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Spinal muscular atrophy

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Spinal Muscular Atrophy

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Introduction

Spinal Muscular Atrophy (SMA) is one of many neuromuscular diseases affecting motor neurons and skeletal muscles. This disorder causes deterioration of the motor neurons (specifically the Anterior Horn Cells of the spinal cord). These motor neurons that control muscles are selectively destroyed resulting in varying degrees of atrophy, weakness and paralysis of the trunk and limb muscles. In this first half of the thesis report, various aspects of Spinal Muscular Atrophy, including history, anatomy/ physiology, diagnosis, theories of its function, types, characteristics, heredity, research, and treatment will be examined. A second portion of this report focuses upon both illustration and interactive computer media and animation as a visual introduction to SMA for the lay audience, patients, and their families.

Spinal Muscular Atrophy has plagued man for generations. Many of the spinal muscular atrophies bear the names of the pioneering physicians who were among the first to describe the clinical signs of the disease in medical literature. Since the turn of the century, several authors have described patients with progressive muscular dystrophy who demonstrated fasciculations on clinical examination. Initially, this was interpreted as muscular dystrophy with secondary anterior horn cell changes and, later, as a transition between, or a combination of muscular dystrophy and progressive spinal muscular atrophy.

In 1850, the first form of the disorder, distinct from the muscular dystrophies, was identified in adult patients by two French physicians, Francois-Amilcar Aran and Guillaume Benjamin Amand Duchenne. Toward the end of the 19th century, two German doctors, Guido Werdnig and Johann Hoffmann, described the disease in children. As recently as the early 1950's a team of Swedish doctors, Eric Klas Henrik Kugelberg and Lisa Welander, identified still another form of the disease that attacks children.

Anatomy

To understand how SMA affects the motor neurons, it helps to understand anatomy of the central nervous system. The spinal cord acts as a pathway for nerve impulses from the brain to travel to various destinations in the body whether it be to voluntary or involuntary muscle or organs. Within it is the grey matter which form the "H" shaped region surrounded by white matter. The grey matter of the central nervous system contains large numbers of cell bodies of neurons. This grey matter includes the cerebral cortex, basal ganglia, and nuclei of the brain and the grey columns of the spinal cord, (or "H" shaped region). (1) The cell bodies of the motor neurons are located in the

anterior horns of the grey "H" shaped region of the spinal cord, hence the name, anterior horn cells. The axon of the anterior horn cell is an efferent fiber innervating a skeletal muscle at various points. (2)

It is these anterior horn cells of the spinal cord that SMA attacks causing them to deteriorate. (With the loss of motor neuron function, the muscles weaken and degenerate). These motor neurons that control muscles are selectively destroyed resulting in varying degrees of atrophy, weakness, and paralysis of the trunk and limb muscles.

Cause and Theories

All of the spinal muscular atrophies are caused by an abnormal gene or genes. Genes act as blueprints for the construction of proteins, the basic building blocks of cells. Exactly how a genetic abnormality leads to the development of any form of Spinal Muscular Atrophy is not known. Why the motor neurons are selectively destroyed and why there are so many variations of SMA are just two of the many questions researchers are trying to answer. Several theories exist as to how nerve impulses and muscles are affected. The first theory is a failed impulse. For example, to contract a muscle, a fast impulse must be sent quickly, smoothly, and follow a series of necessary steps. The brain sends messages down the spinal cord to the anterior horn cells to be sent to the awaiting muscle. Somewhere along the anterior horn cell's axon, the impulse is lost and never reaches the awaiting muscle. Researchers do not know if the problem lies along the axon within the cell body. (The site of muscle innervation is not a problem of SMA but of a similar neuromuscular disease called Myasthenia Gravis).

A second theory of affected impulses is a partial impulse or stimulation. After the electrical impulse reaches the anterior horn cell, the impulse is par-

tially delivered to the muscle. Somewhere part of the message is destroyed along the axon. The muscle is stimulated to contract slightly, not using its full potential, or it partially contracts. Often other symptoms are muscle spasms, or fasciculations, due to constant electrical impulses sent to the muscle to contract and tremors caused by weakened muscles unable to hold a steady position. "Watching a patient with diffuse fasciculations is reminiscent of watching the surface of a pond in summer when the fish are rising: the ripples arise here and there with no seeming pattern...A fasciculation is an involuntary discharge of one motor unit resulting in the contraction of all the muscle fibers supplied by a single nerve cell. When denervation occurs, the several hundred muscle fibers supplied by a particular nerve may become devoid of their nerve supply. Ordinarily they atrophy, but reinnervation from a neighboring nerve cell may occur. This results in the accumulation of additional muscle fibers within the newly formed motor unit. By a constant process of denervation and reinnervation, motor units may come to contain several thousand muscle fibers rather than a few hundred....The origin of the fasciculation is not clear. It is a spontaneous discharge in some part of the motor nerve."(3)

Since there are many innervation points of a branch nerve to a muscle, the defected portion of the nerve could be anywhere along the axon. Therefore, some muscle fibers of a muscle may be stimulated while other muscle fibers of the same muscle may be atrophied or weakened due to the lack of/or partial nerve stimulation as will be discussed later under tissue studies.

Affected Muscles

Spinal muscular atrophy primarily affects the motor neurons that control muscles of the body. This typically includes the proximal muscles (cord to elbow, cord to knee) rather than the distal muscles (joint to farthest point) of

the body. Facial muscles are usually not affected. Affected muscles are the flexors and extensors of the proximal portions of arms and legs. These include, the biceps brachaii and triceps, intercostal, muscles in the gluteal region and pelvic girdle, adductors of the legs, hamstrings, quadriceps, and hypertrophy in gastrocnemius (calve) muscle.

Types and Characteristics

The spinal muscular atrophies are a group of inherited neuromuscular diseases that cause varying degrees of weakness and wasting of the trunk and limb muscles. There are four basic types of SMA, which are classified according to the severity of weakness, age at onset of symptoms, and distribution of muscles affected. (4)

Type I, or Infantile Progressive Spinal Muscular Atrophy (Acute Werdnig-Hoffmann disease), has the earliest onset of symptoms from birth to three months. These individuals have generalized muscle weakness, weak cry, trouble swallowing and sucking, breathing distress usually leading to paralysis of the legs and arms within three months. "Babies with the infantile type cannot roll over, raise their heads, or sit without support....Because of breathing distress and respiratory infection, life-span rarely exceeds age two." (5)

In type II, or Intermediate Spinal Muscular Atrophy, (chronic Werdnig-Hoffmann disease) the age of onset is six months to three years. Disease characteristics include progressive weakness in arms, legs, upper and lower torso, often with skeletal deformities. "During early childhood, the scoliosis is best controlled by means of a back brace which provides passive support. Bear in mind, however, that the child who is walking with great difficulty may be quite unable to do so when wearing a body jacket. As the children attain their teenage years, surgery is usually indicated." (6) The disease progresses rapid-

ly with this form. While most patients survive to early childhood, respiratory problems can further shorten life.

The age of onset for type III or Juvenile Spinal Muscular Atrophy (Kugelberg-Welander disease) is one to fifteen years. Disease characteristics include weakness in leg and hip muscles which makes it difficult to climb stairs, stand up, and turns the child's walk into a waddle. In addition, shoulder, arm, and respiratory muscles are also weakened. Calf muscles are often enlarged. Youngsters with this type can walk, although with difficulty, at least ten years after symptoms become apparent. The disease progresses slowly even though a wheelchair is often required by age 30. Life span is unaffected.

The fourth and last type, Adult Spinal Muscular Atrophy, (Aran-Duchenne disease), starts at 18-50 years of age. Characteristics include weakness in the tongue, hands, or feet, which slowly spreads to other parts of the body. A relatively mild form of SMA, it has little impact on life expectancy.

Diagnosis

Although not all children and adults with these symptoms have SMA, it is important to have a thorough neurological examination to establish a diagnosis. This is to confirm that the symptoms indicate spinal muscular atrophy and not another condition with similar symptoms.

Diagnosis is made by carefully evaluating the patient's medical history and by performing a thorough physical examination. The clinical diagnosis is then confirmed by a series of laboratory tests. Since SMA is a genetic disorder, an inherited disease that can be passed down from one generation to the next, it is also important to check family history.

Diagnosis is unclear sometimes when it is difficult to distinguish

between SMA and other neuromuscular disorders. In these cases, physicians use tests to help them arrive at a diagnosis. First, the physical evaluation includes a manual muscle strength test on a scale from 0-5, (five being normal), according to the Medical Research Council Scale. (7) In this test, strength and range of motion, flexion, extension, internal and external rotation, abduction, and adduction are all measured. Distal hand strength measures include grip strength and flexion in fingers. In addition, the patient's function and mobility is considered when doing self-care activities to determine independence or dependence. (8)

"Examination of the deep tendon reflexes is an important part of the muscle examination. The muscles which are evaluated are those of any standard neurological examination and include the biceps, triceps, supinator, knee, and ankle jerks together with the superficial reflexes of the abdomen and the plantar responses. Reflexes for SMA could be described as either absent, diminished, normal, or hyperactive. In judging whether a reflex is hyperactive, attention is paid to the spread of the reflex to neighboring muscle groups and, most importantly, to the degree of "snap" in the muscle contraction. Ordinarily, when a tendon is tapped, the initial contraction of the muscle has a rather smooth quality before relaxing. In a hyperactive reflex, the tendon jerk becomes more jerky than usual." (9)

After the initial physical evaluation, more clinical tests may be taken. A second procedure, or the muscle biopsy, enables a pathologist to determine whether a disorder is one of the spinal muscular atrophies by studying a small piece of muscle tissue taken from an individual. The tissue sample taken from an affected muscle shows distinct differences between healthy muscle and muscle affected by SMA. Healthy tissue shows muscle fibers to be full and uniform in size. However, muscle affected by SMA have intermixed healthy, or

normal, atrophied, and hypertrophied fibers along with large amounts of connective and sometimes adipose tissue. "Atrophic fibers are randomly scattered and not grouped together. Some atrophic fibers are excessively dark in oxidative enzyme reactions, perhaps because mitochondria are comparatively spared and occupy a greater volume of shrinking sarcoplasm....Based upon a muscle biopsy, the pathologist cannot tell the clinician whether the lesion resides in the motor neuron or in the peripheral nerve." (10)

Another diagnostic test is the electromyogram (EMG). By placing small electrodes in muscle, this test creates a graph that indicates the health of the body's muscles and nerves, and measures muscle activity. For example, "contrary to healthy subjects during quiet standing, SMA patients reveal in addition to the activity of the triceps surae and paraspinal muscles, also the definite presence of activity in quadriceps, hamstrings as well as the tibial anterior muscles...In other words, muscle of SMA patients in respect to electrical activity are much more active when compared with the healthy control group." (11)

The EMG test has also enabled physicians to understand the activity or inactivity of certain muscle groups, as they compensate for inactive ones in the SMA patient. This can be illustrated by one EMG study of healthy verses SMA patients performing various simple exercises. "In the control group of healthy subjects bending forward activates all the lumbar muscles and the muscles of the so-called posterior compartment of the lower limbs (hamstrings, triceps surae) and relax the activity of the quadriceps and abdominal muscles. None of the quadriceps muscle is activated during this maneuver. Furthermore, abdominal muscles have been less active when compared with the activity of other recorded muscle groups....The SMA patient in order to perform this maneuver of bending forward must activate the agonistic and antagonistic

muscle groups simultaneously." (12)

A third clinical test for diagnosing SMA is in administering blood tests to evaluate the levels of certain enzymes, helping to distinguish the spinal muscular atrophies from other neuromuscular diseases.

Tissue Studies

It is not clear whether the destruction of motor neurons in spinal muscular atrophy is initiated at the cell body or along the axon. Examination of the nerves of patients having infantile and juvenile forms reveals a marked depletion of large axons and a high percentage of small axons. This aspect of the pathology, which is still under investigation, could reveal an important clue to the question of where the genetic defect(s) underlying these diseases are first manifested.

"Microscopic examination of muscle from patients often reveals small, underdeveloped fibers which resemble the muscle in a developing fetus. Other studies have indicated that the diseased muscle resembles that of laboratory animals in which motor neurons were severed during development. Whether the appearance of the muscle is an indication that its maturation is somehow arrested at some crucial point during development, or is the result of deterioration of what were once normal muscle fibers is not well understood.

The body is constantly synthesizing new proteins to replace and renew muscle. One report has indicated that the individuals with spinal muscular atrophy may have lower than normal rates of muscle protein synthesis. This suggests that the muscular degeneration they experience may not be due to ongoing destruction but rather to a lack of the normal renewal necessary to maintain healthy muscles. Whether this reduced rate of protein synthesis is caused directly by a genetic abnormality or is merely a secondary result of the

disease process is not yet known.

Another observation that remains unexplained is that an infant with the acute form of spinal muscular atrophy will more often than not lack or have an abnormally small thymus gland- an organ which is involved in immune responses in early life. Having an inefficient thymus gland or none at all could impair immunity and further compromise an infant's weakened condition." (13)

Heredity

When genes are defective, they are unable to properly produce proteins that are necessary for a cell to be healthy. A destructive chain of events is triggered when a protein is absent, when there is too little of it, too much, or if it doesn't work properly for any reason. In the case of SMA, protein abnormalities prevent the normal functioning of motor neurons, leading to their deterioration and muscle degeneration.

The infantile and juvenile forms of the disease are usually inherited in an autosomal recessive pattern- both parents "carry" the defective gene (without having symptoms), each child has one chance in four of being affected. Offspring who are unaffected have a two in three chance of being carriers of the defective gene. (This is demonstrated by computer animation as shown in the printed example of the final screen of **Genetics** labled Figure 3B.)

There is currently no method to detect unaffected carriers. SMA sometimes appears within a family having no previous history of the disease. Such "sporadic" cases may result from a new gene mutation- that is, a disease-causing gene defect may develop spontaneously in the genetic material. In other cases, the defective gene can be passed down for generations without ever being "expressed," so it appears as if the disease never occurred within a family before.

SMA is the most common cause of death in infancy, affecting about one in 6,000 babies born worldwide. (14) It is estimated that the number of silent SMA carriers of the disease gene ranges from one in 40, to one in 80, and if two carrier parents bestow the gene on their offspring, the babe will be born with the wasting disease. (15)

The adult forms may be inherited in several patterns- autosomal recessive, autosomal dominant, and X-linked. In cases of autosomal dominant inheritance, one affected parent can transmit the defective gene to the children, and each child has one chance in two of inheriting the disease. In X-linked inheritance, there is one chance in two that an unaffected mother will pass on the defective gene to her children, but only boys will develop the symptoms; girls who inherit the defective gene will be unaffected carriers.

Genetic Testing for SMA

Scientist have discussed the status of genetic testing for SMA and agreed that, while testing could begin now, it will be more reliable when the precise nature of the genetic defect has been determined. At this time, scientists can identify certain genetic patterns that are associated with the disease in a particular family if affected and unaffected members of a family are available to donate blood samples for testing. However, routine genetic tests for SMA awaits the isolation of the precise genetic defect.

Epidemiology

Studies determine that the spinal muscular atrophies are not found in geographic clusters, since they occur with about the same frequency throughout the world. A 1978 study conducted in England indicated that birthplace, social class, birth order, and parental age have no apparent influence on the

occurrence of the infantile form.

Although the spinal muscular atrophies affect both males and females, the majority of sporadic cases in infancy are males. Other research has shown that more boys than girls develop the juvenile form and that boys appear to be more severely affected.

Investigators in Poland have found that the number of cases of the juvenile form occurring in girls drops significantly after age eight, with virtually no new cases after age 13. Boys, however, continue to be at risk for developing juvenile spinal muscular atrophy throughout adolescence. Some have speculated that hormonal changes may effectively "protect" girls from the disease after a certain age.

Research Approaches

The axon of a motor neuron (Figure 6) can extend as long as a meter or more from the cell body to a muscle fiber. A fundamental question facing neurologists concerned with what causes motor neurons to deteriorate is, how do motor neurons manage to survive in healthy individuals? Just how nutrients, enzymes, and other proteins processed within the cell body are transported through the long axon to the periphery of the neuron has been a subject of intensive research.

The Muscular Dystrophy Association supports the world's largest comprehensive spinal muscular atrophy program, funding promising scientific investigations into these diseases in an effort to find effective treatments and cures. The Association makes every effort to support new experimental treatments whenever there is a reasonable scientific bases for doing so. Under the auspices of MDA's Medical Advisory Committee and its Task Force on Therapeutics, Association- funded scientists intensively search for potential

therapies that might slow, stop or reverse the progress of the disease. (16)

MDA- backed researchers at Columbia University of Colorado Health Science Center, the University of Pennsylvania, and other institutions are studying basic mechanisms involved in axonal transport and axonal regeneration. Certain unknown factors determine whether an injured neuron survives and regenerates its axon or dies. Investigators at Israel's Weizmann Institute of Science are examining the biochemical events that occur when the axon of a neuron is injured. Their work may open the door to the development of drugs capable of improving survival and regeneration of neurons damaged by disease.

Trophic Factors

Another area investigators are looking into is trophic factors, which are substances (ie: chemicals or hormones) that influence muscle development as well as nerve growth, maintenance, and regeneration. Until recently, little was known about these factors, but they have been assumed to be crucial to nerve and muscle survival. Researchers are probing to see if abnormally low or otherwise impaired trophic factors vital to nerve survival results in the nerve destruction that characterizes the spinal muscular atrophies. In addition, researchers at the University of Southern California in Los Angeles and the University of Wisconsin in Madison are evaluating the interactions of TRH (thyrotropin- releasing hormone) and nerve cells. TRH may act as a trophic factor, they have found that it can enhance the survival of motor neurons grown in tissue culture. Injections of the hormone have been reported to temporarily improve the muscle strength of some patients with amyotrophic lateral sclerosis (ALS), a disease that shares many characteristics with spinal muscular atrophy. These and other investigators are working to determine how TRH exerts its influence on nerves and muscles.

Studies are also being conducted to determine why infants with the acute form of the disease often lack or have an unusually small thymus, a gland that is necessary in early life for the immune system to develop normally, as previously mentioned in the section, "Tissue Studies". These kinds of abnormalities may impair the immune systems of babies with the infantile and intermediate types of the disease, worsening their already weakened conditions.

At the University of Chicago, MDA grantees are trying to determine whether the blood serum of patients with spinal muscular atrophies and other neuromuscular diseases contains antibodies that attack a trophic factor secreted by muscle. While previous studies have suggested that thirty percent of ALS patients have such antibodies in their blood, to date there is no evidence to suggest that such antibodies are the cause of either ALS or Spinal Muscular Atrophy.

Why are Motor Neurons Attacked?

Exploring what makes the motor neurons selective targets for destruction in SMA is the purpose of research being conducted under separate MDA grants to researchers at the University of Southern California and the University of Chicago. These investigators are using radioactively labeled antibodies that can "recognize" and attack unique structural components of motor neurons. The radioactive label allows researchers to compare the motor neurons to other nerve cell types and hopefully determine what makes them selectively vulnerable in spinal muscular atrophy.

Another approach was introduced when a clinical investigator discovered that a small percentage of patients with juvenile spinal muscular atrophy have reduced levels of hexosaminidase, an enzyme that seems to be crucial to nerve cells of different types. Researchers at the H. Houston Merrit Clinical

Research Center for Muscular Dystrophy and Related Diseases at Columbia University have been studying how deficiencies of this enzyme affect different nerve types causing a variety of disorders, including juvenile SMA and Tay-Sachs disease, a deadly mental and motor disorder of infancy and early childhood.

The Columbia team has targeted the genes responsible for producing normal hexosaminidase and mapped out their molecular structures. They are now seeking possible gene mutations that may account for the different types of diseases that hexosaminidase deficiency can cause.

Seeking the Gene(s) Responsible

Controversy exists as to whether the many variants of spinal muscular atrophy are caused by different defective genes. Many have suggested that separate genes are responsible, if not for all of the variants, at least for the infantile and juvenile forms. Others are of the opinion that all of the forms are caused by one basic defect which displays varying degrees of severity and progression among individuals.

In an effort to shed light on this issue, MDA is funding a study involving about one hundred families, each of which has one or more members with SMA. Researchers at the Jerry Lewis Neuromuscular Research Center at the Royal Postgraduate Medical School in London are collecting blood samples from patients and as many of their family members as possible. This is the first step toward screening their chromosomes for clues to the location of gene defect(s) using advanced techniques of molecular genetics.

Recent Research

Fortunately, rapid advances in gene mapping (a worldwide ongoing pro-

ject) has provided researchers with breakthrough discoveries regarding SMA. In 1990, "researchers headed by investigator T. Conrad Gilliam, assistant professor of neurogenetics at Columbia University in New York, determined that the chronic childhood forms of SMA are due to a defective gene on chromosome 5." (17) The researchers were also able to deduce that the acute form of childhood SMA probably results from a defect on the same chromosome perhaps even within the same gene.

Once the gene (or genes) involved in SMA and the protein the gene makes have been identified, treatments may be developed that are based on an understanding of the protein's effects in the body. Even before such treatments become available, positive genetic identifications will make diagnosis easier and more accurate.

Until the identification of the genetic defect causing SMA is discovered, a test is available for some people with a family history of the disorder. A number of genetic segments that are often inherited along with the defective gene responsible for SMA have been found by researchers. This information can be used to make presymptomatic and prenatal diagnosis in some cases. The genetic test for diagnosis requires blood samples from family members who have and do not have SMA. Researcher T. Conrad Gilliam of Columbia University and Integrated Genetics of Framingham, Massachusetts, are both able to test for the major forms of SMA, while testing for only SMA type I is available in Boston at the Children's Hospital and at Boston University.

Although the gene was discovered on the proximal arm of chromosome 5, on the q 13 region, the most probable section for the mutation is between loci D5S6 and D5S39, and presently there is no proof for genetic heterogeneity in the disorder. The SMA mutations on chromosome 5 shows consecutive clinical abnormalities. This strongly suggests that the mutations causing the differing

severities (or types) of the disease may be different mutations at the same location similar to the situation observed for Duchenne and Becker Muscular Dystrophy.

The possibilities for the future of SMA research look very promising. Studies have the mutation causing the disease narrowed down to 20-30 million base pairs of DNA. (18) At this stage, progress will then depend on how quickly the gene can be recognized. If the mutation is discovered to be a deletion on chromosome 5, the gene will be relatively easy to find.

Researchers knew the gene lay somewhere on the lower part of chromosome No. 5, in a neighborhood called q 13. "The q 13 area is a jumble of redundant bases, rat-a-tat-tats of meaningless genetic sequences that make that part of the chromosome extremely unstable and likely to break apart and lose pieces of itself. This chromosomal instability probably explains who so many people carry mutant versions of the SMA gene; (from one in sixty to one in eighty people are silent carriers of the disease gene); it sits within a part that gets easily mucked up." (19)

Recently, in January 1995, two independent groups of biologists have reported discovering the cause of SMA. They introduce their findings as exhibits A and B, two entirely different genes. Both genes sit next to each other in the same location of chromosome 5, and each team presents substantial evidence for why its gene is the correct one. However the nature of SMA and its inheritance patterns suggest that only one of the two genes is likely to be the basic cause of the disorder.

In the first case, the gene discovered or the "survival motor neuron gene" as it is presently called, is unlike any other gene scientists have discovered. Judith Melki of the Necker Institute at the Hospital for Sick Children in Paris and 15 co-workers isolated this discovery.

Their gene discovered is small and is not associated with any other gene that scientists have identified to date. This means that researchers do not know the gene's functions the body or how in its mutant form it may cause spinal muscular atrophy. Although in support of their case that the gene is the correct one, the French researchers offer very impressive data.

In their study, the DNA of 229 patients with the disorder was screened. Scientists have found that the newly identified gene was either partly or wholly deleted in 226 of them, suggesting that the absence of the gene leads to the death of the spinal neurons. In the three other patients, researchers detected confirmation of a specific mutation within the S.M.N. gene. In their findings, 100 percent of patients with spinal muscular atrophy had disturbances in the gene, while in patients without the disorder the gene seems normal.

On the other hand, Dr. Alex MacKenzie of the University of Ottawa in Ontario, and 20 colleagues have discovered a gene that is more medically sensible as a potential cause of spinal muscular atrophy. Their gene is similar to another identified gene that prevents cells from destroying themselves, a normal cellular process called apoptosis. Many nerve cells undergo this explosive type of cell death during normal development of the brain and spinal cord. Much evidence indicates that spinal muscular atrophy occurs when the nerve cells continue apoptosis long after the process is supposed to have terminated.

If the gene the MacKenzie team has identified ordinarily serves to inhibit neuronal death, then the loss of the gene through mutation could set the stage for nerve degeneration. With that function in mind, the newly discovered gene is called "neuronal apoptosis inhibitory protein." (20)

Many scientists propose that the loss of the S.M.N. gene is essential for the onset of spinal muscular atrophy, but that if the neighboring anti-cell sui-

cide gene is lost as well, the disease will be far worse, possibly as bad as the lethal type one.

Given both cases, Dr. Gilliam and others familiar with them feel that the gene discovered by the French team is probably the one responsible for the disease, while the other gene described by the Ottawa group could be a secondary factor that if mutated, makes the disorder much worse. A simple blood test for diagnosing SMA either prenatally or in early infancy could soon be developed through new research. Present diagnostic procedures are difficult and expensive and many require confirmation through a painful muscle biopsy.

Treatments

Today, some 20,000 Americans are affected by SMA. There is no treatment beyond physical therapy, to help prolong walking ability and stamina. Therapy generally consists of treating symptoms related to physical therapy, exercises to build unaffected muscles, orthopedic aids, and preventing or correcting curvature of the spine (scoliosis) through bracing or surgery.

Although exercise is an essential treatment for physical therapy, several questions about the history of the disease remains: 1. What is the effect of disease duration on strength on a child with SMA; 2. What is the effect of exercise or overuse on muscles; 3. Is lost range of motion (ROM) or the development of contractures, (a shortening which occurs in the muscle in the absence of any voluntary activity or any electrical signs of muscle activity), a problem in children with SMA; and 4. How does hand strength relate to function?

The potential benefit of any exercise program for children with muscle disease has been questioned. In addition, there is continuing controversy over the use and type of strengthening techniques in children with muscle disease.

There has been only one published report on the effect of exercise in SMA. However, in that study group of five children with muscle disease, there were only three with a diagnosis of SMA II. Dynamic weight training did improve strength and endurance capabilities of individuals with slowly progressive muscle disorders without evidence of muscle fiber damage.

Although there is currently no cure for any form of SMA, many drugs have been tested for their ability to combat these diseases but, thus far, none has proved capable of halting or reversing motor neuron destruction.

The muscular Dystrophy Association supports the world's largest comprehensive SMA program funding promising scientific investigations into MDA diseases in an effort to find effective treatments and cures. Pinpointing the gene and genetic defect responsible for the illness, makes more accurate diagnosis possible and provides a crucial step toward developing a treatment.

Conclusion

Spinal Muscular Atrophy (SMA) is an inherited neuromuscular disease that causes a deterioration of the motor neurons (specifically the Anterior Horn cells of the spinal cord). These motor neurons that control muscles are selectively destroyed resulting in varying degrees of atrophy, weakness, and paralysis of the trunk and limb muscles.

There are four basic types of SMA, which are classified according to the severity of weakness, age at onset of symptoms, and distribution of muscles affected. Spinal Muscular atrophy is the most common cause of death in infancy, afflicting about one in 6,000 babies born worldwide. The disorder ranges from the very severe, rapidly progressive form, present in infancy, to the relatively mild adult form having little or no impact on life expectancy.

It is estimated that the number of silent SMA carriers of the disease

gene ranges from one in forty, to one in eighty, and if two carrier parents both bestow the gene on their offspring, the baby will be born with the wasting disease. Today, some 20,000 Americans are affected by SMA and there is no treatment beyond physical therapy, to help prolong walking ability.

Fortunately, recent discoveries in a worldwide research program, sponsored by the muscular Dystrophy Association, has found the genetic defect to be on the q13 region on chromosome 5. Pinpointing the gene and genetic defect responsible for the illness, makes more accurate diagnosis possible and provides a crucial step toward developing a treatment.

Artwork Report

Computer technology has given the Medical Illustrator another useful tool to educate various audiences. This body of work is a visual introduction to, and explanation of Spinal Muscular Atrophy through the aid of interactive media and animation for the general audience, patients, and their families.

Information in this program was designed to match the background of the lay public. This also included illustrations which had to explain the disorder to those who only have a basic understanding of anatomy.

The interactive collection of work is a series of screens that explain various aspects of SMA and use animation to demonstrate nerve impulses and heredity. These screens are entitled: Anatomy, Genetics, Muscle, Histology, The Motorneuron, Affected Muscles, Classification, and Research.

Artwork was either scanned in or created in Adobe Photoshop 2.5 or Adobe Illustrator 5.5 and imported into Macromind Director 4.0 as pict files. An interactive program like Director allowed the user to control which screen to view by activating the mouse button. Such controls as a reverse, menu, and forward buttons were created to maneuver from screen to screen.

In the development process, the first step was to select the important issues involving SMA, and to then sketch out each screen to best illustrate that issue. For the Title, Menu, and Acknowledgments screens, a marbled paper was chosen. This was also used for the surface color of the buttons. For the other screens to look uniform, a brown background was also selected. These were scanned in Photoshop in 72 dpi, or dots per inch, (for screen viewing and to save memory). (The brown background was also scanned in at 150 dpi to be used in separate files for printing purposes.)

The first screen, or Figure 2, focuses upon the anatomy of the Central

Nervous System (CNS) and the Anterior Horn cells that are affected. For this screen, pen and ink drawings of the CNS and a transverse section of the spinal cord were scanned in at 72 dpi and colorized in Photoshop.

Using animation, this second screen, or Figures 3A and 3B, explains the autosomal recessive pattern in which an SMA gene is passed to a child by carrier parents. To design this screen, two human figures, and the chromosome was created in Adobe Illustrator 5.5 and brought into Photoshop to be colorized.

Figure 4 illustrates the anatomy of a healthy muscle, its fascicles, and myofibrils and was developed in the same manner as Figure 2.

The fourth screen, or Figure 5, shows two examples of histology sections of healthy muscle and muscle affected by SMA. The SMA affected muscle particularly shows the difference between atrophied, hypertrophied, and normal muscle fibers. This involved scanning two black and white photographic examples of muscle tissue and colorizing them. Alterations had to be made to clarify the fibers and connective tissue to bring out the texture.

Figure 6 is a dynamic view of the motorneuron and muscle with animated theories of normal, partial, and failed nerve impulses and muscle spasm.

With superimposed muscles over a human body, this sixth screen, or Figure 7, presents the specific muscle groups that SMA weakens. For experimental purposes in this screen, muscles were drawn in colored pencil on vellum over a black and white photograph of a model. The photograph was then scanned into Photoshop and the opacity reduced for a "ghosting" effect. The vellum drawing was also scanned and adjusted in Photoshop and then superimposed on the nude image.

Figure 8 describes the four types of SMA by using a simple horizontal bar chart. By depressing the mouse on each bar, a separate window pops up

explaining the characteristics of that type.

In this last screen, or Figure 9, a large chromosome 5 illustrates the region in which the SMA gene is believed to be. This screen describes the latest research including the discovery of two suspected genes that cause SMA. In creating this screen, the chromosome was drawn in Illustrator and imported and colorized in Photoshop. In the background, a pattern of chromosomes was made by using the "skew" effect, reducing the opacity (so as not to conflict with the large chromosome in the foreground and type), and then dragging copies of it using the "option" key.

All images and backgrounds were saved as pict files and imported into Macromind Director as cast members. Assembling each screen was then done by dragging each cast member onto the stage. All of the shadowed text was used in Director for simplicity and used as cast members. (This enabled me to move and change text if I needed to, unlike a set image imported from Adobe Photoshop 2.5.) A title, menu, and acknowledgment page was created. In the menu screen, labeled Figure 1, the user can access any of the eight screens by clicking on their prospective buttons. Once on a titled screen, the viewer can move forward, backward, or to the menu by using the Lingo-programmed buttons; at the "Acknowledgment" screen, the user has the option of moving backward, or exiting.

Once all the screens were completed, a projector file was made so the viewer could open and close it. This was necessary because the computer would have to be on during Bevier Gallery hours and the viewer would need to access the program at any time.

In order for the animations to run quickly and smoothly, the computer had to be comparable to a Quadra or Power Mac. This is because the computer's speed had to run fast enough (60 megahertz or more) to load each frame for

15-25 frames per second. Unfortunately, there is a shortage of fast computers to borrow from the computer labs for the full duration of the thesis show.

However, due to the color quality that I strived for, I felt this dilemma may have been eased if a 256 color palate was used instead of thousands. The second step to solve this problem was to create a duplicate file with a separate color palate of 256 colors, and adjust all the cast members to the new palate; but this didn't help an older, slower computer from loading and running the animations any faster. In any case, this was a valuable learning experience.

To my knowledge, in Macromind Director, there is no way of exporting one frame for printing, and since it would be in 72 dpi, quality would be poor. To save as pieces for my portfolio, certain images were not only saved in 72 dpi for the screen, but in 150-200 dpi for printing. These four pieces were recreated (as close as possible) to the way the original screens looked. (Unfortunately, the background and muscle colors were not Pantone colors, and thus printed very dark and muted.) Type was also done in Photoshop (with anti-aliased on) because of better color choices. (Quark Express 3.3 choices for color type were limited). Eventually the whole projector file could be saved onto a compact disk to educate the lay public, patients, and their families about Spinal Muscular Atrophy.

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Screen Artwork

The opposite pages are color copies of the printed versions of screens shown in Macromind Director 4.0:

1. Figure 1
   Menu
   Abobe Photoshop 2.5,
   Macromind Director 4.0

2. Figure 2
   Anatomy
   Pen and ink, Abobe Photoshop 2.5

3. Figure 3A
   Genetics-
   screen before animation
   Abobe Illustrator 5.5,
   Abobe Photoshop 2.5

4. Figure 3B
   Genetics-
   screen after animation is completed
   Abobe Illustrator 5.5,
   Abobe Photoshop 2.5

5. Figure 4
   Muscle
   Pen and ink, Abobe Photoshop 2.5

6. Figure 5
   Histology
   Black and white histology
   photographs, Abobe Photoshop 2.5

7. Figures 6, 6A-6D
   Motorneuron
   Abobe Illustrator 5.5,
   Abobe Photoshop 2.5

8. Figure 7
   Affected Muscles
   Black and white photograph,
   colored pencil, Abobe Photoshop 2.5

9. Figure 8
   Classification
   Abobe Photoshop 2.5,
   Macromind Director 4.0

10. Figure 9
    Research
    Abobe Illustrator 5.5,
    Abobe Photoshop 2.5,
    Macromind Director 4.0

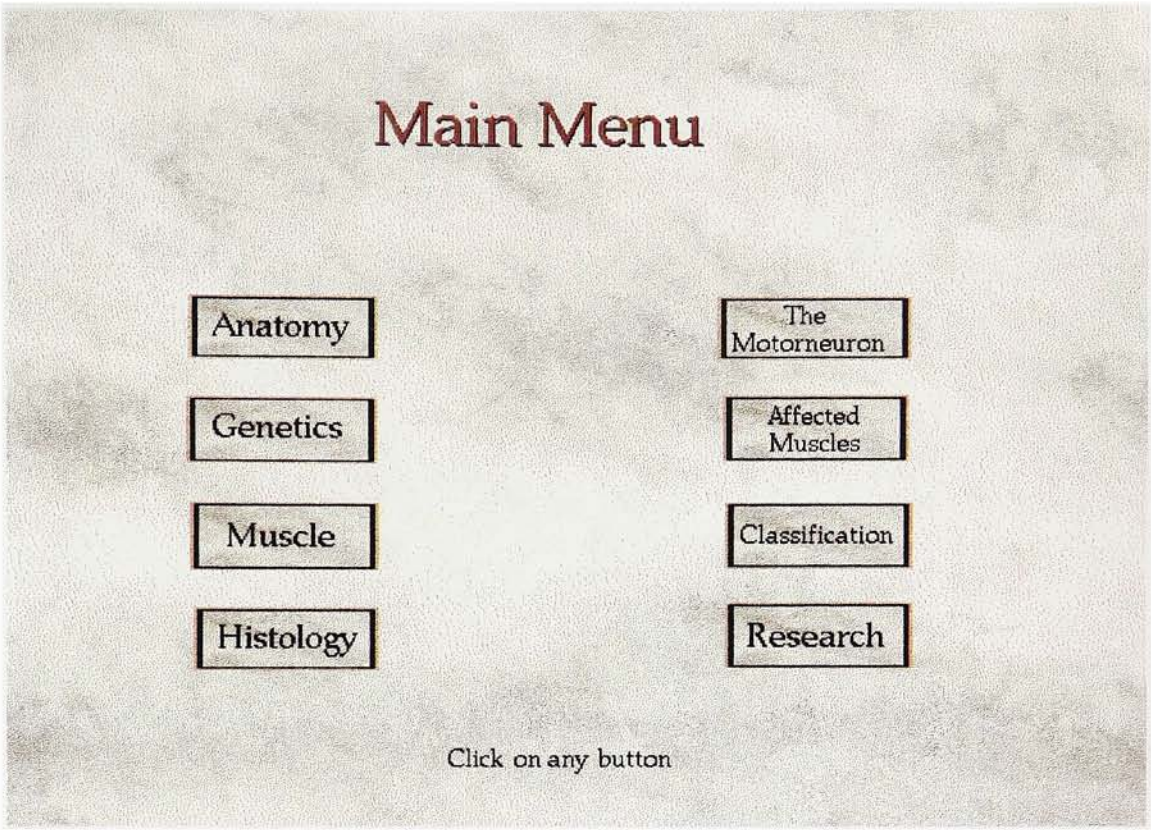

Figure 1. Menu

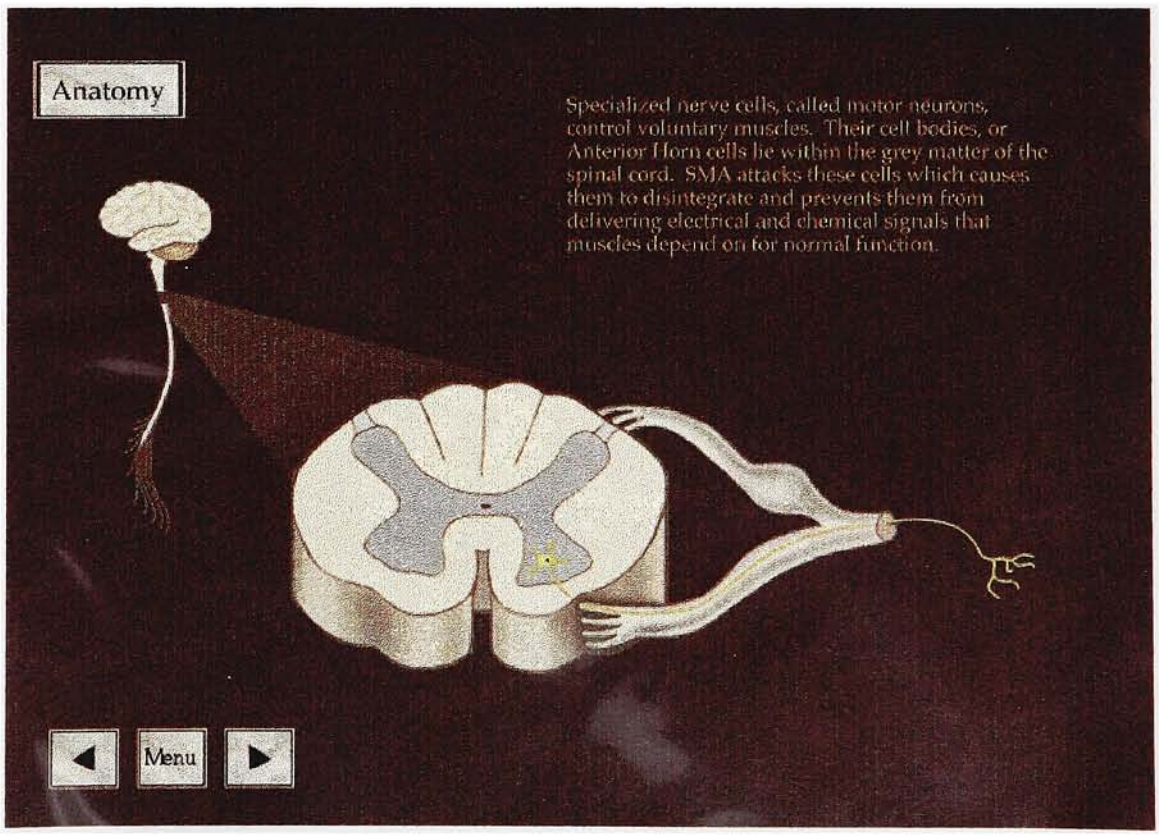

Figure 2. Anatomy

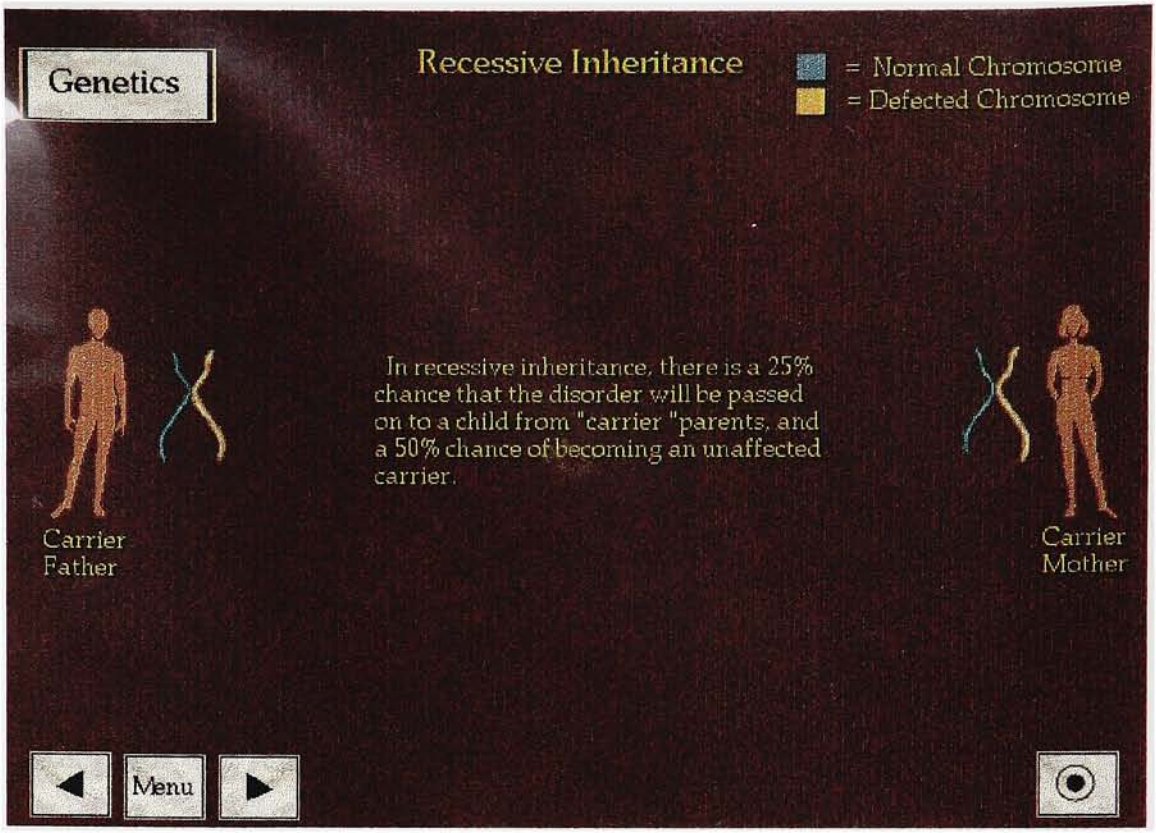

Figure 3A. Genetics

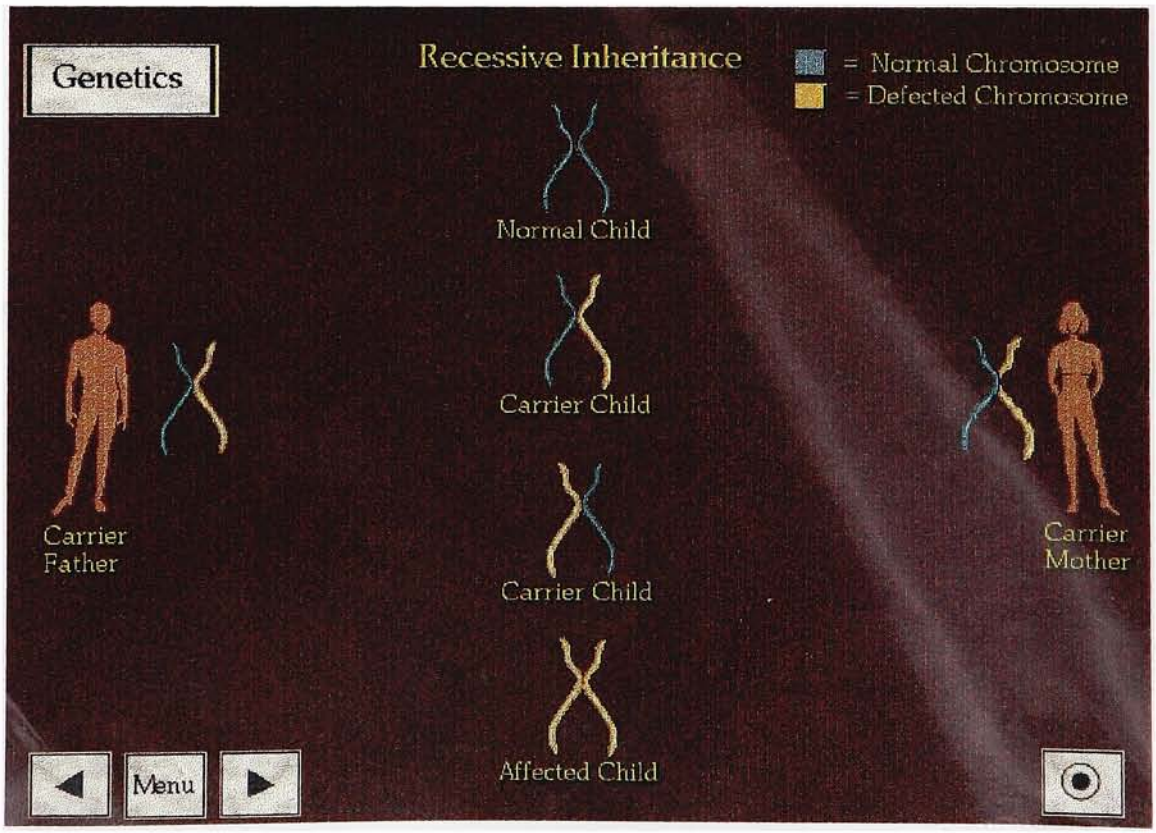

Figure 3B. Genetics

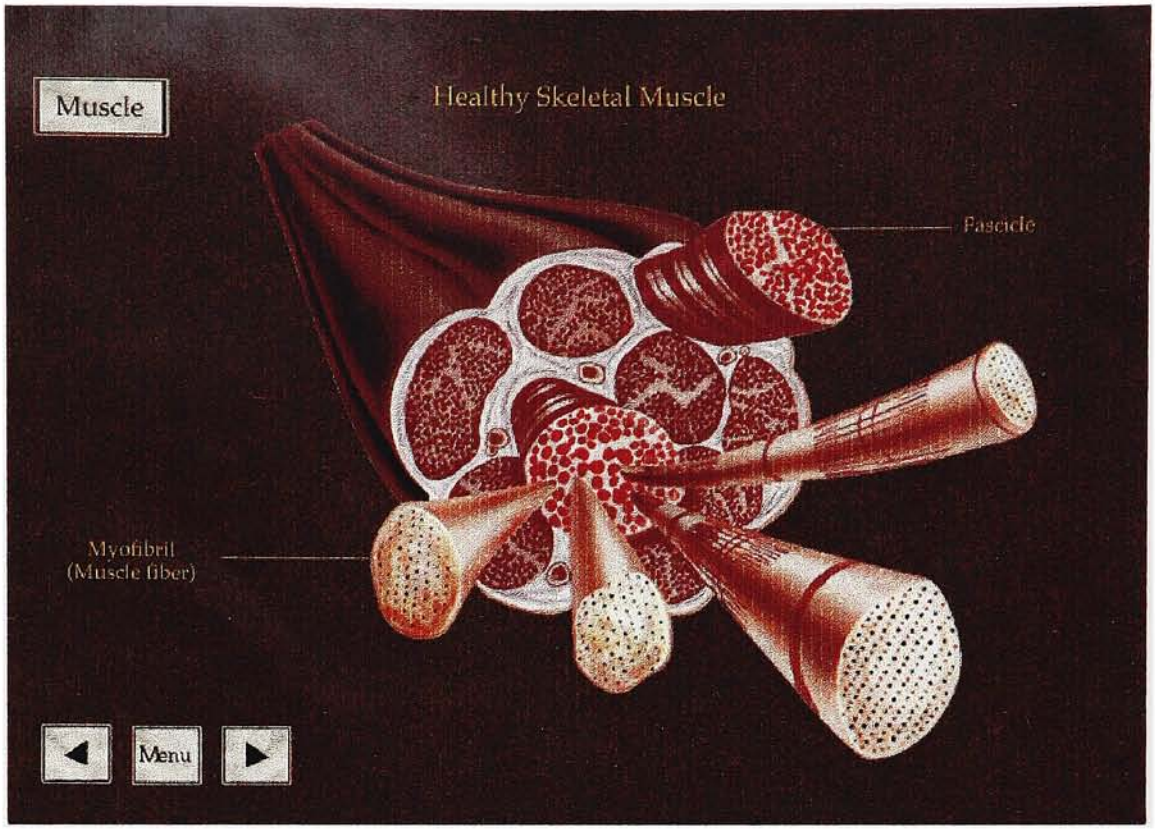

Figure 4. Muscle

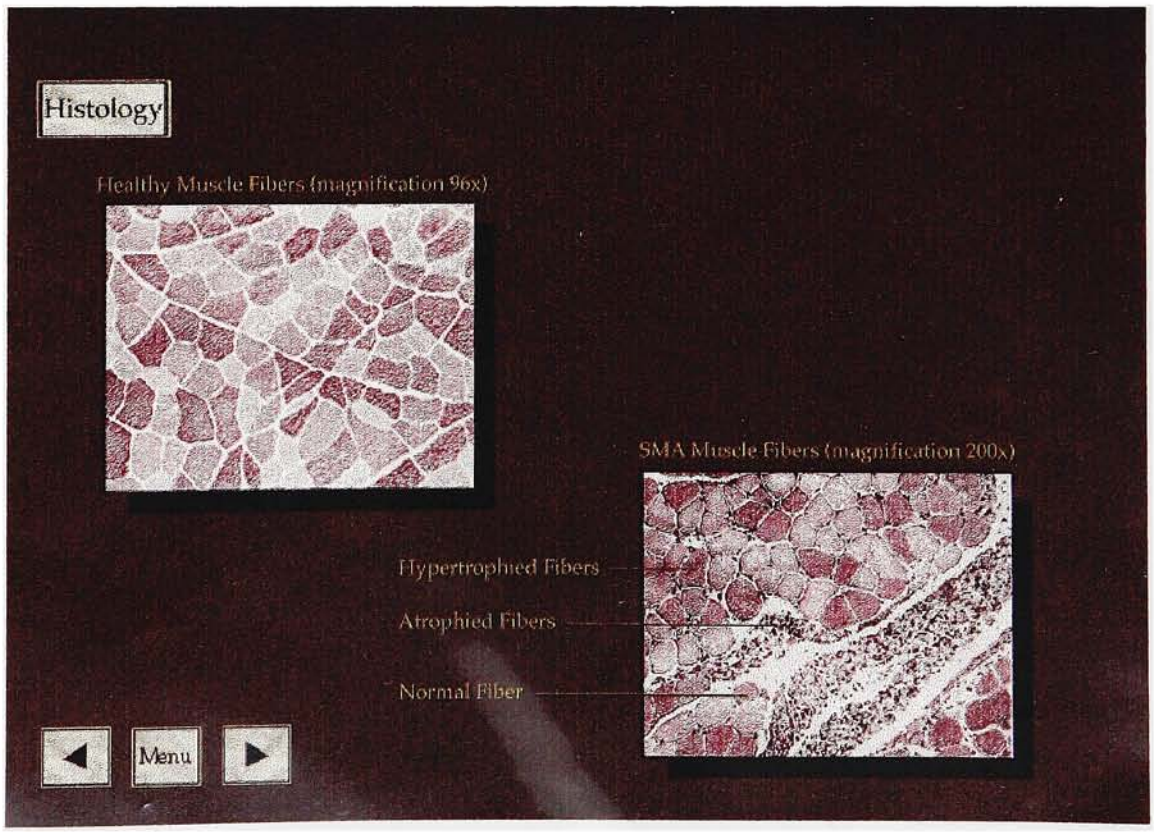

Figure 5. Histology

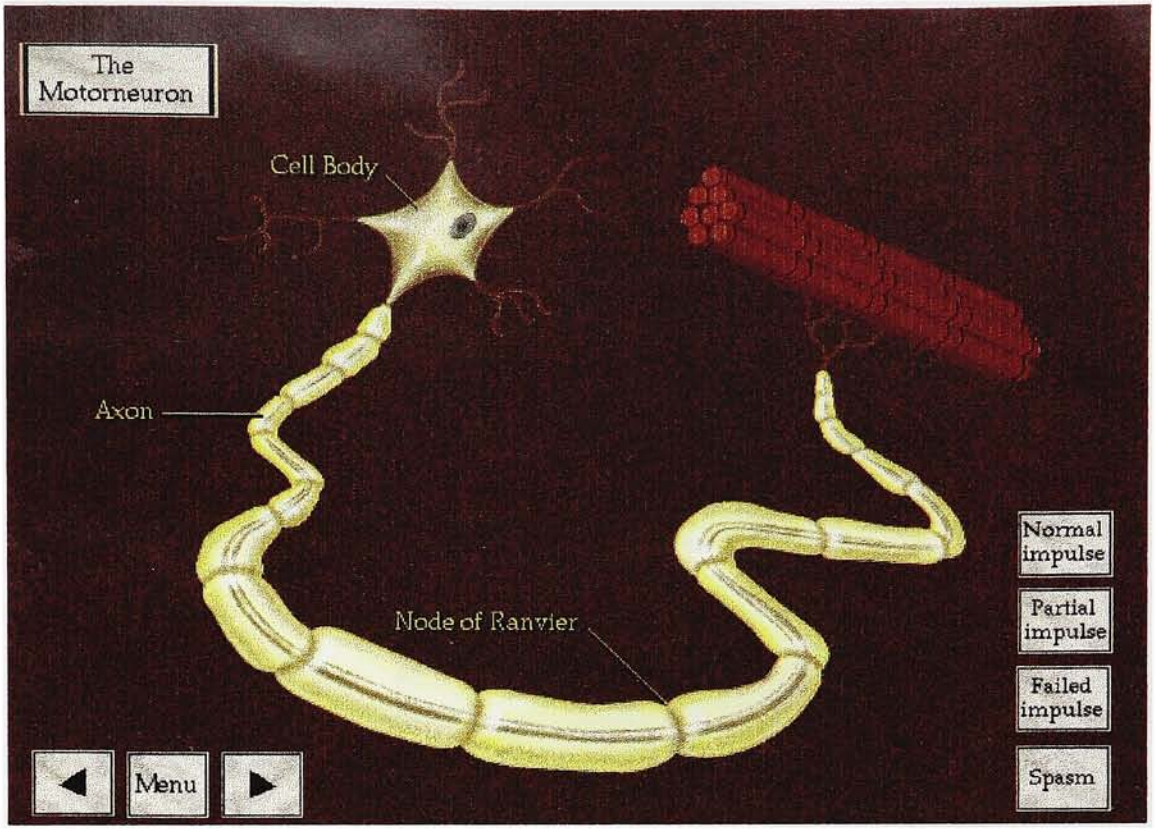

Figure 6. The Motorneuron

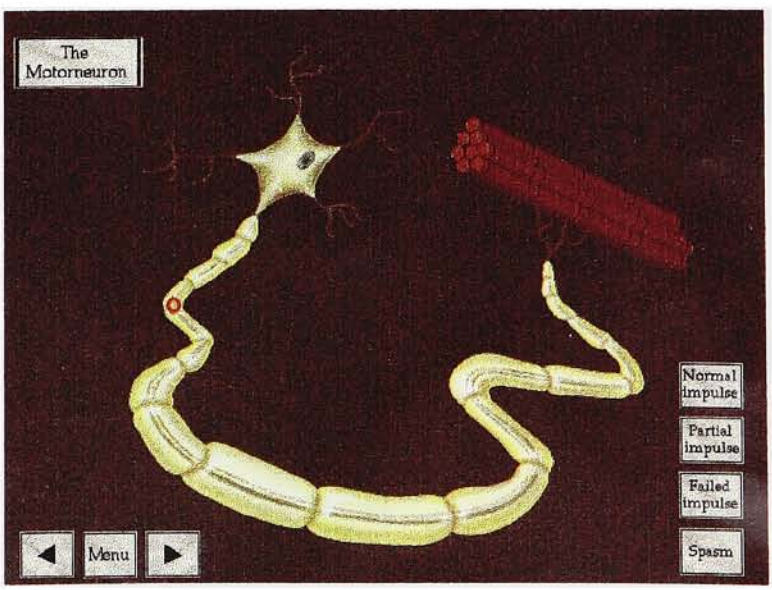

Figure 6A. The Motorneuron; Normal impulse

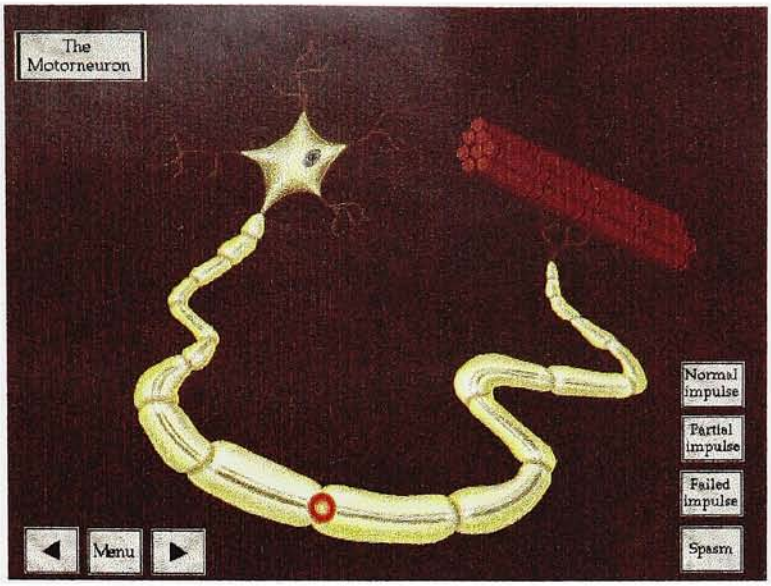

Figure 6B. The Motorneuron; Normal impulse

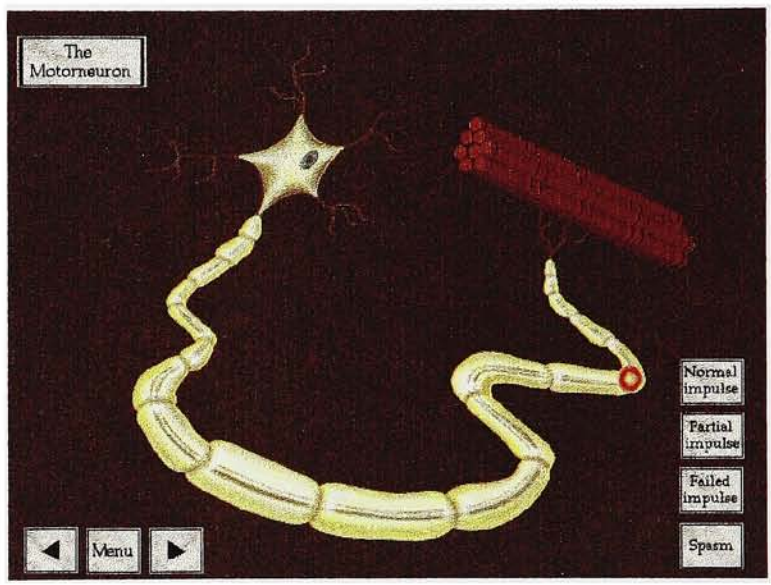

Figure 6C. The Motorneuron; Normal impulse

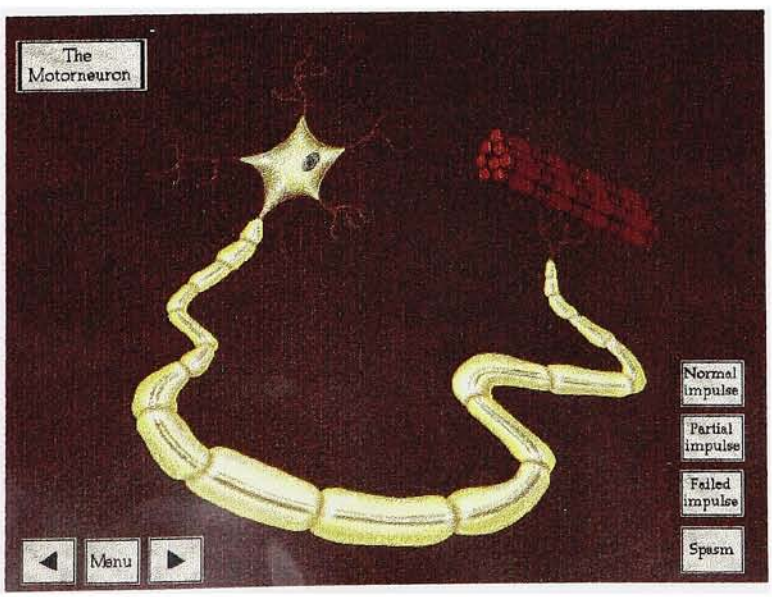

Figure 6D. The Motorneuron; Normal impulse

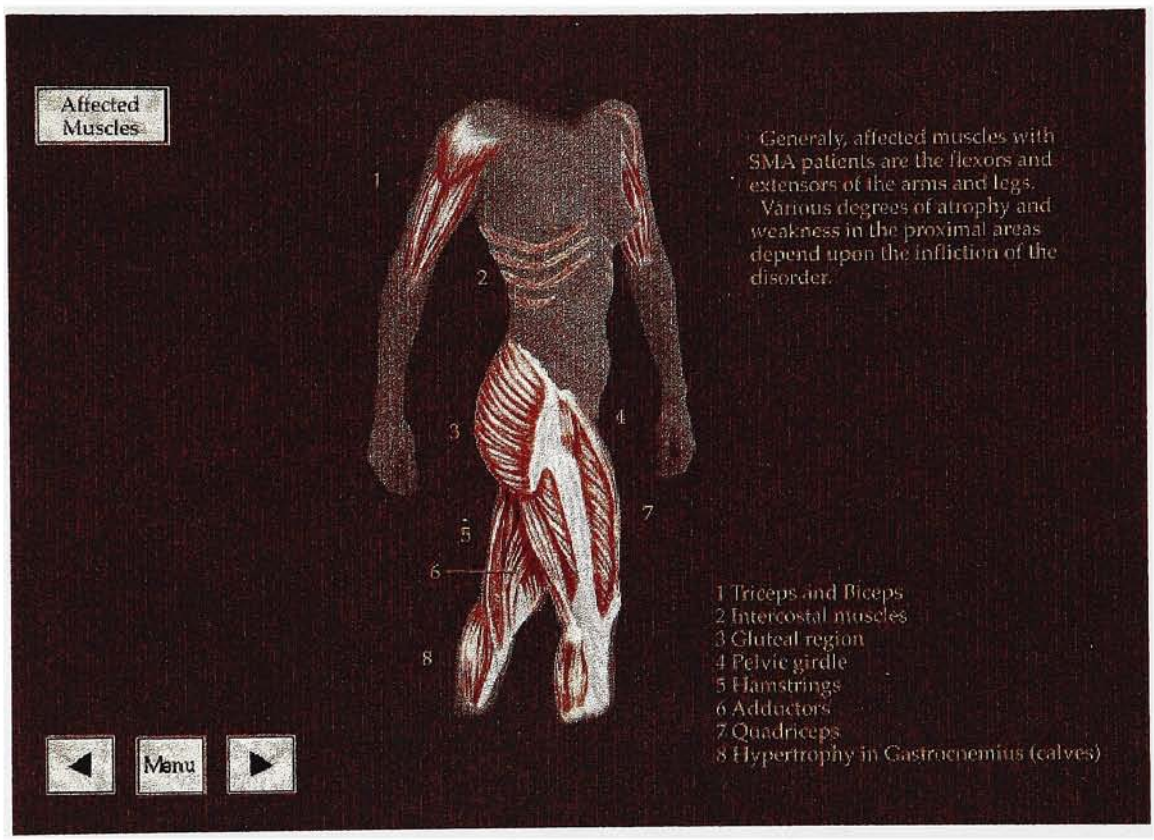

Figure 7. Affected muscles

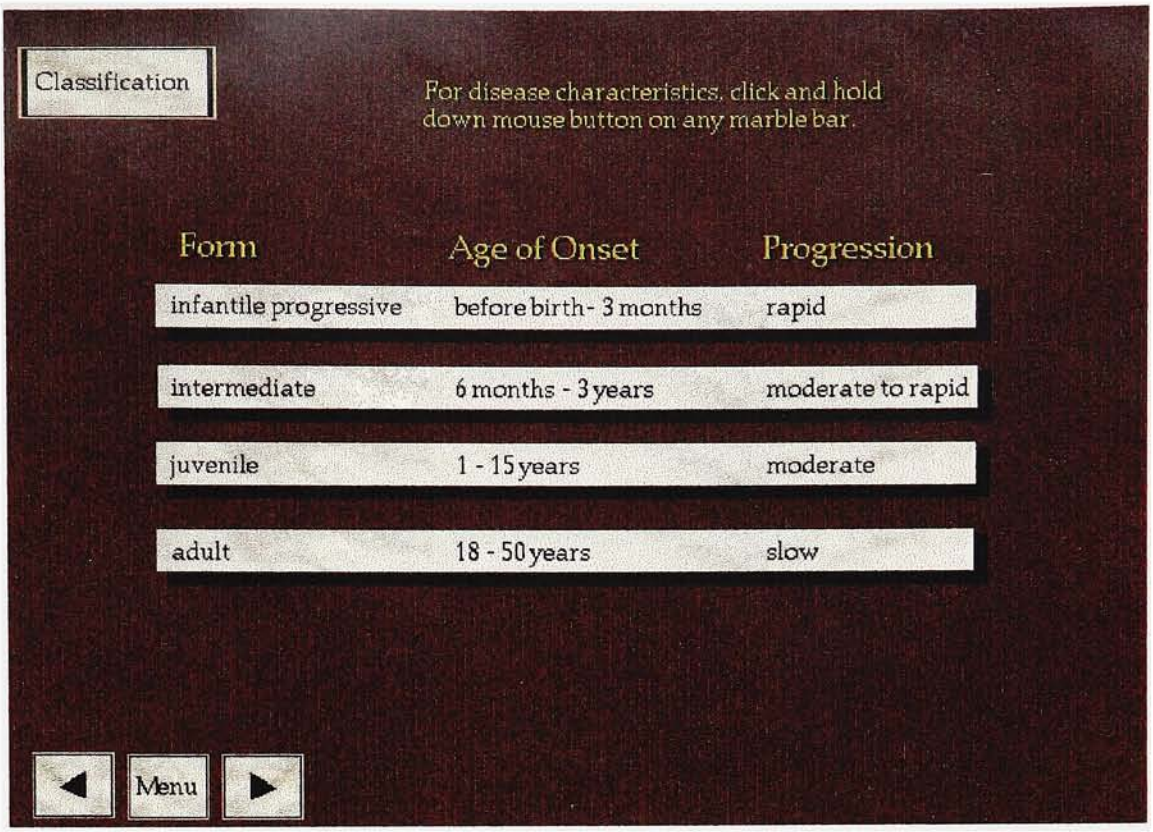

Figure 8. Classification

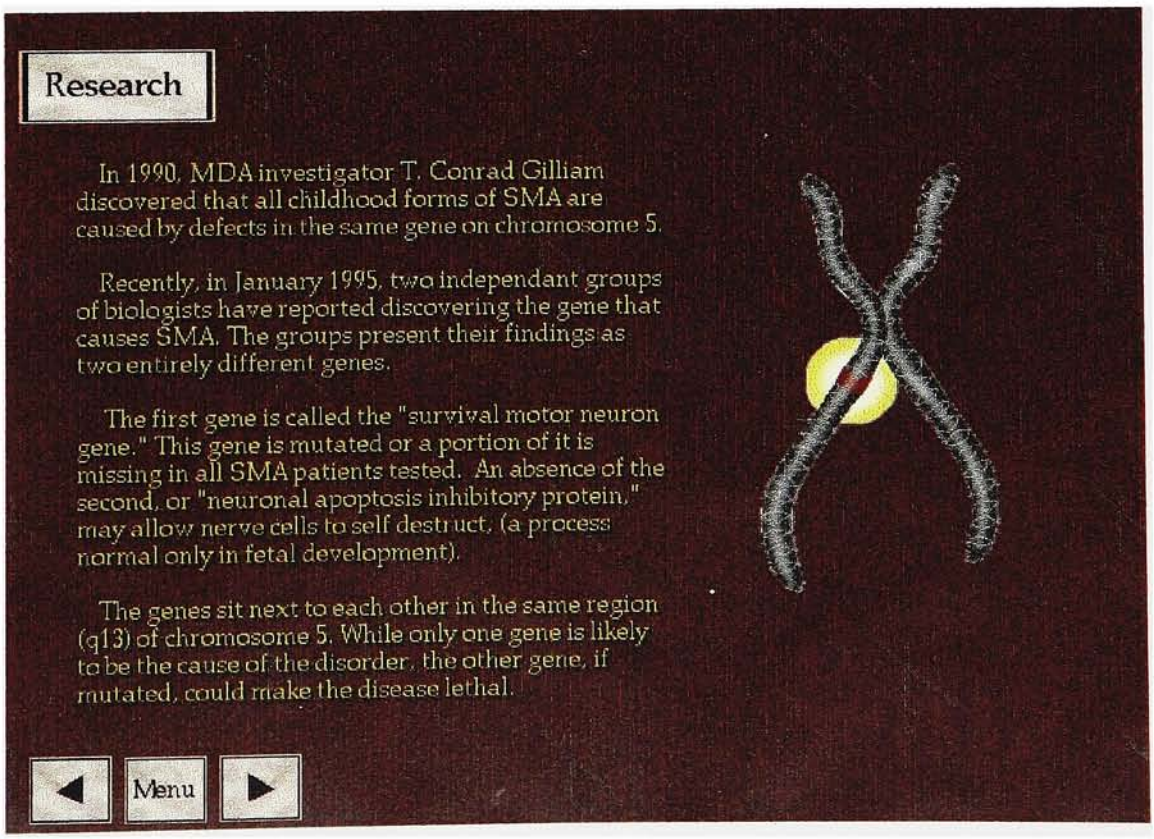

Figure 9. Research