slides. If the original flask had two colonies, one should make two slides. For three or more colonies, one should make three or four slides.

Large epithelial cells have a low mitotic rate. For these cultures Colcimid is added the night before planned harvest and remains with the cells for up to 20 hours. Less than 10% of cultures are handled in this way.

The first flask of an amniotic fluid culture is expected to be harvested at 10-14 days and the second flask usually the day following the first flask. Essentially all cultures are completed with the harvest of two flasks and all work including karyotyping and report are completed on average in 18 days.

*Obtained from the laboratory of M.J. Mahoney and C. Smith, Yale University School of Medicine.

Appendix 4

GENES . . . THE NATURE OF HUMAN DEVELOPMENT
(figure available in print form)

ACROSS	DOWN
1. contain genes	2. female gamete
6. ribonucleic acid (abbr.)	3. male gamete
9. special division to form gametes	4. Locating genes on chromosomes
10. alpha-fetoprotein(abbr.)	5. X-linked chromosome
12. phenylketonuria (abbr.)	6. gene expressed only in homozygote
13. anemia; Mediterranean	7. withdrawal of amniotic-fluid
15. trisomy 21	8. place where gene found on chromosome
16. missing hexosaminodase enzyme	10. chromosomes except sex chromosome
18. corresponding form of a gene	11. anemia; crescent-shaped red blood cells
	14. deoxyribonucleic acid (abbr.)
	17. cystic fibrosis (abbr.)