NEW METHODS OF DISEASE TREATMENT

LEARNING OBJECTIVE:

- To learn about some new genetic approaches for the treatment of cancers and other diseases.
- To examine what is meant by stem cell research and some of the positives and negatives of the approach.
- To take a glance into the future uses of cloning.

INTRODUCTION

The medicine of the future will treat and prevent diseases by changing the genetic makeup of the individual. A profile of ones genes (genome) will permit medial personnel to predict the chances for specific diseases to occur and hopefully to use methods to prevent or at least delay their occurrence. It should become possible to detect genetic abnormalities in the embryo or fetus and correct these. A relatively large number of diseases are now being experimentally treated by genetic engineering. In some cases a missing gene is introduced; whereas, in others, a gene blocker or signal blocker is introduced. In many cases viruses are used as vehicles for the genetic material.

CANCER TREATMENT

A new cancer treatment involves the use of monoclonal antibodies alone or with chemicals attached. The procedure for producing monoclonal antibodies involves taking an antigen from a specific cancer cell and introducing it into an organism, i.e. mouse. This stimulates or activates B-lymphocytes to produce antibodies against the cancer antigen. An antigen is any substance, usually a protein but sometimes a complex carbohydrate that stimulates the production of antibodies. The B-lymphocytes are harvested and fused with myeloma cells. A myeloma cell is a cancer cell, which theoretically can continue to divide infinitely. The fused product is called a hybridoma, which gives a cell that will divide repeatedly and produce antibodies. The myeloma cell gives the fused cell “immortality;” whereas, the B-lymphocyte gives it antibody producing ability. Because the hybridoma produces a specific type of antibody, these antibodies
are called **monoclonal antibodies** (Fig. 33-1). These antibodies with an antibiotic or some other chemical attached are injected into the cancer patient. Supposedly the antibody will go to the specific cancer and destroy it; it is referred to as a **magic bullet**. Unfortunately it has not lived up to its expectations.

![Diagram showing method of producing monoclonal antibodies from a hybridoma.](image)

**Figure 33-1.** *Showing method of producing monoclonal antibodies from a hybridoma.*

Experiments are being performed utilizing tumor cells. Cells of the tumor are removed from the patient and grown in the laboratory. The gene for **interleukin**, a substance that activates T-lymphocytes, is introduced into the cells. The tumor cells, with the new gene, are placed back in the patient. It is hoped that the tumor cells will produce interleukin, which will attract T-lymphocytes to the tumor cells, and they will be destroyed.

Trials are being conducted introducing a gene for an anti-tumor factor called tumor necrosis (TNF) into tumor-infiltrating lymphocytes (TIL). TNF helps kill tumors by cutting off their blood supply. A problem is that it also kills healthy cells. Presently experiments
are being run to determine if TIL can deliver enough TNF to destroy tumor cells without harming healthy tissue.

Experiments are being conducted on ways to alter or inhibit the expression of genes that play a major role in cancer development. Presently an anti-sense DNA segment is being introduced which binds to the complimentary copy of the gene, which codes for a mutant form of the gene and produces cancer. This prevents the mutant gene from being expressed. A second type of genetic information being introduced is for the tumor suppressor gene, p53. This gene normally prevents cells from growing wildly (characteristic of cancer) and in many cancer cells has stopped functioning.

**VACCINES**

Older types of vaccines contained an attenuated form of the virus; this creates the possibility of some viable viruses causing the disease. Some of the newer vaccines utilize a subunit of the virus. A gene, which codes for a surface protein of the disease-producing virus, is placed in a plasmid and introduced to a bacterium. The host cell produces many copies of the surface protein, which is extracted and injected into a human, and the protein stimulates the production of antibodies. Hopefully, the antibodies will react in a similar manner when the individual comes in contact with the actual virus.

Presently researchers are testing a mouse virus as an AIDS vaccine. They are using a non-infectious mouse virus that has been engineered to contain two harmless genes from HIV. This engineered mouse virus is injected into the patient where it is transported into cells; the genes will command the cells to make and display a protein found on the surface of the HIV. This display will stimulate CTLs (cytotoxic T-lymphocytes) to seek out and attack all cells containing the HIV gene. This vaccine is based upon the cellular part of the immune system and not on antibodies.

Presently (Nov. 2004) scientists are attempting to develop a vaccine which employs HIV units, incapable of reproducing, as an antigen to stimulate the human immune system. It has been tested on lower animals, but tests will not be run on humans until FDA approval is obtained. Some scientists, whose research is in HIV and AIDS, believe this is the only way we will ever conquer AIDS; it is necessary for the individuals immune system to resist the disease rather than developing chemical therapies to prevent multiplication of the virus.

**CYSTIC FIBROSIS**

Cystic fibrosis is the most common lethal genetic disease among U.S. Caucasian males. Channels for Cl⁻ (chloride ions) fail to pass the ion through the cell membranes of the respiratory and digestive tract, resulting in a thick mucus secretion. Normally Cl⁻ passes out of the cells followed by water and thus produces a watery layer not a thick mucus one. The gene for CF is on the #7 chromosome. The treatment consists of giving CFTR (Cystic Fibrosis Transmembrane conductance Regulator) in an inhalant in the form of a bioengineered virus placed in a liposome (a liposome is a single layer lipid vacuole). So far it has worked in some patients but only for a brief period and then must be applied again. This is because the epithelial cells, which take up the virus, are replaced regularly and thus will be lost within several months. At the present time this is a treatment not a cure. If the virus could reach the basic cells that give rise to the epithelial cells, then it might become a cure.
PARKINSON’S DISEASE

Scientists are now working on a gene therapy for Parkinson’s disease. They use a gutted AIDS virus to deliver a growth factor gene to the part of the brain that is destroyed in Parkinson’s. The drug was injected directly into the brains of four aging Rhesus monkeys and four young adult monkeys. It prevented the brain-cell death that occurs with Parkinson’s and reversed the symptoms of the disease. Monkeys don’t naturally acquire Parkinson’s; therefore, the scientists artificially induced the disease by giving the younger monkeys a toxic chemical that kills the same brain cells destroyed by the human disease. Before receiving the gene drug, the monkeys were so disabled that they couldn’t reach out and pick up fruit during a test of their motor skills. After therapy, they could. This could be a potent treatment and potential cure for a disease that affects 1 million Americans with some 50,000 new cases diagnosed every year. It will take 3-5 years to gain regulatory approval needed to test the approach in humans and many more years to bring the drug to the market. Caution should be taken in assuming that what works on artificially induced symptoms in monkeys will work on the naturally occurring disease in humans.

SMART GENE

Scientists at Princeton have created a “smart” mouse, Doogie. They injected a gene that codes for a brain protein, NR 2B. Using a tiny glass needle the gene was placed in the nucleus of a fertilized mouse egg. The egg was cultured and the resulting embryo was implanted in the uterus of a mother mouse. Mice developing from such an egg excelled in a range of tasks. They also carried their enhanced intelligence into adulthood when learning ability and memory naturally taper off; and they passed it on to their offspring. This work could lead to a drug to treat memory disorders, such as Alzheimer’s. The prospect of genetically engineered smarter babies raises some ethical questions.

STEM CELL RESEARCH

Stem cell research will be moved a step forward if new federal guidelines are approved that would allow scientists to do funded research with stem cells that have been removed from human embryos. The present rules forbid research on the embryo itself; this is prohibited by federal law. Stem cells form at a very early stage in the gestation of a human being. They are predecessors of all the tissues of the body. Scientists have found that embryonic stem cells can be prompted to evolve into the individual cell types found in each of the organs of the body. Some researchers believe eventually it will be possible to nurture stem cells into whole new organs. (This is being done at the present time with plants.) Stem cells are not embryos and could not themselves develop into embryos. Figure 33-2 shows how stem cells can be obtained and used for production of new cells. The Tribune-Star on Nov. 19, 2002 reported that scientists had been successful in stimulating the production of insulin in mouse embryonic stem cells. The researchers at Stanford University placed embryonic stem cells in an appropriate medium until they developed into a tissue that made insulin. They put the tissue into diabetic mice and showed that the mice were sustained with the insulin produced by the graft. The research did not result in the production of mature insulin producing pancreatic islets, beta cells. It was emphasized that the next steps of
translating the mouse data into human therapy can be a long and difficult process taking many years. Scientists have discovered, while working with mice, that bone marrow stem cells can develop into other types of cells (Fig. 33-3).

**Embryonic Stem Cells**

The embryo develops into a BLASTOCYST four days after fertilization.

A coating, which will become the placenta, surrounds the blastocyst. This coating must be broken to access the stem cells.

The stem cells cannot develop as an embryo when removed from the blastocyst. They can be cultured and grown into different tissues.

**Figure 33-2.** Showing how stem cells from an early embryo can be cultured to develop into a wide variety of cells and tissues.
Figure 33-3. Illustrating the ability of bone marrow stem cells to develop into various types of cells.

CLONING

PPL Therapeutics, the same company that produced Dolly the sheep, is now cloning pigs with the goal of providing pig organs for transplants into humans (Fig. 33-4). Scientists remove the nucleus from the cell of a pig and alter it to inactivate the gene, which is responsible for producing an identifying marker on the pig cells. This marker is recognized by other organisms, including humans, and results in rejection. The altered nucleus is now placed in an enucleated pig egg cell. The egg is permitted to develop for a few days and is then implanted into the uterus of a surrogate mother sow. She carries
it to maturity and then delivers a “knock-out” offspring. A “knock-out” is an animal produced with a specific gene inactivated. Hopefully the organs harvested from these “knock-out” animals can be used as transplants without rejection. The process of transplanting organs of one species into another species is called xenotransplantation.

Figure 33-4. Illustrates the techniques used to produce “knock-out” offspring.
Hormone tells brain to stop eating

Researchers at Imperial College London had found in tests that a hormone called PYY3-36 could suppress the appetites of lean people. They wondered if it would do the same for obese people. Another hormone, leptin, had proved disappointing on obese people. In a limited study both lean and obese people ate 30% less from a buffet lunch after being giving a dose of the hormone. They also found lower natural levels of PYY in obese persons. They think this might explain the reason that obese people eat more. A longer study is needed; the present study only shows that people eat less not that they lose weight. Some researchers believe that PYY might not be a magic bullet, but might help in combination with other drugs.

“Good” cholesterol can clear plaque

In a small study, researchers found that infusions of a synthetic component of “good” cholesterol, HDL, reduced artery disease in just five weeks. HDL that has a component that contributes to larger-than-normal particles is infused into the blood; it is especially effective at removing plaque. The excess cholesterol is removed and transported back to the liver for elimination.

Treatment of varicose veins

Sclerotherapy can be used to treat both varicose and spider veins. The treatment consists of using a tiny needle to inject a medication that irritates the lining of the vein. The vein responds by collapsing and is reabsorbed. This procedure allows veins to be treated at an early state, thus helping to prevent further complications (figure 33-5).

Figure 33-5. Showing varicose veins before and after sclerotherapy. (source American College of Phlebology)

Radiofrequency occlusion procedure is a treatment to surgically strip the greater saphenous vein. A small catheter is inserted into the damaged vein, which delivers
radiofrequency energy to the vein causing it to heat. The heat collapses the vein and seals it shut. The catheter is slowly withdrawn and a bandage or compression stocking is placed on the treated leg (figure 33-6).

Figure 33-6. Shows a diagrammatic representation of the radiofrequency occlusion. (source: American College of Phlebology)

Hearing problems
Hearing loss can be classified as transmission or receptor deafness. Transmission deafness can often be helped by a hearing aid. Figure 33-7 shows the structures of the ear. Transmission of sound waves occurs through the eardrum, tympanic membrane, the bones of the middle ear, and the cochlea. Receptor deafness involves the receptor cells, hair cells, in the cochlea and the auditory nerve. To help people suffering from receptor deafness, a cochlear implant has been developed (figure 33-8). This is an electronic prosthetic replaced for damaged inner ear. The implant consists of:

a. microphone worn behind the ear to pick up sound
b. a speech processor worn on the body
c. a small device placed under the skin near the ear, with electrodes to the cochlea
d. electrodes in the cochlea to stimulate nerve fibers (auditory nerve)
e. a speech processor that filters, analyzes, and digitizes the sound into coded signals

Unfortunately, not everyone can benefit from a cochlear implant. Some hearing loss is due to destruction of the auditory nerve.

Artificial retina--conceptual
This apparatus is still in the experimental stage; it is referred to as the Multiple-unit Artificial Retina Chipset. External electronics capture the image and transmit the image
signal to implanted electrons on the retinal surface. It has components mounted both inside and outside the eye. Light is picked up by a microscope outside the eye, processed and transmitted to a microchip implanted at the surface of the retina. A microchip just three millimeters across can hold 4,000 to 5,000 microscopic solar cells. When light strikes these solar cells, it is converted into electrical signals that travel through the optic nerve to the brain and are interpreted as an image. This piece of silicon (the chip) acts as a replacement for a malfunctioning retina. The chip is about half the thickness of a sheet of paper. A two-hour operation is done through an incision in the white part of the eye (the sclera) and chip is inserted into a pocket beneath the retina. Chips can be placed on the surface of the retina or beneath the retina. Figure 33-9 shows a diagrammatic representation of the human eye. The actual receptor cells of the eye are the cones and rods. Figure 33-40 shows a conceptual drawing of the chipset.

Figure 33-7. Diagrammatic drawing of the ear showing relationships between parts.
Figure 33-8. Cochlear implant (1—microphone, 2—wire to processor, 3—processor not shown, 4—wire to device with electrodes to cochlea, and 5—device.

1. Light travels through layers of transparent neurons—ganglion, amacrine, bipolar, and horizontal cells...

2. …and is absorbed by the rods and cones (the photoreceptive layer) at the back of the retina.

3. Visual information is processed through several layers of neurons...

4. …and finally converges on ganglion cells, which send their axons to the brain.
Figure 33-9. Diagram of the eye showing the makeup of the retina.

Figure 33-10. Conceptual drawing of the Multiple-Unit Artificial Retina Chipset.
UNIT 33

OBJECTIVE QUESTIONS OVER NEW DISEASE TREATMENT

1. Transplanting organs or tissues from one species into another species is called
   (A) xenotransplantation
   (B) hybridization
   (C) cloning
   (D) hybrid transplantation

2. Cystic fibrosis is a disease in which the individual can not pump ______ through the
   membrane of the cells lining the lungs and intestine.
   (A) Cl
   (B) Na
   (C) K
   (D) Ca

3. A hybridoma is a cell resulting from the fusion of
   (A) T-lymphocyte with a B-lymphocyte
   (B) antigen producing cell with an antibody producing cell
   (C) B-lymphocyte with a cancer cell.

4. A ________ has been used as an experimental animal for testing a growth factor
   gene to prevent Parkinson's.
   (A) mouse
   (B) rat
   (C) monkey
   (D) sheep

5. Researchers are testing a mouse virus for use in an AIDS vaccine. If it works, it will
   do so by stimulating the
   (A) cells to produce antibodies
   (B) cells to engulf cells with HIV genes
   (C) both A and B.

6. Stem cells can be obtained from
   (A) early embryos
   (B) bone marrow
   (C) both A and B
   (D) neither A or B.
7. Using pig organs for human transplants requires _______ so the organs wouldn't be rejected.
   (A) giving pigs some human genes
   (B) inactivating some of the immune system genes in humans
   (C) inactivating the gene for cell markers in pigs
   (D) getting pig organs early

8. A _______ has been used in the experiments with the "smart" gene.
   (A) mouse
   (B) rat
   (C) monkey
   (D) sheep

9. Antibodies are produced by
   (A) T-lymphocytes
   (B) B-lymphocytes
   (C) both A and B
   (D) neither A or B.

10. An _____ is any substance, usually a protein but sometimes a complex carbohydrate, which stimulates the production of antibodies.
    (A) myeloma
    (B) histogen
    (C) antigen
    (D) lymphocyte

11. A ________ cell is a cancer cell, which theoretically can continue to divide infinitely.
    (A) myeloma
    (B) lymphocyte
    (C) interleukin
    (D) stem

12. _______ is a substance that activates T-lymphocytes.
    (A) Factor VIII
    (B) Interleukin
    (C) NR 2B
    (D) TNF

13. A tumor suppressor gene called _____ is being studied. When introduced into cells, this gene prevents cells from growing wildly (characteristic of cancer); in many cancer cells, this gene has stopped functioning.
    (A) p53
    (B) Interleukin
    (C) NR 2B
    (D) TNF

14. A ________ is an animal produced with a specific gene inactivated.
    (A) transgenic
    (B) clone
    (C) knock-out
    (D) blastocyst
15. Current research into gene therapy for Parkinson’s disease uses a gutted _________ to deliver a growth factor gene to part of the brain that is destroyed by Parkinson’s.
   (A) cold virus
   (B) AIDS virus
   (C) flu virus
   (D) staph bacteria

16. What does the term monoclonal antibody mean?
   (A) All the antibodies produced by plasma cells
   (B) Product of a hybridoma
   (C) An antibody that is specific for a particular antigen
   (D) Two of the preceding
   (E) All the preceding

17. A hearing aid can often help with (A) transmission deafness (B) receptor deafness (C) both A and B (D) neither A or B.

18. The receptor cells for hearing are located in the (A) outer (B) middle (C) inner ear.

19. The receptor cells for the eye are located in the (A) retina (B) cornea (C) sclerotic coat (D) optic nerve.

20. Varicose veins can be treated (A) by causing the veins to collapse and be reabsorbed (B) by causing the vein to collapse and sealed shut (C) by actual removal of the vein (D) two of the preceding (E) all the preceding.

**DISCUSSION QUESTIONS OVER NEW METHODS OF DISEASE TREATMENT**

1. What is the reason for referring to the use of monoclonal antibodies as a “magic bullet?”
2. What is the advantage of a vaccine made from a gene or genes of a virus rather than one made from an attenuated virus?

3. What could be some of the problems associated with the production of a mouse virus generated AIDS vaccine?

4. Should the Federal government greatly reduce the time and experiments now required to get a new drug on the market? Explain your answer.

5. What are objections to using embryonic stem cells? What are the reasons to proceed with this type of research?

6. Give an example of genetic engineering where the attempt is to prevent a gene present in the individual from working. Explain.

7. What are some of the ethical problems with the introduction of a "smart" gene into humans?
8. What are some of the ethical problems some individuals see with cloning?

9. How does a hearing aid allow one to hear?