PROFESSOR: So today's lecture is Chapter 7, Congenital and Hereditary Diseases. So the term congenital disease refers to from birth, okay. You've heard the word congenital. It refers to from birth, all right, even though it may not be detected until some type after birth. But it occurred from birth.

Hereditary or genetic disease means that it's determined by a chromosome abnormality or a defective gene. Congenital diseases may be determined by hereditary or genetic factors, okay, but they may not be. They may be the result of the external environment, whether it be radiation, whether it be a drug or other adverse situations.

Now, basically, as you know, with chromosomes, they are composed of a double coil of DNA and they contain the genes that determine our genetic makeup. So each chromosome has parking spaces that the gene is placed on. The term genome is the sum total of all the genes that are contained in the cell's chromosomes. So the genome is the same in all cells. And in humans we have 22 pairs of autosomes. The autosomes are nonsex chromosomes, and then we have a pair of sex chromosomes. Of course, the XX is the female and the XY is the male. The term karyotype refers to the representation of a person's set of chromosomes.

Now, in somatic cells, not germ cells, but somatic cells, the chromosomes exist in pairs. Basically, one member of each pair is derived from the male in the parent and the other from the female parent. That's how we get 22 autosomes, 22 pairs of autosomes. Of course, for the sex chromosomes, it's just a little different because from the female you only get the X, they can only provide the X to the egg. And of course, for the male, half the sperm, in theory, have an X chromosome and the other half have a Y.

So if the pairs are similar in size and shape and appearance, they are called homologous chromosomes. Mitosis is the way that cells divide, all right, somatic cells. Not the germ cells, but the somatic cells, okay, the way they divide. Basically, they divide so that each of the two new cells or daughter cells receive the same chromosomes as the parent cell.

Now, so factors in congenital malformations, defects that are present from birth. They can have a genetic background, a genetic cause, hereditary disorders or disease caused by abnormalities in an individual's genetic material. So the congenital disease or malformation will be present at birth even sometimes if it's not diagnosed, obviously. So the four factors in congenital malformations are going to be chromosome abnormalities, abnormalities of individual genes, intrauterine injury to the embryo or fetus or environment factors. We'll go
over all four of these now.

So two to three percent of all newborn have congenital defects. These may be very minor. Sometimes they are very minor or insignificant. Sometimes they can have what we call a vestigial appendage, for example, a small little stub below the pinky finger which could be an extra small finger, very small, which is removed at birth, not a problem. And so some of the congenital malformations are very insignificant.

An additional two to three percent are not recognized at birth, and the developmental defects are demonstrated later as the infants grow older. Twenty-five to 50 percent, okay, of the congenital malformations probably abort as embryos. They abort as embryos or fetuses or some of them are even almost carried to term and they are stillborns.

Now, so chromosome abnormalities. What are some of them? One is nondisjunction. What that is, that's a failure of homologous chromosomes in the germ cells to separate in the first or second meiotic division. Remember, the first meiotic chromosome number is halved. The second meiotic division, the chromosome number is maintained at half the normal number. So the nondisjunction, non-separation can either involve the sex chromosomes or the autosomes. It causes abnormalities in the distribution of the chromosomes between the germ cells. And basically when you have nondisjunction, one germ cell is going to have the extra chromosome, and the other is going to lack the chromosome, okay. So if they don't divide evenly, one cell is going to get the extra chromosome and the other cell is going to be deficient.

So the term monosomy refers to absence of a chromosome in a cell. So there's only one of that particular chromosome and not two.

Trisomy is the presence of an extra chromosome in a cell. Deletions refer to where a chromosome breaks and the fragment that then breaks off during meiosis is lost so that -- and we have a diagram I'll show you that in a minute that maybe explains it a little better.

Translocation is where there is a break in the chromosome, okay, a fragment breaks off. And the end that breaks off tends to be sticky, and it will -- and then it has the potential of sticking to another chromosome. We call that a translocation. So the chromosome fragment from one end of the a chromosome gets stuck to another, and that's called a translocation.

So now there are variations in the normal number of sex chromosomes -- well, the variations are associated with some reduction of intelligence. And of course, we're talking about the Y chromosome, all right. When we talk about the Y, it directs the masculine sexual differentiation. It's associated with the male body configuration regardless of the X chromosomes that are present. It's possible there is an abnormality called Klinefelter's. They have two Xs and a Y. We'll discuss them
later. But as long as the Y is present, then you have differentiation development of the male body configuration.

So with an extra Y, someone is born with an X chromosome and two Ys, they will be male. They have no significant effect as it mainly carries the genes concerned with male sexual differentiation. So an XYY person would be -- basically there would be no obvious abnormality. There has been some reports that men who have an extra Y, so they are XYY, have an increase in aggressive behavior. And a higher percentage of the overall prison population has an extra Y chromosome.

Now, also the term genotype, g-e-n-o-t-y-p-e, refers to the genetic makeup. The term phenotype, p-h-e-n-o-t-y-p-e, refers to the expression. The expression of the gene. So the genotype type for XYY would be -- I've just given it to you, that's the genotype. The phenotype is going to be male. Now, without the Y chromosome, the body configuration is female. So an extra X in female doesn't affect really the body configuration that much because one X chromosome isn't activated anyway. The extra X in the male will have adverse effects. So the genotype of XXY, we call that Klinefelter's syndrome. They will have male development; however, they usually are sterile and they have underdeveloped testes. They have sparse pubic and axillary hair. So they have the male body habitus; however, they will have underdeveloped testes and be sterile.

So the two most common types of chromosome, sex chromosome abnormalities are going to be, in females, are the Turner's Syndrome and Triple X. The Turner's Syndrome is the absence of one X chromosome. So these women only have one X, not two. These women tend to be smaller in stature. They tend to have a barrel type of chest, and they are usually infertile.

When I was a resident in Washington, DC, I worked with an endocrinologist who is really well known in the Washington area. He had a patient who had Turner's Syndrome. They can be intellectually normal. And this patient was intellectually fine, and she was a concert pianist. So she had Turner's. So she only had one X; she didn't have two.

The Triple X Syndrome, so the genotype is XXX. Two most common ones in the male are going to be the Klinefelter's Syndrome with an extra X and the XYY syndrome with the extra Y. Fragile X is interesting in that the Fragile X is linked to a mental deficiency. It's not related to either excess or deficiency of the sex chromosomes, but it's an abnormality of the X chromosome. It has been -- it was discovered when they were doing genetic studies on children who were handicapped, mentally handicapped, mental challenged. They noticed that some of them had an X chromosome that was fragile. It could break. And they began to associate that with intellectual performance. So as a result, it became known as the Fragile X Syndrome and is associated with mental deficiency.

Here is the syndromes, a summary of the syndromes I've
talked about. We have Turner's, Triple X, Klinefelter's, and the XYY.

Autosomal abnormalities. Absence of an autosome results in the loss of several genes; therefore, the development is generally not possible and the embryo is aborted. Deletion of a small part of an autosome can be compatible with development, but usually results in multiple severe congenital anomalies.

Down syndrome is the most common chromosome abnormality and that is due to an extra chromosome. So with Down syndrome -- and it's an extra chromosome 21, which is a very small chromosome. And very often with chromosomal abnormalities, the fetuses are aborted early in pregnancy. That includes those with an extra chromosome 21. Those who live, okay, are born with what we call Down syndrome and basically what happens is this extra chromosome occurs because of improper separation or nondisjunction during the formation of the egg. Now, the increased frequency with advancing maternal age is over 1 in 50. So Down syndrome, the most common cause for Down syndrome is what we called advanced maternal age. So what is considered advanced maternal age? Well, 35 is considered advanced. And the risk of having a baby with Down syndrome is about 1 in 200 women. If you have take 200 women who are 35 at the age of delivery, one will have a baby with Down syndrome. At age 40, okay, the risk is 1 in 100. So take 100 women who deliver when they are 40 years old, one will have a baby with Down syndrome. At age 45, the risk of Down syndrome is one in 50.

Now, a lot of things have developed in medicine. The reason why -- yes?

STUDENT: You said after age is 1 in 100?

PROFESSOR: Age 40 is 1 in 100.

STUDENT: And 45 is 1 in 50.

PROFESSOR: 1 in 50 if the mother is greater than 40 years old. The number I'm giving you is more accurate.

Now, why did 200 become the cutoff? Because obviously, as you women get older, they have increased risk of Downs. First of all, why it is -- does anybody know why it is that women, as they get older, have an increased risk of a chromosomal abnormal baby?

STUDENT: (Inaudible)

PROFESSOR: Right. Prophase of the first meiotic division. So when the female fetus is conceived intrauterine, before birth they always develop the eggs. They have germ cells. They are surrounded by what we call epithelial type cells called ( ) and they start the first meiotic division. Prophase is the first step of the first meiotic division. Remember prophase, metaphase, anaphase, telophase? They start prophase and stop. They then remain in prophase of the first meiotic division until that egg has been through a process of attrition or whatever where it's going to get ready to be prepared to be ovulated within the menstrual cycle. So when a female achieves puberty
and she starts to menstruate, every month -- if she menstruates every month, there's several follicles that start to grow. There's an attrition. One finally does achieve maturation and is ovulated. So that egg that was ovulated, okay, was in the prophase of the first meiotic division until about ten days before ovulation and then went through the meiotic process. So basically a woman who conceives at age 40, her eggs have been arrested in prophase of the first meiotic division for 40 years as opposed to someone who conceives at the age of 20. So what happens is the further they get from birth, the longer the eggs have been arrested in prophase of the first meiotic division, so the greater chance for nondisjunction or lack of separation to occur.

Now, what happened is we used to diagnose intrauterine Down syndrome by amniocentesis. The risk of amniocentesis is miscarriage due to infection or rupture of membranes. And the quoted risk for amniocentesis at the time was 1 in 200. Take 200 women who have an amniocentesis, one is going to have a miscarriage. So the risk of miscarriage is 1 in 200. The risk of Down syndrome at age 35 is 1 in 200. It was practice, commonly accepted practice, that women who were 35 or older had to be made aware of the fact that they had an option to have an amniocentesis. If they were not made aware and then they had a baby with a Down syndrome then that was a malpractice suit. The insurance companies didn't even take it to court to defend it. They just paid it off. They made a payment. So what happened is it was the responsibility for the obstetrician to make sure that any women who was 35 or older at the time of birth was aware of the option of amniocentesis. If they didn't want it, fine. But they needed to be made aware of it.

When I was in practice, we used to have our patients sign the chart saying that they were aware of the option of amniocentesis, but that they didn't want that. Obviously amnio is a personal decision, and we did not influence the decision of any of our patients.

So that's basically it, that at age 35 the risk of Downs equalled the risk of miscarriage. Now, for someone who conceives at age 30, her risk of Down syndrome might be -- and I don't know the exact number, maybe 350, 400. So for a woman who is maybe 30 or 28 to have an amniocentesis, when statistically her baby should not have a chromosome problem, has a greater chance of risk of miscarriage from a 1 in 200 procedure than the risk of chromosomal abnormality.

What is available now is we have an additional blood tests we call prenatal screening. We can do an ultrasound which measures the translucency of a nuchal fold. Statistically, we can compute the risk of this baby having Down syndrome more accurately so that the amniocentesis is not done as often, okay. So women who are over 35, if their prenatal screening is excellent and the ultrasound showing the translucency of the
nuchal fold in the back of the neck is good, then they feel better about -- they're more assured that their risk of having Down syndrome is much less than 1 in 200.

So here is a baby, an infant with the characteristic faces of Down syndrome. And nowadays what happens is a lot of these children have plastic surgery if their parents can afford it. It changes the facial characteristics.

So here we have nondisjunction of meiosis and leading to formation of the gametes with an extra or missing chromosome. So you have your first meiotic division. And on the left, you have normal, okay. And then on the right, you have nondisjunction. So you have a cell line without the X chromosome, and the other cell has two chromosomes. And then the division on the left, you have -- in the second meiotic division, you have nondisjunction. So it's just a demonstration how a nondisjunction can occur in the first meiotic or the second meiotic division.

So let's see. Now, translocation of the Down syndrome, remember translocation refers to where part of a chromosome breaks off and then sticks to another chromosome. So it occurs in a small number of persons, okay, and then the extra chromosome 21 becomes fused with chromosome 14, typically. The total number of chromosomes is not increased, but the genetic material is increased. The amount of genetic material is increased because you've got chromosome 21 stuck to chromosome 14. So the normal chromosomes and the cells of both parents and then the translocation occurs accidentally during formation of the gametes, formation of either the egg or the sperm. And then what happens is when that sticks, all right, that 14 stuck to 21, then the patients become -- then the parents become the carrier. They become a carrier. And that's the type of Down syndrome that can run in families when there is a translocation, when the one chromosome is stuck to the other.

So the 14/21 carrier is going to be in one of the parents. Then the carrier parent is capable of transmitting the abnormal chromosome to his or her children which can result in translocation Down syndrome.

The possible outcomes of pregnancy involving a female carrier, there can translocation of the chromosome. It's not always transmitted. Sometimes it is and sometimes it's not. So if it's not transmitted, then what is going to happen is the child can be normal. If the translocated chromosome occurs and it's possible then that they could be a carrier or if it's cell line without the translocated chromosome, they will be deficient and as a result nonviable. And then you have the possibility of Down syndrome.

So here is an example. Possible offspring produced when one parent is a carrier of a chromosome translocation. So for -- in this diagram, notice the carrier - male. He has -- the top chromosome is broken off, and we're going to call that
chromosome 7, okay. And then where it's broken off, some of the information -- the chromosome that was broken off then got stuck to chromosome 21, the yellow chromosome. So when you look at the carrier male, he has the normal amount of genetic material, genome, that he's supposed to have. It's just been rearranged. It's just been rearranged because of the fact that part of 7 broke off and stuck to 21. So he's totally fine as far as his genetic material goes.

And the normal female is there, okay. So all her eggs are consistently the same. Her eggs are going to have one chromosome 21 and one chromosome 7.

The difference comes from the male. The male then can produce basically four different types of sperm, okay. In A, he produces sperm that contains a normal chromosome 7 and a normal chromosome 21. In B, he produces a sperm that contains normal chromosome 7, but has the translocated piece of chromosome 7, so that sperm contains extra genetic material. As a result the fetus will have excess genetic material and it may result in birth abnormalities. Then in C, okay, he produces the sperm that has the normal chromosome 21, but it has the broken or fractured chromosome 7 which, therefore, is going to be deficient in genetic material. As a result because of the deficiency, there is spontaneous miscarriage. And then in D, what happens is you end up with the fractured chromosome 7, the chromosome 21 with the translocated piece of chromosome 7 on it. And as a result, D is the carrier staying. If you look at D, the sperm that's formed, it is the exact same formation that the carrier male, carrier father, has at the top. So those are the four possibilities when you have a translocation.

Now, so transmission of genetically determined diseases. They can be dominant. They can be recessive. They could be co-dominant, X-linked. Most hereditary diseases are transmitted on the autosomes and few are transmitted on the sex chromosomes.

Let's go over autosomal dominant. I think all you guys understand that. But, you know, a dominant characteristic is a characteristic that is presented or is present because of the gene that's present. For an example, I always use eye color. Brown eye color. When eyes are brown, that is determined by brown-eyed gene. That is dominant over the blue-eyed gene, and it's dominant over the green-eyed gene. So the phenotype is brown eyes. What's the genotype? We really don't know the genotype. We know that one gene is brown eyes, but we don't know what the other one is.

Blue eyes, someone has blue eyes. What that means is they have two blue-eyed genes. They have two genes that determine the blue eye color, because that's recessive. So recessive characteristic or recessive trait requires two genes for the expression of that type.

So for the phenotype blue eyes, the genotype is they have to have two genes for blue eyes.
Now, so for me, I have brown eyes. So my phenotype is brown eyes. What can we say about my genotype? All we can say is that we know I have one gene for brown eyes. The other gene, maybe it's for brown eyes, maybe it's for green. I have three boys. My first son has brown eyes. My second and third sons, they have blue eyes. My wife, she has blue eyes. So then obviously my second and third sons, they have blue eyes, they got the blue-eyed gene from her. But to have blue eyes, you have two genes for blue eyes, so they got the other one from me. My genotype is going to be a brown-eyed gene and a blue-eyed gene. So that's an illustration for dominant and recessive.

Co-dominant inheritance is interesting because it means both genes are expressed. Now, when it comes to hemoglobin within the cell, there are a lot of different hemoglobins. The variations in hemoglobins are due to substitution in the amino acid chain. And all you have to do is substitute one amino acid for another and you have a different type of hemoglobin.

The most common hemoglobin abnormality is sickle hemoglobin, hemoglobin S. That is a substitution of only one amino acid, but it changes the hemoglobin structure. So with -- when people have one gene for hemoglobin S and another gene for hemoglobin A, which is the most common type of hemoglobin, what do we call that? When we have one gene for hemoglobin S and one gene for hemoglobin A, what is that called? Anybody? Sickle trait.

And if they have two genes for hemoglobin S, what do we call that?

STUDENT: Sickle cell anemia.

PROFESSOR: Sickle cell anemia, right. Now, with sickle trait, when they have one gene for hemoglobin A and one gene for hemoglobin S, both genes are expressed. So 50 percent of the hemoglobin is S and 50 percent is A. That's co-dominant. Both genes are expressed. It's not that A is dominant over S or S is dominant over A. Both genes are expressed.

Then X-linked inheritance refers to a genetic trait that is carried on the X chromosome, the most common one is Von Willebrand's disease, which is a bleeding abnormality. It's due to a deficiency of factor 8. They are coagulation factors that are produced by the liver and they are numbered by Roman numerals. It's a series of factors. Factor 8, okay, is called Von Willebrand's disease. What that is is when people are born with a deficiency of factor 8, they tend to have bleeding abnormalities. The bleeding abnormalities are major abnormalities in that a slight trauma causes a large amount of bleeding, tends to be into the joints or into the muscle. And it is on the X chromosome; so therefore, if it's on the X chromosome, Von Willebrand's disease, how is it carried? It's going to be carried on the X chromosome, so it's going to be from the mother.

So hemophilia is on the X chromosome from the mother, and
it is presented in males. It is X-linked and it's from males, only on males. When mothers are carriers for hemophilia, they carry it on the X chromosome, and they pass on the X chromosome to their son or to their daughter. If they pass the X chromosome with the hemophilia on to their daughters, the daughters get another X chromosome from the father, and as a result the hemophilia is not expressed. But if the X chromosome that they pass on to their son, if that has the hemophiliac gene on it, then that's going to be presenting as hemophilia. Because, obviously, they get -- the male gets the X chromosome from the mother and the Y from the father. So that is going to be the presence of hemophilia.

By the way, I think in the beginning I was thinking about Willebrand's disease, but it's hemophilia and it was a deficiency of factor 8. So that's X-linked. That is one of the most commonly used or illustrated X-linked inheritance is hemophilia.

So most hereditary diseases are transmitted on autosomes. Few are carried on the sex chromosomes. Here is an interesting one. This is phenylalanine. Anybody know what foods contain phenylalanine?

STUDENT: Energy drinks.

PROFESSOR: Energy drinks do. What's a type of energy drink?

STUDENT: Monster.


Now, normally what happens is phenylalanine is metabolized to tyrosine. And the metabolism of the phenylalanine to tryosine is just the addition of that simple OH group. And the enzyme present is phenylalanine hydroxylase. So you need an enzyme, phenylalanine hydroxylase to metabolize to tyrosine. Phenylalanine, high concentrations in milk. So PKU refers to a deficiency of phenylalanine hydroxylase, and as a result there's an accumulation of phenylalanine in the blood and in the urine. As a result some of the phenylalanine gets metabolized in phenylpyruvic acid.

How many here have heard of the term PKU before? Anybody? No one? Okay. Just a couple.

Has anyone here been tested for PKU? You all have. It's usually done in the hospital when you're born. Usually the second or third day after delivery, okay, when you've been delivered and you've been fed either breast milk, bottled milk, formula or whatever, you're taking in high concentration of milk, phenylalanine is present. If you are missing the phenylalanine hydroxylase, then you have higher phenylalanine blood levels. The concern about that is if PKU is not detected, then it's associated with a high degree of mental retardation within a year. So the infant develops severe mental retardation within the year.
The way it's treated is you put them on a phenylalanine-free diet, if it's detected. Once they become adults then there is some controversy as to whether you let them go on a regular diet or keep them on a phenylalanine-free diet. That is why there's warning labels for any type of food that contain phenylalanine. Now, sometimes what they recommend is -- one recommendation is that men and women, when they become adults, can eat whatever they want to. Women need to stay on the phenylalanine diet. Others will say women need to stay on the phenylalanine diet only when they are pregnant. That's the whole concern. If a woman has PKU, what if she gets pregnant and she has high levels of phenylalanine and the baby has PKU also, then they may -- the baby may run a risk of being exposed to high phenylalanine levels. So they are not quite sure about that. But this is PKU.

There's also another genetic disease hexosaminidase A, a deficiency called Tay-Sachs. And what happens is there's a deficiency of one of the like 20 lysosomal enzymes that are involved in breaking down gangliocytes within the brain. With Tay-Sachs, they are missing one of the lysosomal enzymes. As a result there is an accumulation of gangliocytes within the lysosomes. And you would think -- if you are missing one and you have 19, you just don't have 20, how bad can it be? Well, it's really very severe in that these children who are born with Tay-Sachs start to have mental deterioration around the ages of one and a half and three. They lose their motor skills. They become deaf. They become blind. They develop severe mental retardation all due to deficiency of hexosaminidase A. Now, Tay-Sachs disease is most common in the eastern European Jewish population. That's another example of a genetically determined disease.

Now, intrauterine injury. What type of injury can occur to the fetus within the uterus? Harmful drugs or chemicals, radiation, and maternal infections, rubella, cytomegalovirus, and toxo are all concerned. Very important that women who are in childbearing years that they've been vaccinated against...

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