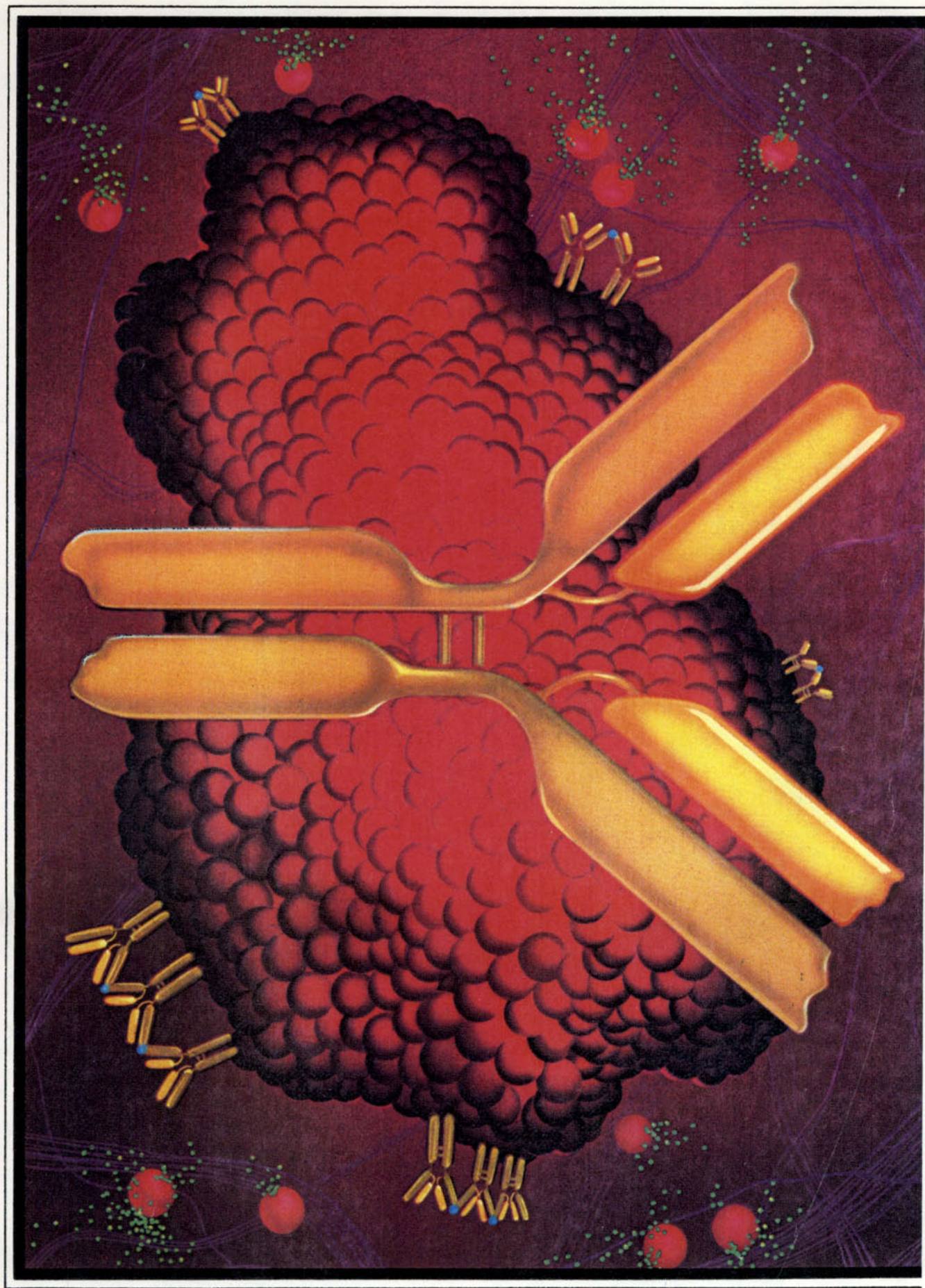


AUTOIMMUNE DISEASE

When the body goes awry

Michael Craig Thigpen

Tennessee Scholars Senior Project



PREFACE

I arrived at this topic for my **Senior Project** (boldfaced for emphasis) for my Tennessee Scholars Program in kind of a roundabout way. For about a year I spent my time working with Dr. Ranjan Ganguly in his molecular genetics laboratory dealing with *Drosophila melanogaster* fruit flies. I feel that my time there was rewarding, but not very productive. For the project I worked on, which I was going to use for my **Senior Project**, produced no real results. Whether this was due to my own character flaws (for I grew tired of counting flies) or truly due to problems within the experiment itself, I do not know. But I did know that if I was to turn something in I would need to find a new project to work on.

I decided upon my present (and final topic) after I had taken a class in immunology in the fall of 1990 where we studied autoimmune diseases in the class for a week or so. The idea of the body's immune system attacking its own tissues intrigued me, so I decided to use this as project. First, however, I had to sell my Tennessee Scholars' advisor, Dr. Bruce Wheeler, on the idea. This was actually no problem because he has always been very supportive of everything the Tennessee Scholars do. I wish to take this time to thank him for the years he spent with my class of Tennessee Scholars. He has been very patient with me and has been a very enjoyable person to work with. I wish him and his new Tennessee Scholars all the best. Now back to the paper.

So with his blessing I began to research my topic. Now as I look back at the time I spent attempting to write this paper, I feel a great sense of accomplishment, but also a great deal of frustration. When I chose to do my **Senior Project** on this topic, I thought that I could write a fairly comprehensive study on the nature of certain autoimmune diseases. What I did not realize was that a comprehensive paper on this subject required a massive amount of research and writing. (I believe that I spent two weeks, almost day in and day out, simply typing this paper.) For the majority of the time I was working on this paper, I felt as though I were working on a book; it was just that tremendous. When I had started I believed that this would not be that demanding, for like most undergraduates who really do not get the opportunity to write such large papers the longest thing I had written was only about ten to fifteen pages long. This project has really opened my eyes to the effort it takes to get any piece of material published (even though I, by no means, attempted to get this project published), whether it is a popular novel or a scientific paper for a journal. For all the reasons above I wish to thank all my friends for helping me and being very patient with me while I struggled with this. I especially wish to thank my friend Wade Hunt for letting me use his computer and taking time out of his busy schedule to help me insert and position all the diagrams within this report. Without his help, I would not have finished this project and I am greatly indebted to him.

In closing, I feel that I have produced a project very worthy of the Tennessee Scholars Program. In fact, I hope that this will aide the Program to recruit the best possible candidates in the future.

Michael Craig Thigpen

Michael Craig Thigpen
Class of 1991

INTRODUCTION

The body (human and otherwise) is a remarkable piece of machinery. It is fairly self-sufficient, needing only a source of energy for nourishment. In addition, it is able to heal itself, to transport itself, to think for itself, and countless other abilities which have only begun to be explored in depth. One of the most remarkable aspects of the body is the ability to defend itself. The body will fight off any invaders which it may encounter and will remember these invaders in order to fight them off more quickly the next time, if they reappear. So what happens when the body's defenses begin to malfunction. Most of the time this simply allows some type of bacteria or virus to cause infection. But what if this system is totally devastated one way or another. A classic example of this can be observed in those who have AIDS. In this case, the body no longer has any defenses against any type of foreign invasion; thus, the body is rapidly attacked and easily succumbs to the invaders. The mechanisms of autoimmune disease are almost exactly opposite that which occurs in AIDS. In autoimmune disease it is not the failure of the immune system which causes problems for the body, but is the hyperactivity of certain immune responses which characterize this type of disorder. Autoimmune disease, specifically, is a disorder which occurs where the immune system malfunctions and begins to produce defenses against the body's own tissues. Common examples of these include lupus, juvenile diabetes, and rheumatoid arthritis. The problem facing most of those who have the disease and those attempting to treat them is that it is unknown what exactly causes autoimmune diseases. So unlike normal diseases, there is not one factor which can be blamed. This makes trying to find a cure a much more difficult process. Many autoimmune diseases have been studied for over three hundred years and some even from the time of Christ. In comparison, the virus which causes AIDS, the human immunodeficiency virus, was isolated in only three years. So, needless to say, there is still a great deal of mystery surrounding these disorders. The purpose of this paper, therefore, is to attempt to dispel some of this mystery.

There are basically two general groups of autoimmune diseases, those called organ-specific diseases and those called collagen diseases (or better described as connective tissue diseases, for collagen is not the only type of connective tissue to be affected). Organ-specific diseases are those where the extent of the disease is generally confined to one organ. The autoimmune responses are also localized against protein compounds located on the diseased organ. On the other hand, connective tissue diseases are generally systemic diseases affecting many different organ systems at one time. The autoimmune response associated with these diseases are often directed against common components (i.e. RNA and DNA) which are seen in all of the diseased organs.

In an attempt to give the reader a better understanding of the processes which occur in autoimmune diseases, an example of each type of disease (the two which probably have been studied the most) will be discussed within the text of this paper. But due to the complex nature of the connective tissue diseases, an example of an organ-specific disease, myasthenia gravis, will be addressed first. Then after this, systemic lupus erythematosus, an example of a collagen-vascular disease, will be discussed.

MYASTHENIA GRAVIS

GENERAL INFORMATION AND HISTORY

Imagine waking up in the morning after a very restful night of sleep and you begin your daily routine. But as the day continues you get weaker and weaker until you can't continue what you are doing. So you decide to take a rest. After an hour or so you feel much better, so you continue your previous activities. Once again you get weaker, but this time after just a little while. This scenario may sound like the person is simply out of shape when he or she actually may have myasthenia gravis, a debilitating autoimmune disease which affects the neuromuscular junction controlling many of the bodies' voluntary and involuntary muscles. This disease mimics the normal symptoms of being out of shape so closely that a person with myasthenia gravis who has not yet been diagnosed will often believe that this is the sole extent of the problems. In fact, this person will often begin a routine of daily weight training to become stronger when actually all he/she is doing is weakening him/herself. In order to prevent this from happening one must try to understand myasthenia gravis itself.

The first mention of myasthenia gravis in scientific literature probably occurred when T. Willis described it in a report published in 1685, but there was still a great deal unknown about this disorder. Over the next two hundred years, there were only about seven cases of myasthenia gravis reported in the journals of period. Then in 1901 there was a breakthrough in the study of this disease. Two German scientists, L. Leopold and C. Weigert, discovered the importance of the thymus in myasthenia gravis as ascertained by the presence of a thymic tumor. This discovery led to the use of thymectomy as a method of treatment. Then in 1961, the association of myasthenia gravis with a problem in the immune system was finally discovered by R. A. Good, et al. and by J. F. A. P. Miller in separate reports published at the same time. Once these physicians made this observation there were many rapid advancements in the treatment and study of pathological mechanisms of this disease allowing much more effective care of afflicted patients.¹

Myasthenia gravis affects about four to six people out of every one hundred thousand (hardly a very common disease, but still one of the best understood). It often affects women twice as many times as it does men. Women often become afflicted between the ages of twenty and thirty, whereas men become afflicted between the ages of forty and sixty. (This pattern of incidence can be seen in many other autoimmune diseases including lupus which will be discussed later.)²

Specifically, myasthenia gravis (MG) is an autoimmune disease where an antibody response toward the acetylcholine receptor in the neuromuscular junction is produced. The term myasthenia gravis comes from Greek meaning "grave muscle weakness," which is actually what happens. Normally, a neurotransmitter (a specific chemical which plays a role in the transmission of an impulse from one nerve fiber to another) called acetylcholine (ACh) is released from the presynaptic terminal of the neuron and crosses the synapse. Once across, it attaches to a receptor specific for it (AChR, shown in Figure 1) on the muscle cell and causes the muscle to contract by producing a membrane depo-

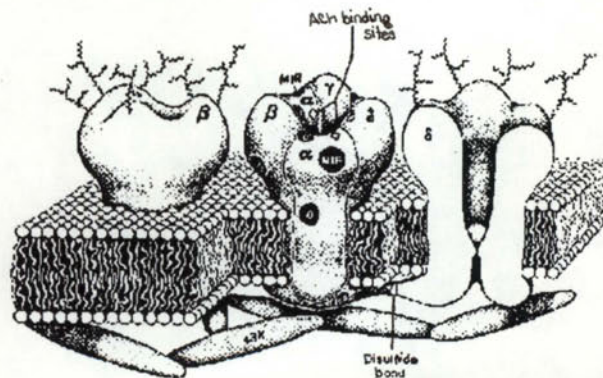


Figure 1. Structure of AChRs in the postsynaptic membrane. Studies have found what subunits (shown in Greek letters) compose this receptor. The MIR is the main immunologic region where most antibodies bind. The other numbers show alternate antibody binding sites.

larization. Next, a membrane-bound enzyme called cholinesterase degrades the ACh, so that the receptor can become free to accept another ACh signal. In myasthenic patients, however, these acetylcholine receptors are destroyed or interfered with so as to produce inadequate binding of ACh to produce depolarization of the muscle. Thus, this makes contraction of the muscle much more difficult, resulting in rapid muscle fatigue.² A diagrammatic summary of this process is shown in Figure 2.

MG AS AN AUTOIMMUNE DISEASE

Much of the research on the mechanisms of myasthenia gravis has been performed on rats which have been modified in a special way. These rats have been injected with acetylcholine receptors from other species in order to get an immune response which would also react to the rat's own AChRs. This cross-reactivity, which is due to the similarity between receptors from other species, allows a condition to develop which is very similar to that of human MG. This condition called experimental autoimmune myasthenia gravis or EAMG was attempted in a variety of species, but the rat produced a syndrome which was most like that of MG. The exact development of EAMG has been shown in Figure 3. The only difference between EAMG and MG in development is that patients with MG do not have any white blood cells which react to the antibody-receptor complex as in EAMG. All other characteristics are almost identical in both.³

It has been found that there are three possible ways that myasthenia gravis may affect acetylcholine receptors. In each of these, the greater the effect is on these receptors, the more severe the disease is. The first theory is the activation of complement (a lytic substance in normal serum that combines with antigen-antibody complex, producing lysis when the antigen is an intact cell) on AChRs. It has been found by electron microscopy that in the membrane of the nerve postsynaptic terminal in myasthenic patients, there are fewer folds than those in normal people. These fewer folds are in turn shallower and thus have a decreased area of contact with the presynaptic terminal as is shown in Figure 4.⁴ It is thought that this occurs possibly because complement along with immunoglobulins (a family of chemical compounds, abbreviated Ig, which include the antibodies), particularly IgG, act on AChRs to degrade and fragment this membrane. In support of this theory, scientists have found the C3 and C9 components of complement located within the neuromuscular junction. In addition they have found a general reduction in concentration of complement in the blood of myasthenic patients which occurs because at any one time there is a limited amount of complement in the body. Thus, if there is an increase in complement activity (a process which includes the degradation of complement), then there must be lower levels elsewhere in the body until more complement is produced. Although complement is an important part of this mechanism, it is not involved in the next two theories myasthenia gravis affects acetylcholine receptors.⁵

The second involves the blockage of the acetylcholine receptor by the antibodies produced against these receptors. Tests have shown that antibodies (also called autoantibodies in this

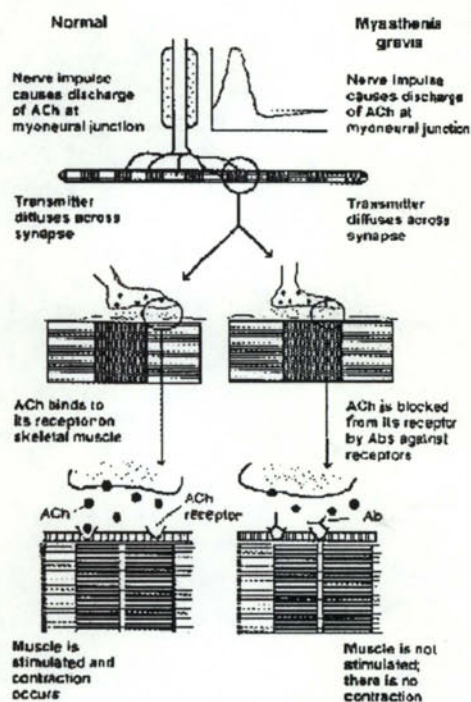


Figure 2. Comparison of normal muscle function and muscle function in myasthenic patients.

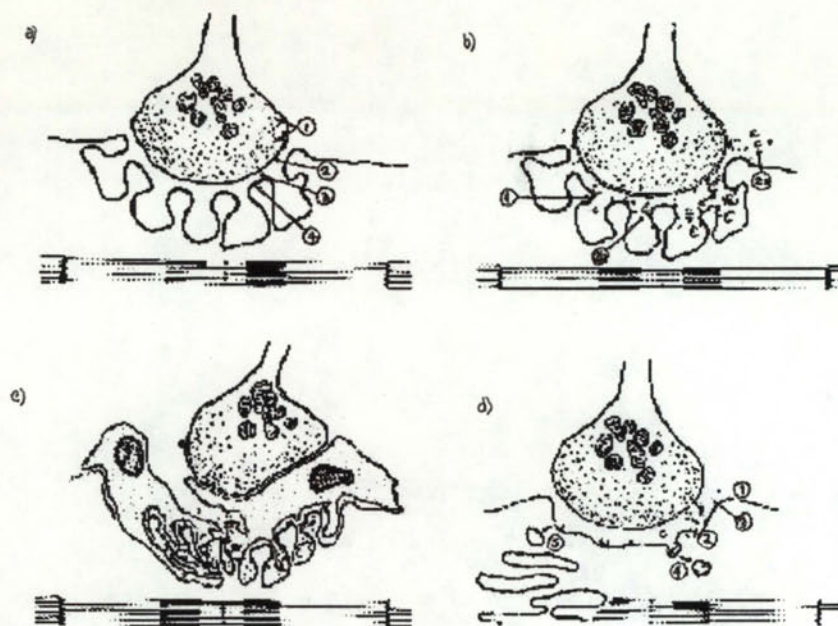


Figure 3. Development of EAMG. a) Normal neuromuscular junction with #1 showing the ACh in the presynaptic terminal represented by #2. The synapse and postsynaptic terminal are represented by #3 and #4, respectively. b) #1 shows Ab binding to AChR. #2a and #2b show activation of complement. c) While blood cells attracted to the area by complement activity begin to attack the postsynaptic terminal. d) The postsynaptic terminal #1 has fewer folds in it. The binding of Ab (#2) and activation of complement (#3) is an ongoing process further simplifying the membrane. #4 and #5 show further AChR degradation.

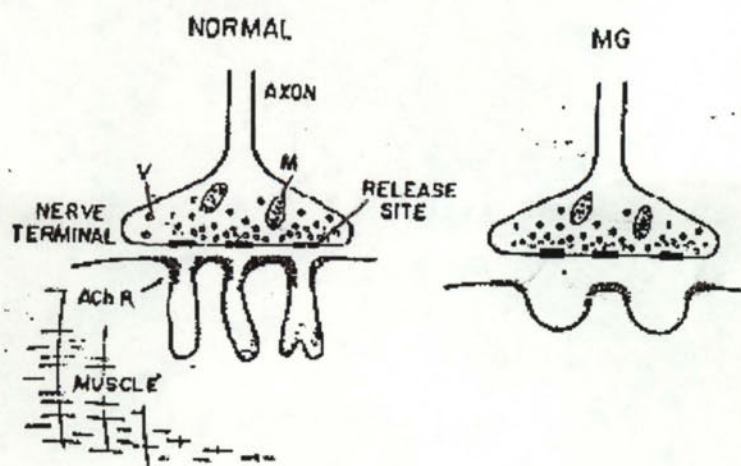


Figure 4. Comparison for normal and MG-associated junctions show increased simplification in the postsynaptic membrane of the myasthenic neuromuscular junction.

case, "auto" meaning self) do bind to a portion of the receptor, but not the part that binds the ACh itself. It is thought that once the ACh binds to the receptor, it produces a special configuration which allows the antibody to bind. Thus, there is no binding of Ab without ACh being present. This model, as is shown in figure 5, also explains how muscle strength decreases as physical activity increases due to the increased levels of ACh present.⁶ This possibility is very remote, though, because further tests in EAMG-afflicted rats have shown that when complement is removed from the junction, antibodies bind to the receptor without negatively affecting the transmission. This leads most to believe that the antibody actually has little to do with the function of the ACh receptor.³

The final mechanism by which acetylcholine receptors are thought to be affected is by accelerated degradation of these receptors (figure 6a). This process has been studied the most of the three. It has been shown that accelerated degradation occurs because of cross-linking of the receptors by IgG antibodies. IgG is Y-shaped, thus is able to bind and link two receptors together. This binding can lead to the formation of large clusters of receptors being formed with as many as sixty receptors in a single cluster (see figure 6b). This allows these receptors to be endocytosed as normally occurs, but at a much higher rate due to the greater concentration present in these areas (figure 6c). Once the AChRs have been endocytosed they are broken down by lysosomal enzymes present within the cell (figure 6d). Since these enzymes are present in concentrations independent of number of AChRs present within the cell, it is thought that the increased endocytosis is the rate-limiting step of this process.⁵

Myasthenia gravis was first thought to be an autoimmune disease for three main reasons. The first involves the association of the thymus with this disease. Of those patients with myasthenia gravis, 75% have problems with their thymus, a gland which is involved with lymphocyte production and maturation. Specifically, 85% of the original 75% have hyperplasia (abnormal growth of normal cells) of germinal centers within the thymus. Within these germinal centers, formation and differentiation of lymphocytes occur; they also involve the parts required for Ab synthesis. In the other 15%, thymomas (tumor of the thymus) have been found.⁴ In either case, both can cause massive changes in the lymphocytes and antibodies being released.

Most physicians also believe myasthenia gravis is associated with disorders in the thymus because there are certain muscle-like or "myoid" cells present normally in this gland. These myoid cells are very similar to normal muscle cells and even have AChRs. Therefore, many scientists hypothesize that these cells provide the antigenic stimulus for an autoimmune response in myasthenic patients. In addition, the location of these cells in the body makes them very susceptible to immune attack. So it is generally believed that some slight change in these myoid cells or in the lymphocytes produced in this area may begin some type of autoimmune response

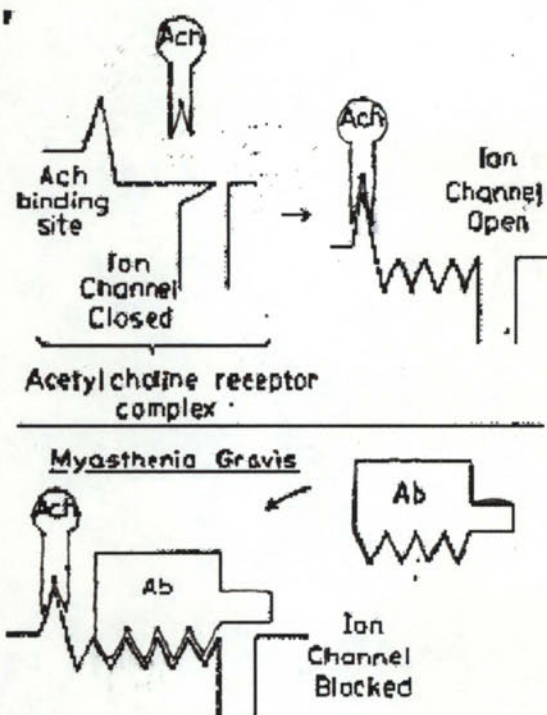


Figure 5. A possible theory on how Ab affects the acetylcholine receptor.

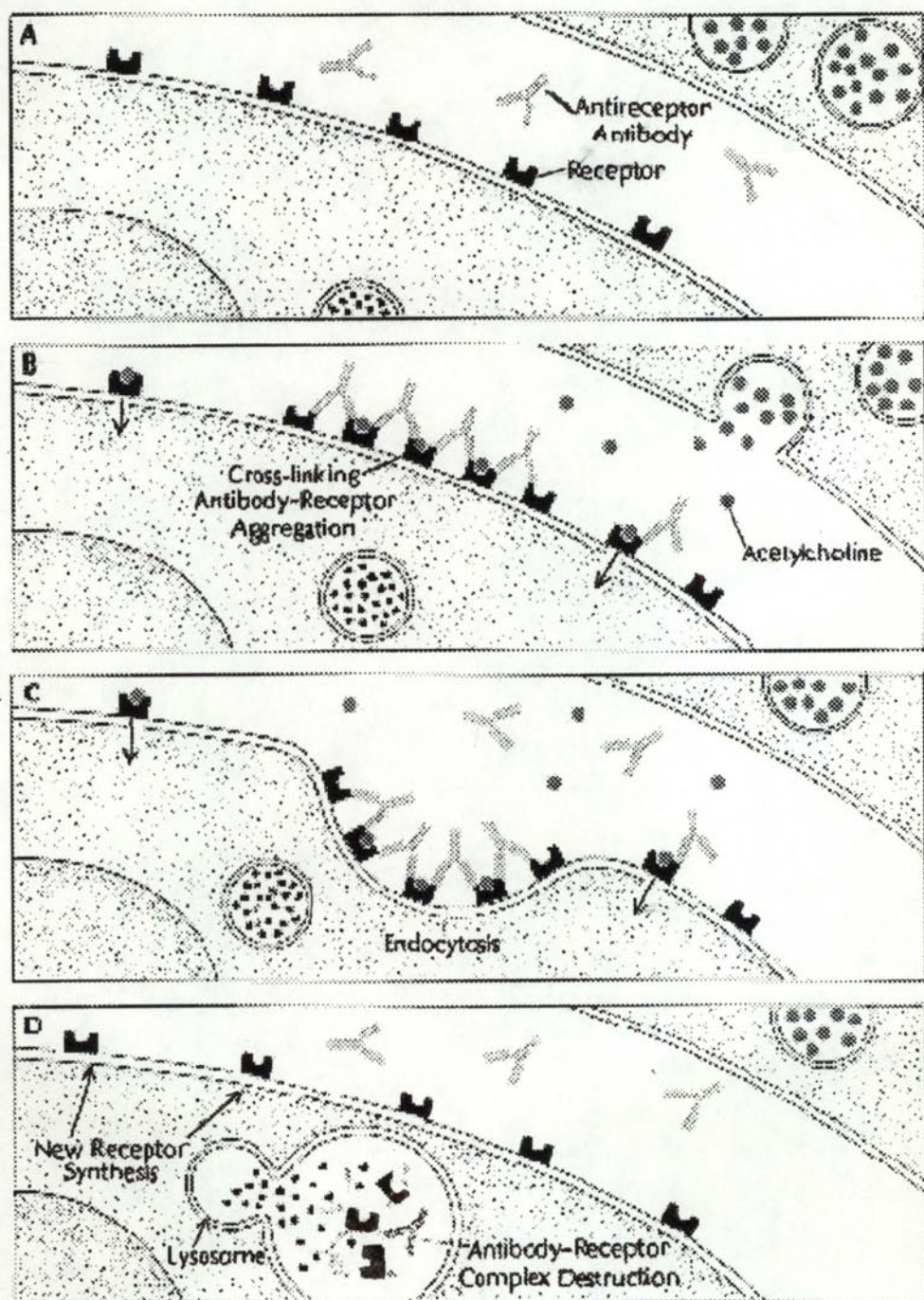


Figure 6. Theory on how antibodies are able to cross link and destroy acetylcholine receptors.

involving antibodies which also react with normal AChRs in the rest of the body leading to a full-blown case of MG.⁵

The second reason that myasthenia gravis was suspected to be an autoimmune disease was that it often co-exists with other autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus.⁵ The final reason involved, the reduced complement levels in an afflicted person's blood, was described earlier. Reduced complement levels are also found in many other autoimmune diseases.

SYMPTOMS AND DIAGNOSIS

For the most part, there is a pattern to the development of symptoms in myasthenic patients. Often the least severe conditions occur first, gradually becoming more debilitating as time goes on. Figure 7 shows the basic symptoms of myasthenia gravis. They often begin with the muscles which control the eye. Patients usually first by complain that they have trouble moving their eyes and eyelids which can cause ptosis or drooping of eyelids and diplopia or double-vision. Next, the muscles which control facial expressions become affected. Instead of having normal expressions, often the person is only able to manage what is called a myasthenic snarl due to weak facial muscles.²

The next muscles to be afflicted are those used for speaking and chewing, which are one and the same in humans.

This causes a myasthenic patient to sound drunk and also to have problems chewing solid foods. But even if a person is able to chew food well enough to swallow, he/she may not be able to because of weakness of the muscles in the neck which are needed for swallowing. These muscles are often next to become diseased. Due to problems with swallowing, more severe cases of myasthenia may require intravenous solutions to be used.²

Myasthenia gravis often attacks the muscles located in the neck (needed for holding the head up), the arms, and the legs next and later on, the respiratory muscles, the last group of muscles to be affected. Problems with these muscles cause many great difficulties for the myasthenic patient, especially with breathing. For this reason, once patients reach this level of severity, medical care is needed almost immediately. Often patients require a mechanical respirator to help them breathe.²

There are three methods for the diagnosis of myasthenia gravis, but usually all three are performed so that there can be no question about what disorder the patient has. The first one performed is usually the electromyogram where a muscle is repeatedly stimulated to get an action potential (the electrical activity developed in a muscle, nerve or the central nervous system during activity). A rapid decline in action potential is a sign of myasthenia gravis. The next method to test for MG is the Tensilon test. Tensilon (edrophonium chloride) is a very short-acting anticholinesterase drug which destroys the cholinesterase which in turn destroys ACh. Thus, there

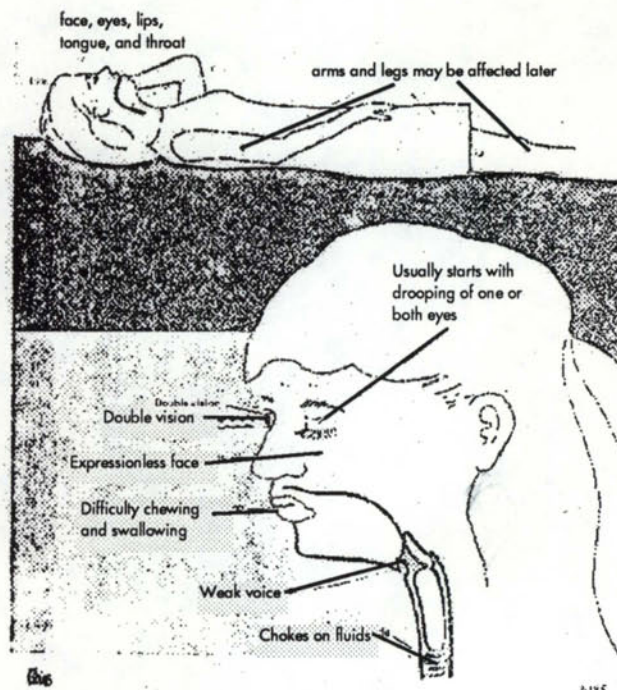


Figure 7. Diagram which shows the primary areas MG can affect and the basic symptoms which occur as a result.

is more ACh present to enhance contraction. Thirty to sixty seconds after Tensilon is given, muscle strength dramatically increases. This improvement usually lasts for about four or five minutes. Such a result is a positive test for MG. The final test for myasthenia gravis is a blood test which simply tests for the presence of antibodies made against the acetylcholine receptors. If all three of these tests are positive, then it is safe to say that the person has this disease.²

TREATMENT

Although there is no cure for myasthenia gravis (in humans at least), there are several ways to treat it. The first is the use of the anticholinesterase drugs which are given to help improve the effects of acetylcholine on muscle, as was described earlier. These drugs often include pyridostigmine bromide (commonly called Mestinon), neostigmine bromide (Prostigmin), and ambenonium chloride (Mytelase). Table 1 shows the many side effects of these drugs. The next method of treatment also involves the use of drugs, but these drugs suppress the immune response involved with myasthenia gravis. Steroids such as prednisone are often the drugs given as immunosuppressants. They work by inhibiting the release of Ab and by slowing the other immune responses associated with MG.⁷ These drugs must be administered in a closely regulated environment due to their effect on the entire immune system. The side effects of steroids as immunosuppressants are also displayed in Table 1.² Other immunosuppressants could also be administered instead of steroids, but these are often given only as a last resort because of the harsh side effects (as shown in Table 1) they have and the devastating effect they have on the immune system. These immunosuppressants often include drugs such as azathioprine and cyclophosphamide.² (These drugs will be discussed at length in the lupus portion of this report.)

The next two methods of treatment are more physical than the chemical nature of the last two. The first is the surgical removal of the thymus gland, which lays on either side of the trachea. This procedure was first performed only on patients with thymomas until physicians realized the benefits that this procedure provides to other myasthenic patients (as was realized from Leopold's and Weigert's report). There are two different ways that the thymus may be removed. The transsternal approach involves the splitting of the sternum in order to gain total access to the thymus. Because this procedure has a little more involved with it than the next, there are many problems associated with this method. These complications include a slightly longer rate of recovery and a somewhat higher death rate associated with this approach because the sternum is totally split. The other method of thymectomy is the suprasternal approach where only a small incision above the sternum is made in order to reach the thymus. The thymus then is surgically removed. The main problem associated with this method is that the entire thymus may not be removed. Either approach is readily acceptable, though.²

The final method of treatment is by plasmapheresis a procedure that simply lowers the amount of autoantibodies to the AChRs in the patient's blood. In this procedure, blood from a myasthenic patient is removed and centrifuged to separate the cells (red blood cells, white blood cells, others) from the plasma which contains the antibodies. The cells are then returned along with fresh plasma to the patient's bloodstream.² This procedure, not totally accepted in medicine, is used only as a temporary measure to help.

One of the major problems with treatment with drugs is the possibility of either a myasthenic or a cholinergic crisis occurring. A myasthenic crisis occurs when there is a removal from or a change of medication. This crisis can last up to a few months. During this time a patient may require a ventilator and/or an intravenous line to gain needed fluids. This condition is often treated by increasing doses of medication or returning to the medication formerly given. A cholinergic crisis may result from an overdose of anticholinesterase drugs. A cholinergic crisis is treated often by an antidote called atropine sulfate, a cholinergic drug which blocks ACh activi-

ty. Diagnosing the proper crisis is often very difficult, though, because they both have very similar symptoms as is shown in Table 2. The main way to distinguish between the two is to perform a Tensilon test. If a person is having a myasthenic crisis, then after the Tensilon is added the patient gets dramatically better until the drug wears off. Whereas if a cholinergic crisis is occurring, then patient will not respond to the addition of the Tensilon.²

While there is no absolute cure for MG, one may be on the horizon. Some experiments have successfully been performed where EAMG rats have been cured of this disorder. One method involves the growth of cultures containing certain lymphocytes (a type which suppresses immune responses in normal individuals) specific for AChRs and the receptors themselves, in the presence of immunosuppressants. After these lymphocytes are combined with lymphocytes from an afflicted individual, the mixture is reinjected into the diseased rat. Results have shown that the autoantibody response is inhibited without affecting normal immune response.⁸

Another method which has been used involves monoclonal antibodies (MAb) directed against the lymphocytes which encourage such an autoimmune response. Monoclonal antibodies are antibodies which are produced by a clone of antibody-forming cells and, therefore, are identical. In this approach, researchers tagged these antibodies with a chemical which is toxic to the lymphocytes. Since the MAb are specific for only the proper lymphocytes, only those secreting autoantibodies were killed. Hopefully, tests of both procedures in humans will be as promising.⁸

Still there are many problems involving myasthenia gravis encompassing every area discussed above. The greatest problem though is understanding the disease itself. As with other autoimmune diseases, very little is known about how the disease starts. Until this is discovered very little can be done to find a cure. And without a true cure, thousands of people will have to continue to suffer with only hope keeping them going. The future for those with lupus is even more dismal. Because of its systemic nature and potential fatality, this is even more true for those afflicted with systemic lupus erythematosus or simply lupus. This disorder will be discussed in the next section.

SYSTEMIC LUPUS ERYTHEMATOSUS

GENERAL INFORMATION AND HISTORY

"The Great Imitator," that is how lupus has been described in modern-day medicine. "The Great Imitator" was a title which physicians reserved for syphilis or cancer in the past because of the way they would mimic other diseases while becoming insidiously more destructive in the meantime. But with the advancements of science and medicine in the twentieth-century, these diseases have become much easier to diagnose. Only lupus remains a mystery.⁷ "The Great Imitator," how else would you refer to a disease in which no infectious agent has ever been isolated and the symptoms most often seen at the onset are fever, general malaise, and occasionally a rash, yet the disease only ten to twenty years ago was almost always fatal within five years. While life-expectancy has increased dramatically in recent times, due in large part to more liberal use of drugs to curb the autoimmune reactions, much is still unknown about lupus, reflected by the amazing number of incorrect diagnoses of lupus. Table 3 shows a list of a number of diseases which have been incorrectly interpreted in patients later found to have lupus. So how can lupus be treated when it is difficult to diagnose. This section will discuss this, along with the symptoms, known physiological information, and the methods of treatment presently used (along with the side effects which arise due to these treatments).

Systemic lupus erythematosus (SLE) was probably first described two thousand years ago by Hippocrates when he wrote of a disease which eroded away the skin and flesh of the face. He spoke of this affliction as something which all people including physicians feared. It was not until the 19th century when the name lupus was given to the disfiguring condition characterizing this disease. Lupus, meaning wolf in Latin, was named so because many thought the disorder looked as if it had been caused by the bite of a wolf.⁷ In a paper written by Pierre Cazenave in 1852, he was the first to name this disease, lupus erythemateux or lupus with redness.⁹ It was not until 1872 that SLE was first thought to be a systemic disease by Moritz K. Kaposi (as in Kaposi's sarcoma, seen most often in AIDS patients), an idea which was later proved in 1895 by William Osler.¹

One of the major events in the history of lupus was the discovery of the LE cell, which later became the first diagnostic test for SLE. The LE cell, discovered by Malcolm M. Hargreaves, was later found to occur in as many as 80% of those with lupus compared to only about 4% of those with rheumatoid arthritis (although some studies show this to be as high as 27%)¹⁰ and less than 1% of patients with other autoimmune diseases, according to figures published by the American Rheumatism Association, the governing body which oversees the treatment of many autoimmune disorders including SLE.⁷ One of the most important aspects of this discovery, however, was the association of the LE cell with antinuclear antibodies (ANA), antibodies which are directed against the nucleus and nuclear material of a cell. What Hargreaves described was the attack of one white blood cell called a polymorphonuclear leukocyte (PMN) on another of its own kind. Apparently in this process, the healthy PMN enters the cytoplasm of the altered PMN possessing the ANA and phagocytoses (engulfs) the other's nucleus, resulting in what is called a LE cell (Fig. 8). The cytoplasm, however, is not bothered by the invading phagocyte, only the nucleus. The engulfed nucleus most often will assume the shape of a round purplish (due to the stain used in the test) sphere of uniform nature, resulting from the ANA attached

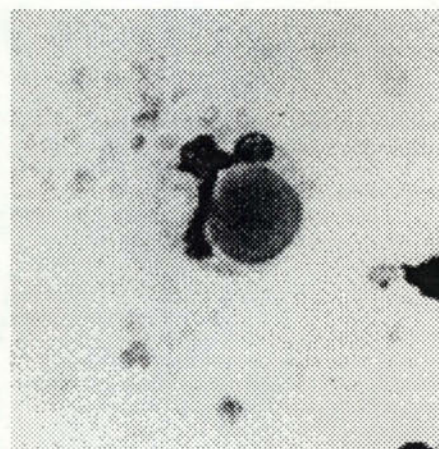


Figure 8. Classic example of an LE cell.

on the outer surface.⁹ This discovery led to many others, which will be discussed later, involving the role of ANA in lupus.

INCIDENCE

Systemic lupus erythematosus can occur in men and women alike, of all ages, but a large proportion of those affected are women of childbearing age. About 89% of the cases of SLE are in women with an average age of onset being around 29 or 30 years old. This is opposed to the average age of onset in men which is around 51 years old. During the childbearing years, the ratio of women to men with SLE is around ten to one, if not fifteen to one. After menopausal age (around fifty-five), the ratio drops to only about two to one as shown in Figure 9. This imbalance, thought to be caused somehow by the sex hormones, will be discussed in length at a later time.⁷

In the general population, lupus is thought to affect around one in every eight thousand.¹⁰ Yet it affects about one in every seven hundred white women between the ages of 20 and 64 and one in every two hundred and forty-five black women within the same age range.¹¹ Although there are no concrete theories on the reasons for this higher incidence of SLE in non-white ethnic groups, there have been some statistical studies of the various autoimmune diseases, revealing an increased prevalence of some diseases in certain latitudinal regions. For example, studies have shown that multiple sclerosis is most prevalent between the latitudes of 40° north to 60° north and 40° south to 60° south. It is about forty times more common in Minnesota than Mexico City.⁷ In addition, one study by Marian Ropes showed a higher percentage of those with SLE in the study from the latitudes of the Mediterranean countries. Of the 134 patients in the study, 60 (46%) were from Mediterranean countries, another was from the West Indies (which has the same range of latitudes as those countries along the Mediterranean), two more were Afro-Americans, and one final patient was Asian-American. Even including the final three patients in the previous listing as non-Mediterranean natives, the incidence of patients from all areas other than those of the Mediterranean was only 54%.¹⁰ Whether this correlation simply reflects local environmental factors (or prevalence of viral influences) in these areas which activates autoimmune disease at a higher rate or whether this, in fact, reflects a basic genetic difference which evolved over time in different ethnic groups of various regions is unknown. But this no doubt could explain why SLE is more evident in non-white groups, especially those of Afro-American and, to a lesser degree, Asian-American heritage.

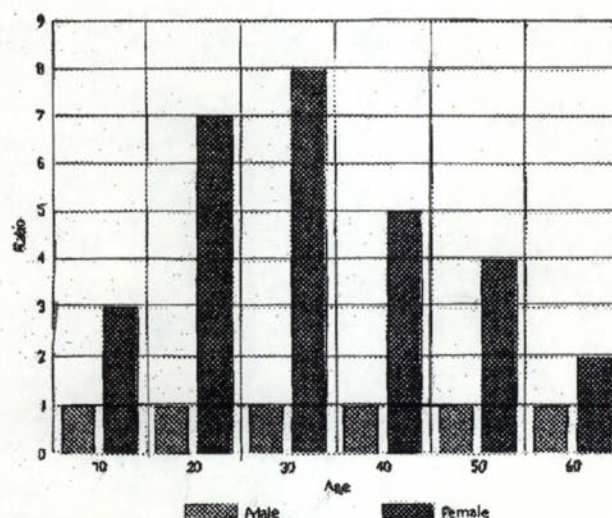


Figure 9. Ratios of women to men with SLE of different age ranges.

SYMPTOMS

The symptoms of systemic lupus erythematosus are wide-ranging and dependent on the patient, for any patient can develop only one or all of the symptoms. In addition, unlike in myasthenia gravis, the symptoms of SLE do not follow any type of sequence. Symptoms which are more severe in nature can develop at the onset of the disease almost as frequently as those which

are less severe. The most common of the symptoms are general malaise, weight loss, fever, and generalized weakness. Those diagnosed with SLE experience fever at the onset about 25% of the time,^{9,10} a persistent fever later after diagnosis about 80% of the time, and fever at one time during the course of the disease at least 90% of the time.⁷ This fever generally remains around 100°F during the course of the disease, although a majority of patients have a fever of over 103°F at any one time. Fevers as high as 106° and 107° have also been reported.¹⁰ Malaise is seen in about 18% of cases at the onset and in almost 100% of cases at any one time.⁹ In addition, those with SLE have weight loss and fatigue in about 65% and 75% of patients, respectively.⁷

One of the major areas affected by SLE is that of the skin. The manifestation which is most commonly associated with lupus is the classic "butterfly" rash. The rash, one of the first symptoms described as being due to lupus, was first named this by Ferdinand von Hebra in the 1840s when he wrote of it as being "not dissimilar to a butterfly."⁷ The rash itself, often found in 50% of SLE patients,¹² consists of a general redness of the skin (due to congestion of localized capillaries) mostly located on the cheek bones and meeting across the bridge of the nose (figure 10).⁹

Many other lesions are sometimes associated with SLE. The most common, called discoid or disk-like skin lesions, are found in about 20% of patients. In general, discoid lesions are elevated, reddish patches of rough and scaly skin located on the face mostly and at other times on the ear lobes, the back of the neck, the chest, the shoulders, the back, the arms, the hands, the fingertips, and the feet. Doctors also often see in around 40% of patients a sensitivity to the sun which makes the rash break out worse.⁹ Discoid lesions can also occur as two subtypes which differ somewhat from other discoid rashes, vasculitic and another subtype described as lupus profundus. Vasculitic lesions are mainly tender to the touch, hardened somewhat, and are mostly located on the forearm, fingertips, or soles of the feet, and also on occasion found around the ankles where they often become ulcerated, later infected, and generally have difficulty in healing. The lesions associated with lupus profundus are generally deep cutaneous nodules appearing as hardened lumps which can be either tender or nontender. These lesions are not as common as the vasculitic type.¹² Several examples of discoid lesions are shown in figures 11, 12, and 13.

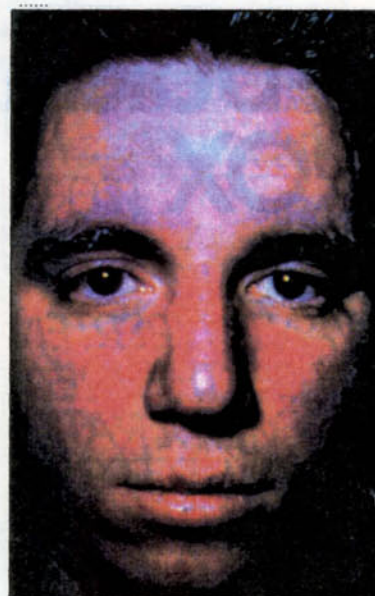


Figure 10. Classic example of butterfly rash as seen by a slight redness of certain areas.

Other skin lesions can include the maculopapular lesions which are characterized by the presence of small elevated bumps, often discolored compared to the rest of the body's pigmentation. (figure 14) Ulcerated lesions of the mucous membranes in nasal and oral regions can also be observed in as many as 40% of those with SLE. These lesions are often painless at first, becoming tender and much deeper as the disease progresses (figure 15).¹² Loss of hair due to the affliction of the scalp with various types of lesions, as shown in figure 16, is also observed. This occurs in anywhere from 25% to 50% of patients depending on the study.^{7,12}

The joints and muscles of the patient are usually the next areas of affliction commonly observed. The joints are affected in about 90% of patients at any one time.⁷ The joints most often troubled are those of the hands, knees, and wrists; less common are the joints of the ankles, the elbows, and the shoulders (occasionally also the spine and the hips are affected).⁹ It is also fairly common (found in about half of patients) for severe morning stiffness to occur.¹² The occurrence of joint pain can also be coupled with swelling, occasionally causing a diagnosis



Figure 11. Rough scaly, lesions characteristic of a discoid rash.



Figure 12. Cutaneous lesions in 22-year-old woman.

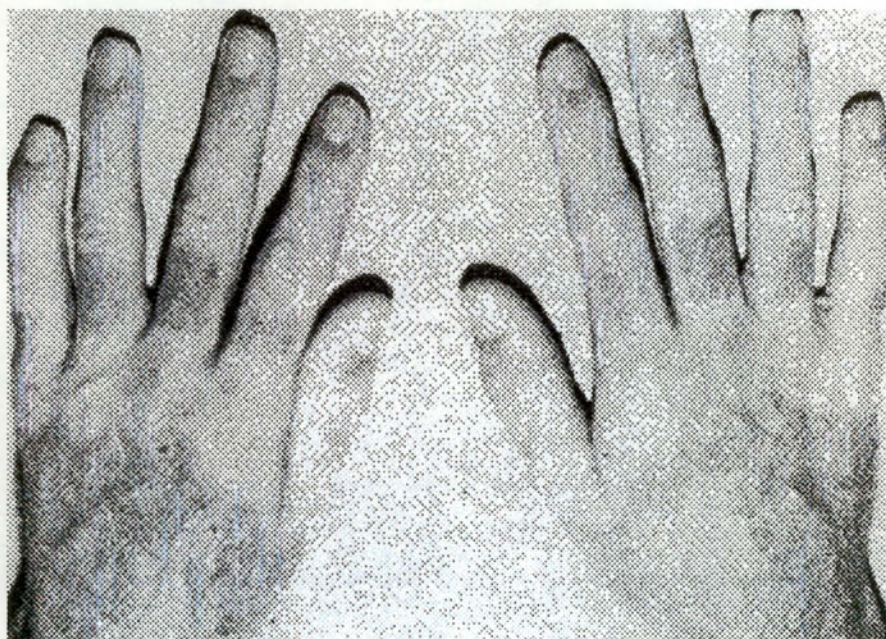


Figure 13. Discoid lesions appearing as a scaly rash.



Figure 14. Maculopapular rash on the elbow of a 22-year-old male.

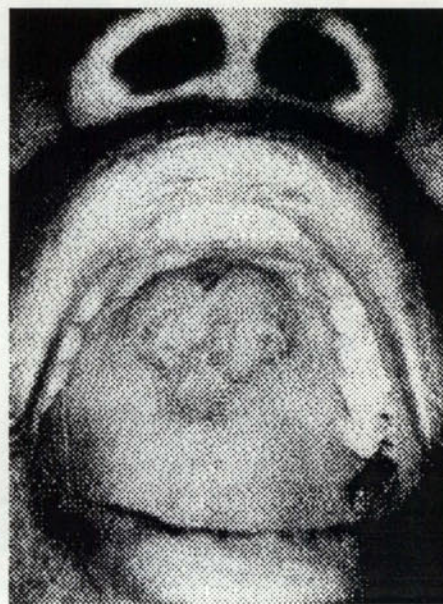


Figure 15. Rash on the bottom of the tongue of a 22-year-old white male.



Figure 16. Loss of hair due to infection of the scalp caused by SLE.

of either rheumatoid arthritis (RA) or rheumatic fever to be reached. One study found the changes caused by SLE to be identical to those caused by RA in about 25% of the patients they studied. Figure 17 shows an example of arthritis known to be caused by SLE, yet appears to be very characteristic of RA.⁹ Comparison of SLE and RA in regard to differential diagnosis will be discussed at a later time. About one-fourth of the patients known to have SLE complain about myalgia or muscle aches.⁷ Occasionally in more severe cases, the muscles of the hands become weak and atrophied, in addition to the normal aches seen. This condition, however, is not very common.⁹

SLE also often affects the circulatory system including the heart. In SLE, all three layers of the heart - the pericardium, the myocardium, and the endocardium - can become afflicted; about one-half of patients have some type of heart involvement.⁹ Inflammation of the pericardium, the membrane which surrounds the heart, is diagnosed most often, with an occurrence of about 25%. The infection of the myocardium, the actual heart muscle, is observed less often in diagnosis (less than 10% occurrence, according to one study)¹⁰, but upon autopsy can be seen in about 42% of cases.¹² Endocarditis, infection and inflammation of the internal lining of the heart, is also not observed very often in diagnosis, but is present in as many as 50% of patients upon autopsy.¹³ Most of the pathological nature of endocarditis and pericarditis involves the formation of fibrinous tissue over that of the normal tissue. In pericarditis, fibrin (an insoluble protein which is responsible for the essential portion of a blood

clot) attaches itself to the pericardial membrane, causing the membrane to become very rough. This new texture of the pericardium often causes a type of murmur (a gentle blowing sound heard during heartbeats upon direct examination of the chest) due to the increased friction between the membranes. This murmur is often followed by entry of fluid into the pericardial sac.¹⁴ In one study this pericardial murmur, or rub as it is also called, was found in about 30% of the patients tested, along with a presence of pericardial fluids in 17%.¹⁰

The endocardium is also affected by the growth of fibrin on its tissue. The fibrin associated

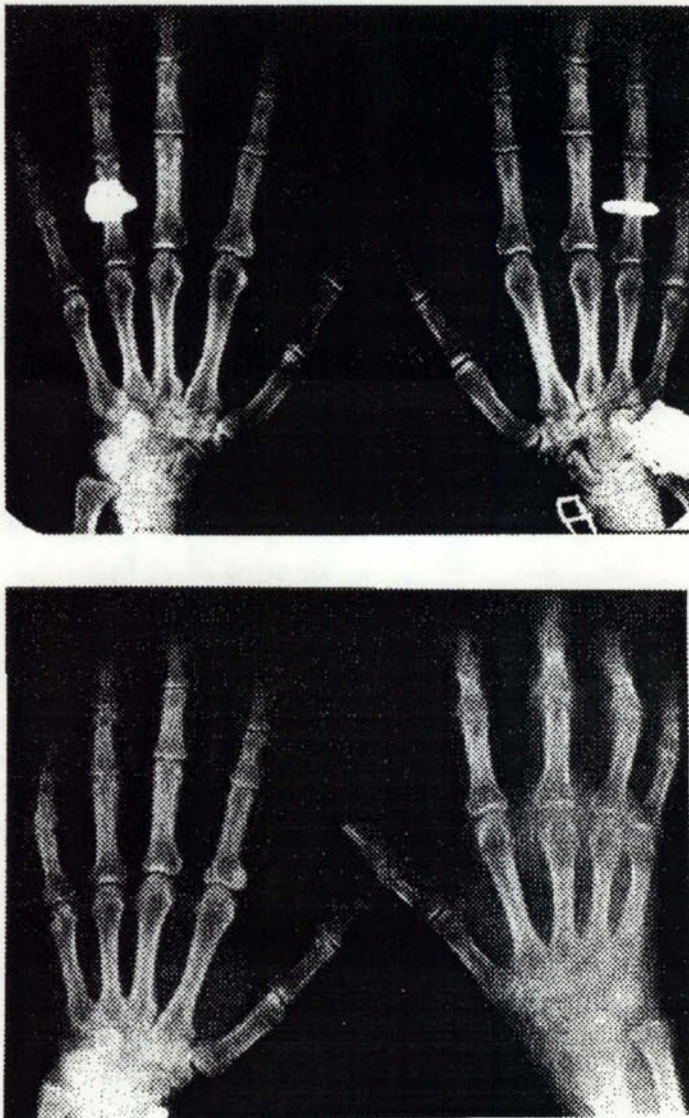


Figure 17. Generalized swelling and decalcification of the bones of the hands as seen in the same man four years later. These conditions are almost identical to those seen in RA.

with endocarditis forms vegetations mostly upon the valves of the heart which have become ulcerated by the disease. According to one report, these ulcerated lesions are found in approximately 23% of patients with SLE, compared to that of only 3% occurring within the normal population. The same study showed that the vegetations are found in about 7% of those with SLE, compared with 0% prevalence in the control group. However, there was a much higher incidence (16%) of these vegetations occurring in SLE patients who had antibodies against compounds called phospholipids, which are located in the heart as well as much of the rest of the body, than those who did not have these antibodies (1%). Therefore, most believe that the presence of these antibodies are responsible somewhat for the formation of these fibrinous growths.¹³ Endocardial murmurs, found at about the same rate of incidence as the pericardial murmurs, are also associated with these growths on the endocardial tissue.¹⁰

Myocarditis, on the other hand, does not usually involve fibrin growing on the outside of tissue, but instead fibrous tissue often develops between the layers of heart tissue. Symptoms which are in this type of infection are as follows: dyspnea (difficult or labored breathing), orthopnea (inability to breathe except in an upright position), enlargement of the heart, and occasionally heart failure. Despite the severity of myocardial involvement, there is usually little reason to worry, for the possibility of this happening at all, much less to this degree, is very remote.⁹

The lungs become affected in SLE at about the same frequency as the heart and the circulatory system. At the time of diagnosis, inflammation of the pleura (see the glossary), usually accompanied with accumulation of fluids, is present in approximately 11% of patients. About 45% of SLE patients experience pleuritis

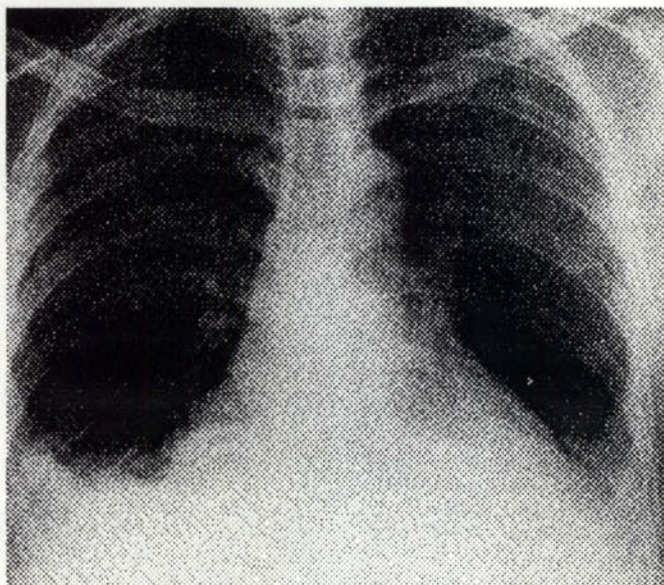


Figure 18. X-ray showing large amounts of pericardial and pleural fluids, along with inflammation of the pleura.

at one time or another during the course of the disease. Figure 18 shows inflammation of the pleura along with pericarditis, as was described earlier. One main disorders which can accompany pleuritis is acute lupus pneumonitis (inflammation of the lung without gross toxemia) usually seen with vast hemoptysis (bloody sputum), cough, chest pain, dyspnea, and bleeding within the lung.¹²

The kidney is perhaps the most involved organ in SLE; renal dysfunction is seen in at least half of patients at some time during their affliction. The most common way to test for deterioration of the kidney is by urinalysis, which detects the presence of protein and cellular components in the urine. Although an abnormal urinalysis indicates kidney disease to some degree, a normal one may not be a sign of normal renal function. Tissue samples from the kidneys of some patients can show severe damage, yet the person may not have any of the signs of renal dysfunction.¹² Even if urinalysis may not always be proof positive of disease, it still is a good test to discover the beginning stages of SLE, for the presence of protein and blood components in urine may actually occur before the formation of skin lesions. Later as the disease progresses, amounts of leukocytes (type of white blood cells), erythrocytes (red blood cells), and protein are excreted in the urine along with casts of transparent cellular material and fine

granules (examples of the casts are shown in figure 19). A severely affected kidney later will show casts of red cells, white cells, and coarse granules. Other symptoms of renal dysfunction are anasarca (generalized swelling throughout the entire body), hypoalbuminemia (abnormally low albumin content in the blood), and only a small change in blood pressure. SLE-associated kidney disease is not the only affliction possessing these symptoms, however. Other types of nephrosis also possess a majority of these symptoms; the one distinguishing factor between the two is the fact that patients with non-SLE kidney disease often have elevated levels of cholesterol in their blood, a factor which does not occur in SLE.⁹

Other less commonly affected organs include, according to frequency (depending on the study), the central nervous system (CNS), the lymph nodes, the gastrointestinal tract, the eyes, the liver, the pancreas, and the spleen.^{9,12} One of the main symptoms used for diagnosis of SLE is the presence of certain mental disorders which can include

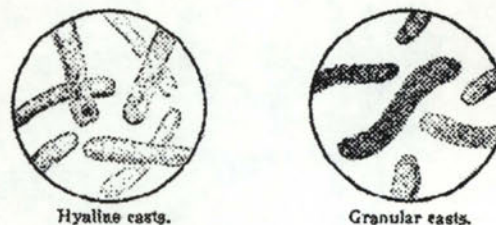


Figure 19.

convulsions, involuntary jerky movements, drooping of eyelids, double-vision, psychosis, meningism (a hysterical simulation of meningitis), aphasia (defect of the power of speech, writing, or signs, or of comprehending spoken or written language), and paralysis. Other conditions such as irritability, restlessness, disorientation, confusion, and even coma* can be seen in SLE patients. Unfortunately, many of these afflictions can also occur in a variety of other mental disorders such as multiple sclerosis, epilepsy, and mental instability. In fact, one study showed that a patient had received psychiatric care for seventeen years before a diagnosis of SLE was finally ascertained.⁹

The prevalence of these disorders also make it difficult to reach the correct diagnosis. Those with SLE have some type of mental syndrome affecting the CNS (which includes the brain and spinal cord) at least 37% of the time and at the most around 75% of the time, depending on the study. Interestingly enough, the peripheral nerves (which include all the nerves outside the CNS) are rarely affected, usually only in 10% of cases at the most. This may be due to a high incidence of white blood cells, specifically lymphocytes and PMN leukocytes, and protein in the fluid which surrounds the central nervous system. The formation of lesions within the vascular system of the brain may be a direct result of this. These lesions are thought to be responsible for many of these conditions, primarily the convulsions. They are not commonly found in those with peripheral nerve involvement, however. Involvement of peripheral nerves can be observed by an increased activity of reflex actions and spasms, inflammation of the nerves, and the loss of certain senses.⁹

During the course of SLE affliction of the lymph nodes may occur, occasionally leading to the diagnosis of lymphoma or mononucleosis.¹² Enlargement of the lymph nodes, sometimes to the extent actually observed in lymphoma, assists the doctor in making an incorrect diagnosis. Those which are most often afflicted are, in order of frequency, the axillary lymph nodes (located under the arms), the cervical lymph nodes (located in the neck), and the lymph nodes of the abdomen and chest. These conditions occur more often in children than in adults and more often in blacks than in other groups.⁹ Overall, approximately half of those with lupus will

* There have been many reports of patients which show no other manifestations of SLE, except for the fact that they remain in a catatonic state for months at a time. These patients seem to be somewhat conscious of their situation as can be seen in their eyes. But for the most part, they have no other acknowledgement of the world around them. Movements (except for the eyes) can be non-existent for the entire duration of this episode. Catatonic states such as this begin without warning and can disappear just as quickly, leaving the patient generally able to perform tasks as usual. The cause of these episodes is unknown.¹⁵

experience lymph node involvement.¹²

About 40% of people with SLE have some gastrointestinal tract problems. Common symptoms, which can range from almost non-existent to extreme severity (usually requiring surgery), include nausea; vomiting, often including blood; loss of appetite; abdominal pain and cramps; and diarrhea, which can also include blood. Occasionally, a patient will also have inflammation of the colon and ileum (both part of the intestinal tract), difficulty swallowing, and a burning feeling within the abdomen. Many of these symptoms result from complications involving the circulatory vessels within the gastrointestinal wall. Inflammation of arteries and formation of ulcers on the bowel wall are common examples of these complications. However, some symptoms may be the result of problems in the liver, pancreas, spleen, and lymph nodes.⁹

Although damage to the eye is uncommon in SLE, some studies have shown that the eyes can be affected in as many as thirty percent of cases (one study even reported an incidence of over fifty percent). SLE usually causes hemorrhaging, inflammation of the optic disk, and general accumulation of fluids with the eye. Retinal atrophy, which also occurs on occasion, often results in the formation of fibrin patches replacing these areas (figure 20). Less commonly observed symptoms include a hardening of the eye (often with an excess of blood in the eye) and inflammation of membranes and tissue immediately surrounding the blood vessels in this area.⁹

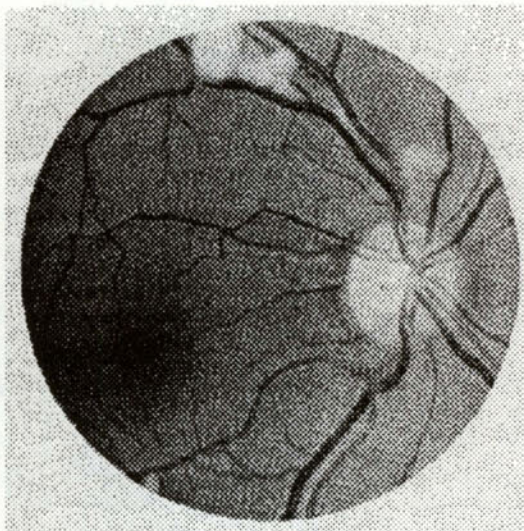


Figure 20. Retinal exam shows many white patches which are fibrin growths replacing areas of retinal deterioration.

The pancreas, liver, and spleen are the last organs to be discussed. Enlargement of the liver (hepatomegaly), along with increased levels of liver enzymes, occurs in about 30% of SLE patients. This percentage is even higher in those who take large amounts of nonsteroidal anti-inflammatory drugs (NSAIDs) which include aspirin and ibuprofen.¹² Occasionally a condition called "lupoid hepatitis" characterized by the presence of LE cells, large amounts of antinuclear antibodies, and active liver disease occurs. Laboratory tests (excluding tissue sampling) rarely show liver disease in those SLE patients with this affliction, however; thus, the probability of recovery from this syndrome is very low.⁹

Infection of the pancreas (very rare)¹⁰ and the spleen (around 20% of cases)¹² also occur occasionally, often due to other conditions. Inflammation of the pancreas usually is present in those who previously had disease of the pancreatic arteries. Symptoms attributed to enlargement of the spleen (splenomegaly) and other malfunctions commonly begin after or actually are the result of hepatomegaly. Furthermore, disease of both the liver and the spleen may, in return, be associated with the affliction of the abdominal lymph nodes.⁹

DIAGNOSIS

As has been referred to many times previously, diagnosis of SLE is a very difficult process facing the physician. Years ago, it was solely at the physician's discretion as whether to diagnose the disease that a certain patient had, in fact, as systemic lupus erythematosus. This decision usually correlated with the physician's experience, although not totally. An inexperienced physician could miss the correct diagnosis for many years, as could an experienced physician when presented with a set of symptoms, which he/she had not come across before as signifying SLE.

Then in 1971, the American Rheumatism Association (ARA) published a list of criteria to aid in the diagnosis of SLE. The list, shown in its entirety in table 4, was compiled by surveying large numbers of physicians in both the United States and Canada as to which symptoms most commonly occurred in cases of SLE. The ARA then judged these symptoms on how specific they were for SLE and only SLE. Out of nearly sixty items, fourteen of them made the list; of these fourteen, the occurrence of four at one time or another would positively prove the presence of lupus. Although this list greatly helped physicians, others criticized it for having some symptoms which were not considered specific enough and excluding others which were well-known to be indicative of SLE. In order to remedy some of the disagreement over the list, the ARA revised its list in 1982, cutting the number of criteria to eleven (as with the previous list, the occurrence of four of these still proved the diagnosis of SLE) while modifying those which remained.⁷ Table 5 shows this list in its entirety.

There are a couple major differences between the two lists. Raynaud's phenomenon (Figure 21) and alopecia which are very general symptoms found in a wide range of other disorders were not included in the revised list. But perhaps the greatest change between the lists is the introduction of tests for antinuclear antibodies. When the ARA produced the first list of criteria, there was not enough information on the significance of ANAs. It turns out, however, that ANAs are very specific for SLE. Around 90% of SLE patients have high levels of ANAs, compared to less than 5% of other patients.¹² (Some people within the normal population also have these antibodies, along with some other types of autoantibodies, but in extremely small proportions; Table 6 shows a list of autoantibodies found within the normal populations of certain species.)¹⁷ Those with rheumatoid arthritis also have these antibodies about 67% of the time, but generally in

lower levels. (Some "drug-induced" lupus patients also show some types of ANAs, but not all.)⁷ The presence of these antibodies allow SLE to be tested for much more easily. There are many types of antinuclear antibodies as shown in table 7. These antibodies are for specific antigens and, therefore, require more specialized tests in order to discover exact levels of these. Usually, a general ANA test is first performed to discover the presence of ANAs and then other tests are



Figure 21. An example of the two phases seen in Raynaud's phenomenon. The photo at the top shows the first phase, that of increased paleness in certain fingers. This phase ends as blood begins to circulate in these areas. This leads to the next phase which is shown in the photo at the bottom.

done to find the specificity of the antibodies. Figure 22 shows the technique behind the ANA test. The test begins by adding serum from a patient, possibly possessing antinuclear antibodies, to a container layered with antigens, known to bind the antibodies which are being tested for. If the proper antibodies are present, then they will bind to the antigen substrate. Whereas if the antibodies which are present are not specifically produced against these antigens (e.g. antibodies which are not ANAs), then there is no binding. After the mixture is washed to remove the unbound antibodies, a fluorescently marked antibody reagent, which binds to the antibody-antigen complex, is added to allow the detection of these antibodies visually. Thus, a sample will fluoresce if ANAs are present and will not, they are not present.¹² A sample, positive for ANA, is shown in Figure 23.

One of the problems with SLE, however, is that antibodies against a wide range of other tissues are produced (as shown in Table 8) and not just antibodies to nuclear material. These antibodies cause a wide range of other important conditions (all of those mentioned below are on the ARA list of criteria) which can be detected by other laboratory tests.* One of these conditions is acute hemolytic anemia found to occur in less than five percent of SLE patients as a result of antibodies produced against the red blood cells (erythrocytes). Other problems such as high bilirubin content in the blood, an abnormal increase in the number of

young red blood cells, and enlargement of the spleen often accompany this condition. Corticosteroids have been found to suppress this activity, but not without certain side effects as will be discussed later. Occasionally, a doctor recommends a splenectomy for the patient to alleviate some of the symptoms, even though this procedure has not been proven to help cure the anemia.⁹ In addition, splenectomy does make the SLE patient more susceptible to certain infections, especially pneumonia, however.⁷

Laboratory tests also occasionally show leukopenia (reduction in the number of leukocytes in the blood) in some SLE patients; studies show that 71-81% of SLE experience this on one occasion during the course of the disease. The reduction of leukocytes, a type of white blood cell, is also a result of autoantibodies directed against these cells. Specifically, leukopenia occurs when the cell count goes below 5,000 per cubic millimeter;⁹ one study even reported finding a patient with a leukocyte count as low as 450 per cubic millimeter.¹⁰ Normal values range from 4,500 to 11,000 leukocytes per cubic millimeter.¹⁸ Another autoantibody mediated condition, a general reduction in platelets (thrombocytopenia), is encountered in about 50% of patients with SLE. Some hemorrhaging of capillaries may accompany this condition, which is defined as occurring when there are less than 100,000 platelets per cubic millimeter.⁹ (Normal values range from 150,000 to 400,000 platelets per cubic millimeter)¹⁸. Some studies have reported counts as low as 7,000.¹⁰

One of the more unusual lab findings associated with SLE is that of the chronic false-positive

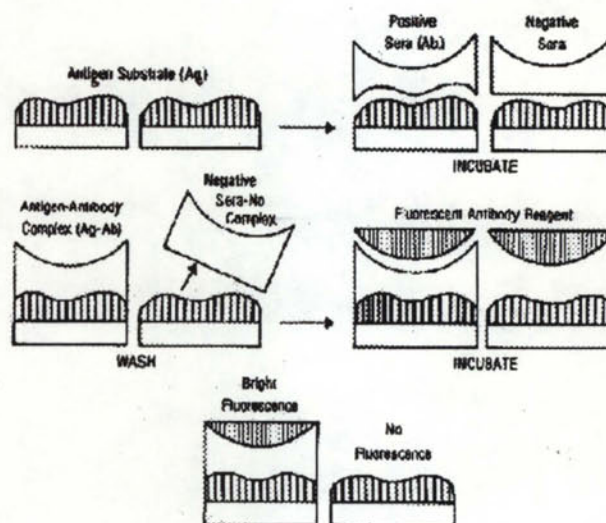


Figure 22. Principle of ANA Test

* These conditions could have been possibly described in the section on symptoms, but the author thought the direct correlation between these and autoantibody activity necessitated their discussion in this section.

test for syphilis which occurs in approximately 10-20% of patients, who have no other signs of syphilis. This false-positive test usually remains positive over long periods of time (ARA guidelines for diagnosis of SLE require the patient to be false-positive for at least six months before the test can be indicative of SLE). While the exact cause is unknown, there has been some evidence linking autoantibodies to this phenomenon.⁹ To prove a positive result is actually a false-positive, one of two more specific tests can be performed. One is the *Treponema pallidum* (the organism which causes syphilis) immobilization test which is slowly being replaced by another more sensitive test, the fluorescent treponemal antibody absorption test.¹¹

Diagnosis - Relation to other Diseases

Even with all the lists and criteria to help with the diagnosis of SLE, there are still many problems associated with distinguishing SLE from other diseases. The greatest problems are with distinguishing rheumatoid arthritis, discoid lupus, and "drug-induced" lupus from SLE. Rheumatoid arthritis has many of the same general symptoms as SLE does; symptoms like fever, malaise, loss of weight, and inflammation of muscles and joints are very common in both. But since rheumatoid arthritis occurs at a higher rate, many cases of SLE have been diagnosed as RA. In some patients

there is very little evidence to contradict this diagnosis. X-rays can show very little difference and, in fact, many of the laboratory tests come up the same for both. For example, one study conducted in 1957 showed that 28 of 83 patients (34%) with SLE had positive tests for rheumatoid factor which is usually characteristic for RA.⁹ Rheumatoid factor, specifically, is a type of autoantibody directed against immunoglobulins, mainly IgG; so, in other words, it is a type of antibody directed against other antibodies.⁸ It is present in approximately 75 to 80% of those with RA.⁷ But this overlap between diseases was shown in another study published in 1957 to occur in both directions. This study showed that of those with rheumatoid arthritis 27% (25 of 91) had LE cells present. Another study showed that 17% of RA patients had LE cells in addition to symptoms like increased inflammation of the lung, enlargement of the spleen, uncharacteristic urinary specimens, and false-positive tests for syphilis. All of these symptoms seem much more indicative of SLE than RA. Physicians now believe that up to 10% of those with SLE have symptoms very similar to RA.⁹ Regardless of all the similarities, there are still ways to distinguish between the two diseases (as shown in Table 9).

Discoid lupus erythematosus (DLE) often begins with the same cutaneous manifestations as SLE. A rash of scaly, red lesions occurs on the face, ears, and scalp in patients with DLE (see Figure 24). This is also the same type of rash seen in SLE. The two diseases can be fairly easily distinguished by the incidence of involvement of internal organs. DLE rarely afflicts any other organs other than the skin.¹¹ It has been shown, however, that DLE can disseminate into full-fledged SLE in some cases. One study showed that 20% of SLE patients in the study had DLE at

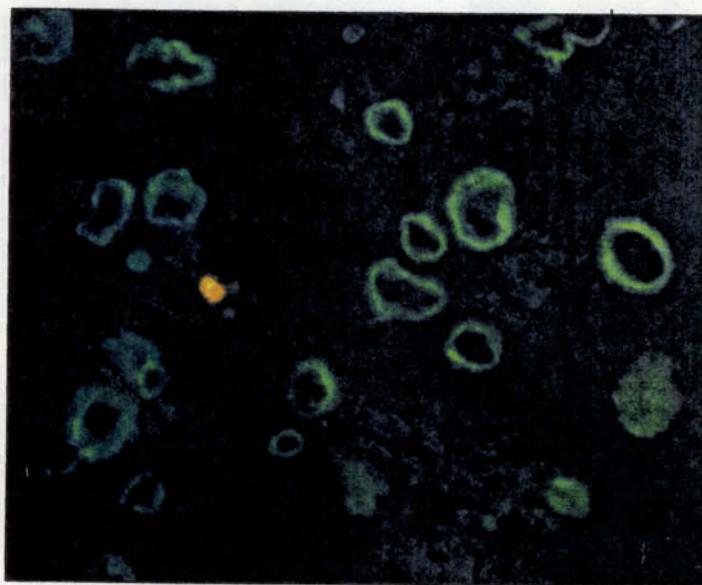


Figure 23. An example of a positive ANA test. This pattern of fluorescence indicates the presence of anti-DNA antibodies.

one time. In addition, of those with sub-acute SLE (lupus which has not fully disseminated) who were in the study, 26% had discoid lupus at one time. Some of the factors, thought to possibly cause these changes in lupus states, include the exposure to X-rays, UV radiation, certain antibiotics, and certain vaccines. There have also been some reports of patients who have reverted back to DLE from SLE after treatment.⁹

"Drug-induced" lupus can also be misdiagnosed for SLE and vice versa. In fact, one study showed that about 10-12% of patients diagnosed with SLE actually had "drug-induced" lupus.⁷ Many of the symptoms of "drug-induced" lupus are the same as those in SLE. Typical symptoms include fever, arthritis, and inflammation of the pleura and pericardium at about the same rate of occurrence as seen in SLE.¹¹ In addition, some laboratory tests are similar in both "drug-induced" lupus and SLE. Specifically, tests for the presence of ANA show about the same rate of incidence in both; anti-nRNP antibodies are also present in "drug-induced" lupus although in lower levels.⁷ Anti-histone antibodies found primarily in "drug-induced" lupus can occur in as many as 95% of patients with this affliction.¹⁶ (Other tests which are positive in SLE such as for anti-DNA and anti-Sm are negative in "drug-induced" lupus, however.)¹¹ Other symptoms of "drug-induced" lupus (usually present in much lower percentages than in SLE) can occasionally include rash, anemia, swollen lymph glands, renal or gastrointestinal problems, and emotional or mental disturbances. One of the main distinguishing characteristics between the two diseases involves the distribution of groups primarily affected. As in SLE, the majority of cases of "drug-induced" lupus are women, but not at nearly as dramatic a difference as with SLE.⁷ In addition, the ages normally affected between the two disorders differ greatly. The majority of patients with "drug-induced" lupus are either older people receiving treatment for irregular heartbeat and/or high blood pressure or children receiving drugs to control their convulsions. The medications used to treat these conditions are primarily to blame for causing "drug-induced" lupus, even though it can be caused by a variety of different drugs. These drugs include procainamide HCl (under the drug names Procan or Pronestyl) and hydralazine HCl (Apresoline) to treat hypertension, diphenylhydantoin or just phenytoin (Dilantin) to treat convulsions in epilepsy, isoniazid (Laniazid, Nydrasid, or Teebaconin) to treat tuberculosis, penicillamine (Cuprimine or Depen Titratabs) to treat rheumatoid arthritis, and even the antibiotic tetracycline when it is improperly stored.^{7,11} Most of the symptoms associated with "drug-induced" lupus generally disappear after the patient has been taken off the medication, but in up to 40% of cases the patient can continue to have these conditions for long periods of time (over six months).^{11,1}



Figure 24. Characteristic lesions of discoid lupus in a 26-year-old male.

SLE AS AN AUTOIMMUNE DISEASE

As with myasthenia gravis, experimentation with animals has provided most of the information known about the mechanisms of SLE. It was very fortunate, therefore, that a type of mouse was found to have a naturally-occurring disease which is very similar to that of SLE. Discovered by three scientists in 1959, this mouse, named NZB - short for New Zealand black (referring to the place of origin and color of the mouse), develops autoimmune hemolytic anemia naturally (a condition which can occur in SLE). Later tests showed that this mouse also develops increased antibodies and renal dysfunction similar to that of lupus. But even more remarkable was the discovery that by crossing this mouse to a New Zealand white (NZW) mouse produced a disorder almost identical to that of SLE. (For example, the hybrid mice generally die from kidney dysfunction, as in SLE, whereas the NZB strain develops lethal hemolytic anemia predominantly.) There are a couple of differences between the disorders, however. Firstly, the mice with this disease (both NZB and NZB/NZW) do not have any skin or joint problems at all. Secondly, all NZB mice, not just a few, become afflicted with this disorder, although some do so before others. But even with the differences, there is a very close similarity between the two, especially when referring to the internal manifestations of both. Other aspects of these mice will be referred to at later times.⁷

Origins of the Disease

Mechanisms which make cause systemic lupus erythematosus are still widely unknown. There are, however, a broad range of theories which may explain this mystery. The first theory suggests that a patient must have a genetic predisposition in order for SLE (and many other autoimmune diseases) to occur. This is no doubt the case in the NZB mice, for all mice develop this disease soon after birth. Researchers have also shown that this disorder is not passed from mother to fetus; an egg transplanted from a healthy mouse to a NZB mice will develop and be born as it would normally, without any of the signs of autoimmune disease. One of the many studies using humans researched a lupus patient and the patient's close relatives to try to find some type of connection. What this study found was a broad range of unusual disorders affecting these people. One of the patient's four sisters and a niece both had SLE. The patient's mother, two of four sisters, and a brother along with five nephews and a niece all had increased levels of antibodies in the blood. Another niece had evidence of rheumatoid factor and still another nephew had levels of both rheumatoid factor and other antibodies in the blood. These discoveries are far from common in normal populations.⁷

Cases like the one above prompted scientists to look for a genetic mistake common to all SLE patients. Due to other discoveries correlating the occurrence of certain disorders and the presence of genetic factors found within the MHC region (which stands for major histocompatibility complex, so called because of the importance of this area in organ transplantation), researchers began searching this region for a common denominator. Found on the sixth chromosome of every human cell, the MHC region is different in everyone on earth except possibly identical twins. It is this region which codes for a number of antigens to be presented on the cell surface; these antigens allow the immune system to differentiate between an object which is part of the host and something which has invaded the body (so-called self and non-self). This region (also called the HLA region, for human leukocyte-associated antigen where it was first located) has been found to be made up of many different little subregions (or genetic markers as they are also known) which individually are responsible for producing a specific type of antigen or other gene product. It is this variability which gives each person their own unique immune system and is why there is such great difficulty in finding compatible donors for organ transplants.⁸ After studying the MHC region for some time, researchers managed to locate a couple of possibilities within this area. There has been a higher incidence of subregions DRw2 and DRw3 and a some-

what higher incidence of subregions A1 and B8 being present within the HLA region of patients with SLE. (Figure 25 shows a map of the major histocompatibility complex as seen in humans.) Specifically, a higher incidence of subregions DRw2 and DRw3 correlates to approximately 54% and 45% of SLE patients, respectively. In contrast, 26% and 20% of controls have also had these respective subregions. These figures are not startling, but they do present a basis from which further research can be conducted. Some researchers have theorized that these markers may work in concert with each other as well as individually. One study showed that almost 74% of SLE patients had either DRw2, DRw3, or both compared to 43% of controls. Another study showed that an A1-B8-DRw3 connection was present in 35% of lupus patients compared to 16% of the controls. Again the differences are not that astounding.⁷

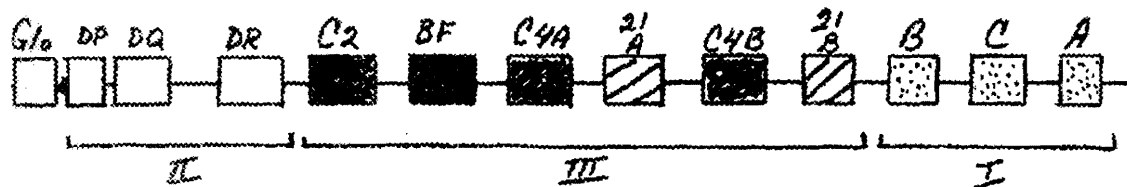


Figure 25. Human Major Histocompatibility Complex

There have been some connections made between types of markers present and the occurrence of other significant aspects of the disease, such as presence of certain types of antinuclear antibodies. One study found that in SLE patients with anti-Ro antibodies, 81% had the B8 marker and 100% had the DRw3 marker. (Those without these antibodies had the B8 subregion 41% of the time and the DRw3 subregion 25% of the time.) Another study found 70% of patients with anti-DNA antibodies had the subregion DRw3 compared to 37% of those without these antibodies.⁷ There is no doubt that the occurrence of these genetic factors will be greatly researched in the future.

Another important theory discussing the origin of SLE involves the possibility of viral (and somewhat less possible, environmental) influences in causing this disorder. Scientists and physicians have long suspected that viruses may be the cause of certain autoimmune diseases including lupus. Scientists have used two main methods to try to detect the presence of viruses. As with the testing of all other suspected infectious agents, the first test is for the existence of antibodies specific for viral antigens, whereas the second simply involves the isolation of the organism. Although a specific virus has not been implicated yet, a variety of virally-associated products can be found in SLE. One study found antibodies produced against a group of viruses called *reoviruses* in 55% of those afflicted with SLE, compared to only 3% in the controls. *Reoviruses* have, on occasion, been found in some other illnesses, but nothing definite. Another group of viruses which has been determined to play a possible role in SLE are the *paramyxoviruses*, which include the viruses which cause measles, mumps, and rubella (also called German measles). Several studies have shown high levels of antibodies to the mumps virus in large percentages of SLE patients.⁷ Other studies of SLE patients have shown high levels of antibodies to viruses such as the Epstein-Barr virus (a type of herpesvirus), the influenza B virus, and the Sendai virus (a relative of the mumps virus).¹⁷ Similar results have been seen in NZB and hybrid mice.⁷

As of yet, no one virus has been isolated from patients with SLE. There have been virally-associated particles found within the nuclei of cells from afflicted patients, however. In the late 1960s, Dr. Ferenc Gyorkey first found these particles in the tissues of a patient with SLE. He described the particles as being "myxoviruslike" and as being not entire viruses. (The *myxoviruses* are a class of viruses similar in nature to the *paramyxoviruses*; the root "myxo" comes from Greek meaning "mucus.") These viral particles have primarily been isolated from the nerve

cells, skin cells, white blood cells, and kidneys of SLE patients, but have not been isolated from any person within the normal population, whatsoever.⁷ Although these particles were originally isolated from those with SLE, similar structures have now been found in a wide range of autoimmune diseases including hepatitis virus particles in autoimmune liver disease and retrovirus particles in Graves' disease (an autoimmune disease which primarily affects the thyroid gland).^{19,20}

If these particles are derived from viruses which can cause autoimmune diseases, it is not understood how this occurs. During even the most severe disease activity, no viruses can be isolated. It is thought that perhaps that the particles are the result of a persistent viral infection which remains dormant for long periods of time. This has been found to be true in a disease called subacute sclerosing panencephalitis or just SSPE. This disease, which is always fatal, affects the brain by degrading it along with all the other systems that the brain controls. SSPE, also known as Dawson's encephalitis, also contained particles which were "myxoviruslike." Later, scientists found that those afflicted had high levels of antibodies directed toward the measles virus. Finally in 1970, one researcher isolated the measles virus from a patient; it had apparently been present all along, but had been "lurking" within the tissues of the central nervous system and lymphatic system waiting for the proper time to reactivate.⁷ Whether this type of mechanism also occurs in autoimmune disease is difficult to tell without further research, but there are signs that this may be how they occur. One experiment has shown that in both tissue cultures and live animals viruses can lay dormant within cells for perhaps the entire lifetime of the animal, if certain conditions occur. This experiment showed that a virus called LCMV (lymphocytic choriomeningitis virus) when injected into a healthy animal will kill it due to an effective immune response against virus-infected host cells. But if the virus is injected into an animal which is either newly born or immunosuppressed (both of which have incomplete immune systems), the virus will remain inside of cells indefinitely, causing no harm except for inciting the formation of antigen-antibody complexes, a product which is common in SLE-mediated kidney disease.¹⁶

There are many theories which try to explain how such a virus would cause an immune response to the host's own cells. Three of the main ones will be discussed here. Firstly, however, a little about how a virus usually infects cells must be explained. In a normal viral infection, the virus attaches itself to the host cell, penetrates into the cytoplasm (the internal fluid of the cell excluding the nucleus), and releases its genetic material which codes for its replication. After replication, the multiple copies of the virus now reassemble and leave the cell either by budding off of the cell or by rupturing the cell. One of the theories deals with what happens after replication. The author of this theory believes that something goes wrong with the host cells causing the virus to not be released. In fact, certain viruses require a specific enzyme to be present in the host cell, in order to become operational. Thus, if this enzyme is not present, then the virus would be "doomed" to remain within the host cell. Since an immune reaction occurs in response to any viral presence, the body produces antiviral antibodies which attack the only thing they can, the host cells where the virus is in hiding.⁷

Another theory states that possibly the virus remains within the cell in a semi-dormant condition, inactive except for mechanisms which affect the host cell, so that the immune system no longer recognizes it as being "friendly". Instead the host cell is attacked as a foreign organism. The third theory also involves the belief that the virus tricks the immune system into believing the host cell is a foreign invader. This theory assumes that the genetic material from the virus splices itself into the host's genes (which in some cases it has been shown to do) where it begins to code its own proteins. These proteins then become incorporated into the host cell's membrane where they are perceived as being foreign by the immune system. The immune system then responds by producing antibodies against these foreign proteins, thus attacking its own cells.⁷

The possibility of environmental factors as a cause of lupus has gained a great deal of atten-

tion lately. Many scientists had discarded this belief as being nothing more than being a secondary possibility. But with the recent diagnosis of Graves' disease present in President Bush, environmental factors have jumped to the forefront of autoimmune research. For in addition to the president, the First Lady, Barbara Bush, also has Graves' disease (she underwent treatment only one and a half years ago for this condition); even the dog Millie has a form of canine lupus. The odds of these events occurring naturally have been estimated at 20 million to one. Even so, most scientists still do not believe that there is a connection. One such scientist (Joshua Cohen of George Washington Medical Center) has said, "If I had to bet money, I'd bet that a specific factor linking these two cases isn't going to be found. It deserves careful thought, but it could be discovered they both just had a genetic susceptibility coincidentally." Vice-President Dan Quayle has not totally given up on such an idea, however. He seems to think that there are lead pipes in the Vice-Presidential mansion which have caused these autoimmune disorders in the Bushes while they lived there. Until there are a wide range of tests performed there will not be any concrete answers to this problem.²¹

The next theory involves the role of sex hormones in SLE. It has long been known that a large majority of SLE patients are women. This also occurs in many other autoimmune diseases like rheumatoid arthritis and myasthenia gravis. It has, therefore, been proposed that perhaps somehow estrogen acts as a type of accelerator and that the male hormones act like a kind of inhibitor of the disease. As was mentioned earlier, it is true that approximately 89% of those who get SLE are women, often around the age of 29. (If the reader remembers correctly, the average age of onset for men is 51.) In addition, before the menopausal age of women the ratio of women to men who are afflicted with this disorder is between 10 to 1 and 15 to 1. This ratio drops to 2 to 1 after the menopausal age (around 55). (Figure 9 printed earlier shows the change in proportions of women to men with SLE, as it corresponds to age.) Furthermore, studies show that men who have the congenital disorder, Klinefelter's syndrome (this occurs when a male baby picks up an extra X chromosome, thus having an XXY pattern, instead of the normal XY pattern), are more likely to get SLE than other men. Those with Klinefelter's syndrome often have higher levels of female hormones and are usually sterile.⁷

In addition, researchers have found that the removal of the testes along with the addition of male sex hormones tends to suppress disease activity, whereas removal of the ovaries along with replacement injections of female sex hormones makes the disease worse in most cases.¹⁶ One very interesting study supporting the importance of this discovery was published in 1975. This report described a pair of identical twins, who were forty-four at the time, in which only one had developed SLE. The other had, in fact, undergone treatment for ovarian cancer, where she had surgery to remove the both the ovaries and the uterus twenty-three years prior to the study (she did not receive any type of hormone injections to replace those lost by removal of these organs). Although both had false-positive tests for syphilis and the presence of high levels of antibodies, only the one with SLE had positive tests for LE cells and antinuclear antibodies. All other symptoms of SLE were absent in the woman who had undergone the surgery. So with this evidence, some researchers began to try to find a direct correlation between sex hormones and autoimmune disease.⁷

There have been no large scale studies so far, but there have been a variety of smaller studies performed to measure levels of sex hormones in SLE patients. One study of male SLE patients, performed to see whether male sex hormones (the androgens, as they are sometimes called) had some type of protective role in SLE, showed anything but promising results. Although some of the men did show occasional lower levels of certain hormones, the majority showed no change. What researchers did discover from such studies was that the metabolism of female sex hormones, which are also present in men in small levels, occurred differently in those with SLE than in normal patients. Estrone (a type of estrogenic hormone), normally broken down into 2-

Hydroxyestrone, was instead metabolized into 16 alpha-hydroxyestrone as shown in figure 26. One study by Dr. Robert Lahita showed that in the normal patients this compound comprised only about 5% of the total metabolic products excreted in their urine, compared to almost 17% in male SLE patients and almost 21% in female SLE patients.⁷ While scientists still do not know the exact role of this metabolite in those who have SLE, they do know that this compound acts as a more powerful feminizer than those which are normally produced.¹⁶

Whether any or all of the above possible causes of SLE and other autoimmune diseases are involved remains to be seen. But most researchers now feel that it is not just one of these factors, but possibly all of them as shown in figure 27. A person with such a disorder probably must have a genetic predisposition, accentuated later by the effects of sex hormones and their derivatives, activated by the presence of an outside force whether it is a virus or some type of environmental factor, all leading to the production of autoantibodies (antireceptor antibodies in the case of the figure).¹⁶

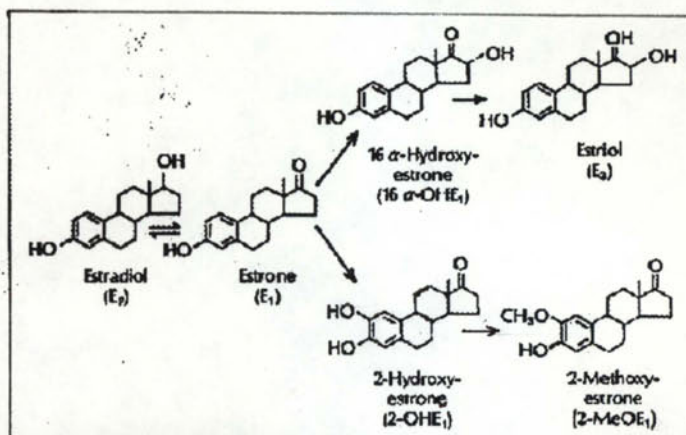


Figure 26. Two pathways by which estradiol is metabolized. The metabolites from upper pathway are found in increased levels in patients with SLE.

Physiological Mechanisms of SLE

While the theories explained above attempt to describe how autoimmune diseases begin, there are some definite changes within the body to help this to occur. These changes are especially seen within the specific subgroups of the white blood cells called lymphocytes. There are two main types of lymphocytes, the B cells and the T cells. The B cells, which originate in the bone marrow (thus, being partially responsible for the B in the name), are further subdivided into the general B cells and the plasma cells, which are sensitized B cells that secrete specific antibodies. The T cells, which differentiate and mature in the thymus (where the T comes from), can also be subdivided into four groups: the cytotoxic T cells (Tc) which recognize, bind to, and destroy foreign cells; the helper T cells (Th) which release substances to encourage an immune response; the delayed-type hypersensitivity T cells (Td) which secrete substances to influence other attack cells; and the

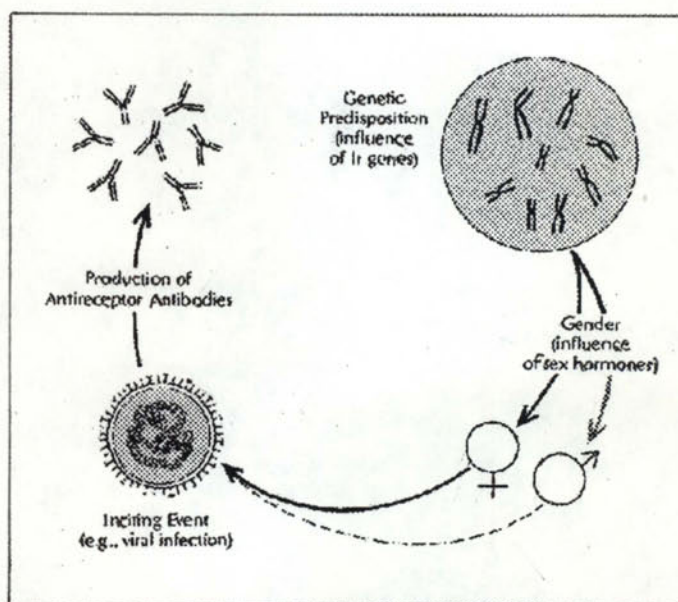


Figure 27. Theory of how autoimmune diseases may arise.

suppressor T cells (Ts) which turns off an immune response to a foreign antigen.⁸ In SLE, it appears that the suppressor T and plasma cells are affected the most. The suppressor T cell population in SLE appears to be greatly reduced for some reason. A couple of studies suggest that the suppressor T cells may be the target of autoantibodies directed against these cells and the precursor cells from which they are derived. In one study using tissue cultures, it has been shown that the blood serum from a patient with SLE can disrupt the normal maturation of precursor T cells to suppressor T cells in samples from normal individuals.⁷ This activity, therefore, would reduce the number of T cells available to regulate the action of the B cells. Suppressor T cells, specifically, block the transformation of antigen-sensitized B cells into antibody-secreting plasma cells. So if there was a lack of Ts cells, then plasma cells would theoretically be able to secrete antibodies indefinitely. Figure 28 shows this mechanism. There are a few problems with this theory, however. For one, in the NZB/NZW hybrid mice which were described earlier, their spleens tend to increase, and not decrease, the number of T cells which they secrete over time. In addition, immune responses to virally-infected cells still seem to occur normally. Lastly, a recent report has shown normal B and T cell functioning occurs in all ages of NZB/NZW mice (i.e. activity does not wane with disease severity or with age). These actions should not occur if there is some type of suppressor T cell malfunction.¹⁶ This idea of suppressor T cell deficiency is still widely held by most scientists.

Even more intriguing is the recent discovery that in SLE patients there is also a hyperactivity of B cells and plasma cells, above that which could be attributed to simple T cell deficiency. This study showed that there are eight to ten times more B cells in SLE patients than in normal individuals and that these B cells are unusually active.⁷ It has also been found that certain compounds, such as lipopolysaccharide (compound which is found in certain cell membranes) shown in figure 29, act as B cell activators. These compounds cause plasma cells, even from normal individuals, to produce many different types of antibodies, including autoantibodies. It has been hypothesized that such an occurrence would overwhelm an already malfunctioning Ts cell population preventing a total suppression of this activity.¹⁶

So how does all of this information add up to help one discover what causes SLE? The answer include all of the above factors. This author feels that it is possible that SLE may be activated by some type of foreign influence whether it is viral or environmental in a person who is already predisposed by genetic and hormonal factors (see Fig. 27 again). The foreign influence could possibly be the viruslike particles (which may be dormant viral genetic material) which have been found in many of the autoimmune diseases. These particles could act as activators to elevate B cell activity to extremes. Such an action would thus cause these B cells (which would, in turn, differentiate into plasma cells) to produce autoantibodies to a wide range of tissue types including to the suppressor T cell and its precursor. Only once this occurs could SLE be fully active.

TREATMENT AND FUTURE CURES

Although there are no definite ways to remedy the problems of SLE, there are many different treatments directed at alleviating the symptoms. Treatments are often used depending on the severity of the present affliction. Due to the disease's irregular and insidious behavior, there is really no way to use preventive medicine in treating SLE. For many of the simple problems of SLE, NSAIDs are used. NSAIDs, which stands for nonsteroidal anti-inflammatory drugs, include many common medicines such as aspirin and ibuprofen. These drugs are most commonly used to treat simple aches and pains and a slight fever. They are also often used in the treatment of rheumatoid arthritis. Even with these simple drugs, however, there are some side effects. Some of these drugs have been found to occasionally cause high blood pressure, kidney dysfunction, and even some central nervous system problems. It must be understood that these side effects

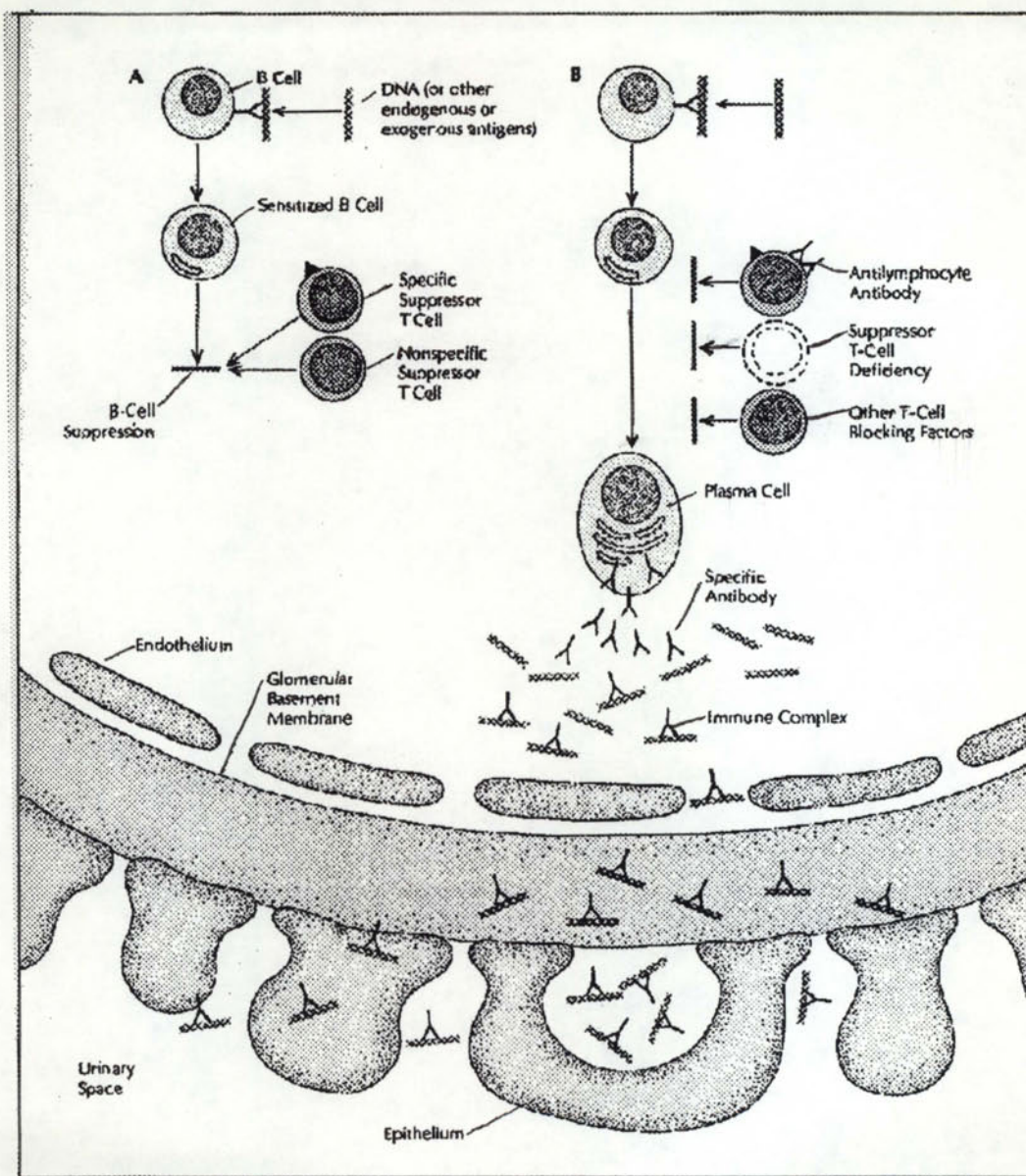


Figure 28. Comparison of normal and abnormal suppressor T cell function. Abnormal T cell function would allow plasma cells to produce autoantibodies indefinitely, resulting in immune complex formation. The formation and deposition of these complexes are the primary way that the glomerular basement membrane of the kidneys is damaged.

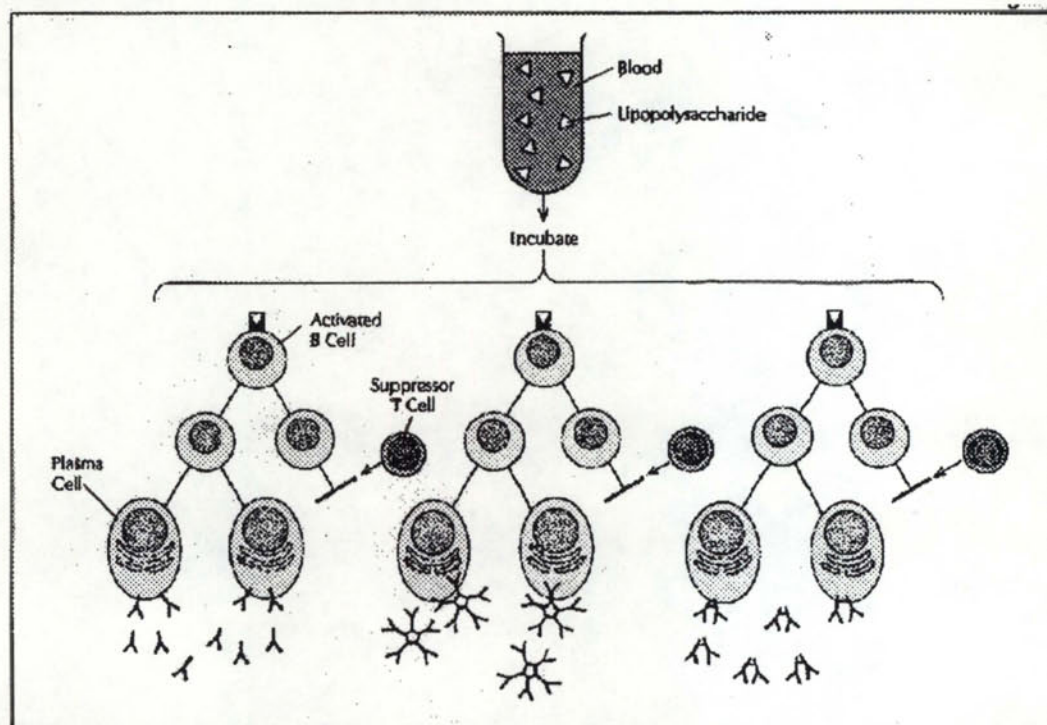


Figure 29. B cell activation. The lipopolysaccharide stimulates B cells to the point that they begin to produce a wide variety of antibodies including autoantibodies suppressor T cells, even if working normally, would be overwhelmed.

are very rare in cases of SLE.⁷ However, many patients with SLE are "allergic" (in a sense) to these drugs and can have some adverse liver reactions due to this sensitivity.¹¹ This phenomenon can actually be quite common. One study showed that 35% of SLE patients had in the past some type of allergic reaction to drugs compared to only 20% of normal individuals. Most often, these SLE patients are sensitive to a variety of drugs largely because of their faulty immune systems. This presents something else a doctor must be careful of when treating a patient with lupus.⁷

For the treatment of skin lesions, antimalarial drugs, especially quinine derivatives, are very useful. These drugs which include quinacrine (known by the drug name, Atabrine), chloroquine (Aralen), and hydroxychloroquine (Plaquenil) have been used less often in recent times. One of the reasons for this is that there have been many side effects associated with this group of drugs. Damage to the eye is, perhaps, the side effect of greatest concern. This damage can range from a temporary blurriness to permanent blindness.⁷ Instead of using antimalarial drugs, many physicians have opted to use topical corticosteroids which have very few side effects. A topical corticosteroid cream applied to skin lesions can help clear up these symptoms in both SLE and DLE.¹¹

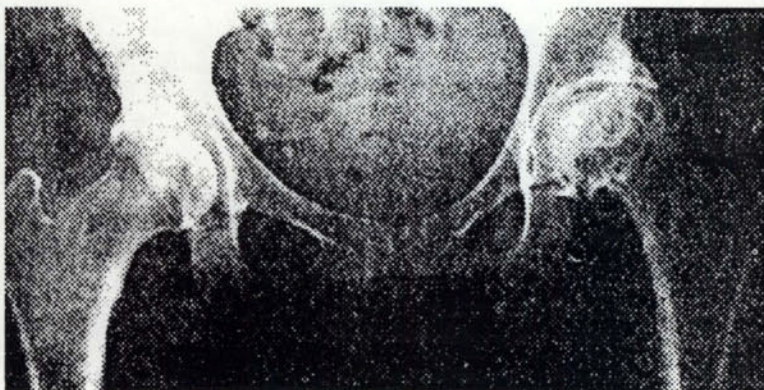


Figure 30. X-ray showing osteonecrosis of the femoral head at the right.

Physicians most often prescribe general corticosteroids, such as prednisone, when symptoms become more severe. These drugs can be used in either low doses for long periods of time or in extremely high doses if the conditions are severe enough. It is thought that corticosteroids act by inhibiting the secretion of antibodies and may also inhibit the response of helper T cells which were discussed in the last section.⁷ Physicians often use corticosteroids to treat a wide range of conditions including kidney and CNS involvement. One problem with the use of corticosteroids for the treatment of SLE involves the many side effects which occur as a result. Side effects can include acne, abnormal hairiness, fluid retention and weight gain, high blood pressure, skin rash and streaks, muscle disease, cataracts, and disrupted sugar metabolism.²² Other side effects can include susceptibility to infection, stomach ulcers, delayed healing time after injuries, increased the possibilities for diabetes, and, less often, emotional disturbances.⁷ The emotional problems may be due to the wide range of other side effects which are occurring. What young woman would not be disturbed by abnormal growth of hair on the body and enormous weight gain (up to as much as 60 to 80 pounds), in addition to all the other conditions caused by both the disease and the drug treatment. So often depression sets in as a result.¹¹

Large doses of drugs in treatment can also be very debilitating later in life. Many patients who have received large doses at one time or another often develop osteoporosis (reabsorption of bone by the rest of the body), osteonecrosis (death of bone cells, often associated with bone disintegration - an example of this is shown in Figure 30), and atherosclerosis (blockage of blood vessels by plaques containing cholesterol). Two studies by autopsy have shown that almost one-half of those SLE patients, who had at one time or another received high doses of corticosteroids, had at least one coronary artery three-fourths of the way blocked by plaques. This has also been found to occur in smaller amounts in patients who receive low doses of drugs. This

seems to occur because of increased levels of cholesterol in the blood caused by these drugs.²²

The next group of drugs which are used for SLE treatment are the immunosuppressants. These drugs are used in only dire situations because they are so potent. The two main drugs of this group are azathioprine, which acts by inhibiting cell growth (cytostatic), and cyclophosphamide, which acts by killing certain cells (cytotoxic). These drugs are mainly directed at stopping the growth of the rapidly proliferating B cells, as was described earlier. The only problem with these drugs is that they not only attack the B cells which produce the autoantibodies, but also the B cells which help fight off other infections. As a result, a patient who undergoes treatment using these drugs are extremely susceptible to infection of any kind.⁷ The most common type of infection is by herpes zoster viruses which cause inflammation of the cerebral nerves. Herpes zoster is the virus which causes chickenpox, but afterward it often remains in nervous tissue until it becomes reactivated. Other side effects caused by these drugs, as shown in Table 10, are largely due to the cytostatic and cytotoxic actions of these drugs on other growing cells. Because of the many severe side effects, these drugs are falling out of favor with physicians.²²

There are other methods used to treat SLE, but these are not as widely used as that of drug-therapy. These treatments are more of a physical nature as opposed to a chemical one. Surgery is occasionally performed by physicians in order to treat some of the conditions associated with SLE. Splenectomy is the most common surgical procedure; it is often used to alleviate the hemolytic anemia which is often a disorder seen in SLE. There are few side effects caused by this procedure, mainly because the liver and the lymph nodes assume the normal responsibilities of the spleen.⁷ The benefits of this procedure are not totally clear, however. For this reason, many physicians do not recommend this procedure.

In the case of kidney failure, a patient usually first begins a procedure called dialysis where an external machine filters the blood of the patient. Occasionally, the kidneys will respond and begin performing normally again. Studies have shown that about thirty to forty percent of patients regain normal kidney function after dialysis. If this does not occur, then kidney transplant is the next option. With recent strides made in the area of organ transplantation, physicians can transplant a new kidney with great success. Normal function of the transplanted kidney over a five year period continues in about 75% of patients.⁷

One of the last methods of treatment is plasmapheresis as was discussed in the section on treatment of myasthenia gravis. This procedure simply removes a large portion of autoantibodies which are present in the blood. But due to varying reports on its success and great cost of the procedure, plasmapheresis is rarely used.⁷

There are relatively few prospects at the present time for the complete cure of patients with SLE. There are two types of treatments which are being tested now which may become possible cures in the future. One of these involves bone marrow transplantation. Extensive clinical tests in mice show that if bone marrow, taken from a healthy mouse with no signs or history of autoimmune disease whatsoever, is transplanted into one of the NZB mice, then the NZB mouse will begin to get better until it no longer has any symptoms of autoimmune disease. Most researchers believe that this technique manages to cure all the disorders within the NZB mouse by presenting genetic material essential to the normal functioning of the mouse's immune system. Further tests will need to be conducted to see how effective this type of treatment is in humans and what side effects, if any, it causes.⁷

The other method of treatment is called total lymphoid irradiation (TLI). This technique, which is really just a way to handle the malfunctioning immune system, involves the exposure of the patient's lymphatic system (which includes the lymph nodes and spleen) to high doses of radiation. Exposure is limited to only the lymphatic system by the use of large lead plates to protect the other tissues. Doses much larger than that which would normally kill a human being can be used by splitting up the treatment into about four sessions per week until the total

dosage is reached. This technique, which is already used in humans for the treatment of other disorders, uses dosages of about 200 rad per session. Whereas humans can not normally survive a single dose of radiation over 400 rad, this technique amasses dosages of over 4,000 rad over a period of time.

TLI seems to be most beneficial in suppressing unnecessary immune responses, while still allowing reactions to foreign invaders. It is currently being used to treat Hodgkin's disease (a potentially fatal disorder where the lymphatic tissues all over the body enlarge in enormous amounts) and immune responses from organ transplantation. In addition, it has been shown to be very helpful in treating disorders in NZB mice and in other animals with autoimmune diseases. Another promising discovery is that TLI has been found to have relatively few side effects associated along with it. Some of the common side effects include diarrhea, general weakness, loss of appetite, and abdominal cramps. Other less common side effects are herpes zoster infection (in about 30% of patients), thyroid abnormalities (in about 20% of patients), bone marrow depression, and pneumonitis (the last two occur in less than one percent of patients).⁷ For some people, these side effects may seem severe, but when compared to all the serious side effects seen in immunosuppressive drugs, these disorders are relatively benign.

So what can a person with SLE expect out of his or her life in the future? Well, although there are some new types of treat-

ment being tested now, a cure for SLE does not appear to be any time soon. Even so, a person with SLE can live a fairly normal life, for this disease is no longer a death sentence as it was at one time. Survival rates have increased remarkably over the past few years, partially due to the increased use of drugs in treatment and partially due to better methods for the detection of SLE (i.e. ANA tests). Less than 40 years ago, the chances of living for five years after SLE was diagnosed were less than 40%. In addition, death within one year after diagnosis was rather common.⁷ But in the present, those with SLE have over an 80% chance of surviving at least ten years.²² (Figure 31 shows a graph mapping the changes in survivorship as reported in various studies over the past thirty years.) So what can an SLE patient expect? This person should expect to live for many years to come. And as future treatments surpass those of today, such a person will be able to live a normal life with very few problems. So it is in the patient's best interest to keep an optimistic outlook of his or her affliction because things will only get better.

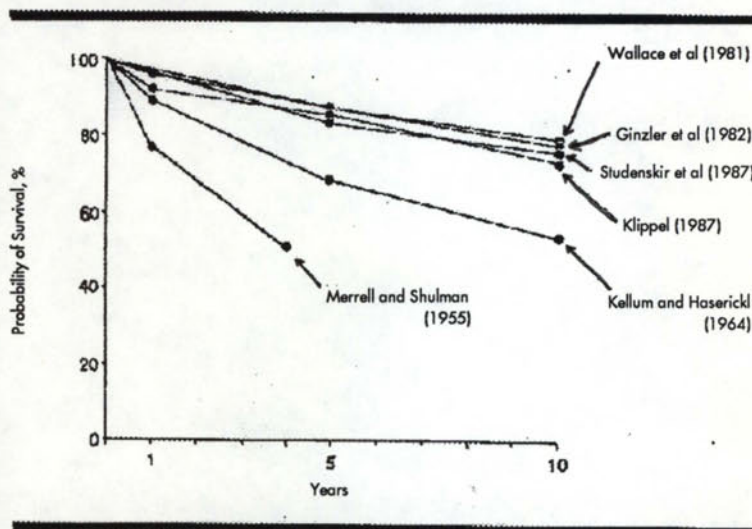


Figure 31. Various studies of survival rates of those with SLE

CLOSING REMARKS

The realm of autoimmune disease has much left to be explored. But before scientists can attempt to contemplate the real mechanisms of these diseases, there must first be an attempt to try to understand the immune system itself much better and all the interactions between the cells which make up this system. Once this is achieved only then will real advances be made in the area of autoimmunity.

For the reader, hopefully this has presented some insight into autoimmune diseases. It was meant to give the reader some understanding of what these people are going through. For the reader who is afflicted with one of these diseases, it must be understood that these diseases are not necessarily fatal; they are simply conditions which are chronic. And do not worry if you have just been diagnosed, for the day will come when medical science has caught up to these disorders. One just has to be patient. It is not that far away.

TABLES

Table 1**SIDE EFFECTS OF ANTICHOLINESTERASE DRUGS(2)****On Muscarinic Receptors (involve smooth and cardiac muscle and glandular tissue)**

Dizziness & Jitters
 Mental Confusion
 Nausea & Vomiting
 Abdominal Cramps & Diarrhea
 Urinary Frequency
 Bronchospasm (contraction of the walls of the bronchi)
 Hypotension (lowered blood pressure)
 Bradycardia (abnormal slowness of the heart beat)
 Increased Salivation
 Sweating

On Nicotinic Receptors (involve skeletal muscle and ganglion cells)

Fasciculations (small local contractions of muscles)
 Muscular Weakness
 Fatigability

SIDE EFFECTS OF STEROIDS (AS IMMUNOSUPPRESSANTS)

Acne
 Hypertension (increased blood pressure)
 Edema (accumulation of fluid in tissues)
 Gastrointestinal Irritation
 Hypokalemia (abnormally low potassium content in blood)
 Growth Suppression in Children
 Susceptibility to Infection

SIDE EFFECTS OF OTHER IMMUNOSUPPRESSANTS

Nausea & Vomiting
 Pancreatitis (inflammation of
 Esophagitis these organs)
 Ascites (effusion of serous fluid into the abdominal cavity)
 Mouth Ulcers
 Bone Marrow Depression
 Leukopenia (reduction in number of leukocytes)
 Anemia (reduction in number of erythrocytes)
 Thrombocytopenia (decrease in number of blood platelets)
 Hepatotoxicity (poisonous effect on liver
 Nephrotoxicity and kidney, respectively)
 Alopecia (loss of hair)

Table 2
CRISIS SYMPTOMS²

Symptoms of both myasthenic and cholinergic crises

1. Severe muscular weakness involving generalized muscles and those necessary for breathing, chewing, speaking, and swallowing
2. Apprehension and restlessness
3. Increased bronchial secretions, sweating, salivation, and lacrimation

Distinguishing symptoms of a myasthenic crisis

1. Positive response to the Tensilon test
2. Increased pulse rate
3. Absence of cough and gag reflexes

Distinguishing symptoms of a cholinergic crisis

1. Negative response to the Tensilon test
2. Nausea and vomiting
3. Diarrhea and abdominal cramps
4. Diplopia
5. Bradycardia and hypotension
6. Fasciculations
7. Onset 15 to 45 after an anticholinergic medication is taken

Table 3**INCORRECT DIAGNOSES IN THOSE LATER FOUND TO HAVE LUPUS⁹**

Acute nephritis (inflammation of the kidney)
 Acute psychosis (prolonged behavioral disorders)
 Acute rheumatic fever
 Brucellosis (infection caused by one of the species of *Brucella*)
 Cerebral vascular accident (copious extravasation - discharge - of blood within the brain)
 Dermatomyositis (inflammation of the skin, subcutaneous tissue, and underlying muscle)
 Drug reaction
 Epilepsy
 Erythema multiforme (complex characterized by numbers of various types of lesions which appear suddenly)
 Felty's syndrome (comb. of chronic arthritis, enlargement of spleen, reduction of leukocytes, and spots on the skin)
 Fever of unknown origin
 Lymphoma (cancer of the lymph nodes)
 Meningitis (inflammation of the meninges - membranes surrounding the brain and the spinal cord)
 Nephrosis (any disease of the kidney)
 Peripheral neuritis (inflammation of the nerve endings)
 Pleurisy (inflammation of the pleura - membrane lining the lungs and thoracic cavity)
 Pneumonia
 Polyarteritis (inflammation of several arteries at the same time)
 Purpura (condition characterized by pinpoint, purplish red spots)
 Raynaud's phenomenon (paling and numbing of fingers or toes)⁷
 Rheumatoid arthritis
 Scleroderma (autoimmune disorder characterized by hardening and leather-like appearance of the skin)⁷
 Septicemia (presence in the blood of bacterial toxins)
 Subacute bacterial endocarditis (inflammation of the lining of the heart caused by bacteria)
 Syphilis
 Trichinosis
 Tuberculosis

Table 4**PRELIMINARY CRITERIA FOR THE CLASSIFICATION OF SLE (1971 ed.)**

1. **Facial erythema** : Diffuse erythema, flat or raised, over the malar eminence(s) and/or bridge of the nose; may be unilateral (butterfly rash)
2. **Discoid lupus** : Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions; may be present anywhere on the body
3. **Raynaud's phenomenon** : Requires two-phase color reaction, by patient's history or physician's observation (see Fig. 21)
4. **Alopecia** : Rapid loss of large amount of the scalp hair, by patient's history or physician's observation
5. **Photosensitivity** : Unusual skin reaction from exposure to sunlight by patient's history or physician's observation
6. **Oral or nasopharyngeal ulceration**
7. **Arthritis without deformity** : One or more peripheral joints involved with any of the following in the absence of deformity : (a) pain on motion; (b) tenderness; (c) effusion or periarticular soft tissue swelling
8. **LE cells** : Two or more classical LE cells seen on one occasion or one cell seen on two or more occasions, using an accepted published method
9. **Chronic false-positive serologic test for syphilis** : Known to be present for at least 6 months and confirmed by *Treponema pallidum* immobilizing or Reiter's tests
10. **Profuse proteinuria** : Greater than 3.5 gm/day
11. **Cellular casts** : May be red cell, hemoglobin, granular, tubular, or mixed
12. **One or both of the following** : (a) Pleuritis, convincing history of pleuritic pain; or rub heard by a physician; roentgenographic evidence of both pleural thickening and fluid; (b) pericarditis, documented by electrocardiogram or rub
13. **One of the following** : (a) Psychosis; (b) convulsions, by patient's history or physician's observation in the absence of uremia and offending drugs

14. One or more of the following (a) **Hemolytic anemia**;
(b) **leukopenia** : on two or more occasions, white blood cell count less than $4,000/\text{mm}^3$; (c) **thrombocytopenia**, platelet count less than $100,000/\text{mm}^3$

Table 5**1982 REVISED CRITERIA FOR CLASSIFICATION OF SLE¹²**

1. **Malar rash** : Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. **Discoid rash** : Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. **Photosensitivity** : Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. **Oral ulcers** : Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. **Arthritis** : Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, effusion
6. **Serositis** : (a) Pleuritis : convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion; (b) Pericarditis : documented by ECG or rub or evidence of pericardial effusion
7. **Renal disorder** : (a) Persistent proteinuria greater than 0.5 grams per day or greater than 3+ if quantitation not performed; (b) Cellular casts - may be red cell, hemoglobin, granular, tubular, or mixed
8. **Neurologic disorder** : Seizures - in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance; (b) Psychosis - in the absence of offending drugs or known metabolic derangements (see above)
9. **Hematologic disorder** : (a) Hemolytic anemia : with reticulocytosis (b) Leukopenia - less than 4,000/mm³ total on 2 or more occasions (c) Lymphopenia - less than 1,500/mm³ on 2 or more occasions; (d) Thrombocytopenia - less than 100,000/mm³ in the absence of offending drugs
10. **Immunologic disorder** : (a) Positive LE cell preparation; (b) Anti-DNA : antibody to native DNA in abnormal titer; (c) Anti-Sm : presence of antibody to Sm nuclear antigen; (d) False positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test

11. **Antinuclear antibody** : An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and the absence of drugs known to be associated with “drug-induced” lupus syndrome

Table 6
AUTOANTIBODIES IN NORMAL POPULATIONS

Species	Autoantibodies (AA)
Man	Anti-lymphocyte AA Anti-tubulin AA Anti-nuclear AA Anti-smooth muscle AA Anti-double-stranded RNA AA
Mouse	Anti-lymphocyte AA Anti-nucleoprotein AA Anti-IgG AA
Rat	Anti-lymphocyte AA
Rabbit	Anti-tubulin AA
Calf	Anti-tubulin AA
Pig	Anti-tubulin AA

definitions for those listed above are in the glossary, all information from reference #17

Table 7
DEFINED ANTIGEN SPECIFICITIES

Antibody to:	Incidence:
Nucleic Acid Ag	
Deoxynucleoprotein (anti-DNP)	70% in SLE ¹⁶
Deoxyribonucleic acid (anti-DNA)	mainly SLE, low levels in chronic active hepatitis, JCP, some normal population
<i>single-stranded DNA</i>	70-80% in SLE ⁷
<i>double-stranded DNA</i>	90% in SLE ⁷
Ribonucleic acid (anti-RNA)	40-80% in SLE ¹⁷
Nucleolar RNA (4-6s RNA)	40-50% in PSS ¹⁶
Histones (anti-histone)	30% in SLE, 90% in "drug-induced" lupus
Non-Histone Nuclear Protein Ags.	
Smith (anti-Sm)	only 30% in SLE, non-existent in others
Ribonucleoprotein (anti-nRNP)	95-100% in MCTD, ¹⁶ 40-45% in SLE, 20% in "drug-induced" lupus ⁷
Sjogren's Syndrome A (anti-SS-A & anti-Ro)	70% in Sjogren's Syndrome, ¹⁶ some with SLE (30-40%) ¹⁷
Sjogren's Syndrome B (anti-SS-B, anti-La, & anti-Ha)	60% in Sjogren's Syndrome, ¹⁶ 20% in SLE
MA-1 (anti-MA-1)	only in SLE (20%) ¹⁷
Scleroderma 70 (Scl-70)	15-30% in PSS
Prolif. cell nuclear Ag (anti-PCNA)	less than 10% in SLE
Ab to Other Ags.	
Chrom. centromere (ACA)	80-90% in CREST scleroderma ¹⁶
Mitotic spindle apparatus (anti-MSA)	variety of connective tissue disorders
Nuclear matrix	rare, found in 0.05% w/ANA
Mi-1 (anti-Mi-1)	in MCTD & those w/anti-nRNP
Jo-1 (anti-Jo-1)	first found in dermatomyositis (% unknown)
Ku (anti-Ku)	in polymyositis (30%), dermatomyositis (rare)
PM-1 (anti-PM-1)	55% in both polymyositis & scler., rare alone
SL (anti-SL)	specific only for polymyositis (55%)
Rheumatoid Arthritis nuclear Ag (anti-RANA)	seen in those with both SLE & SS
	high levels (85-95%) ¹⁶ in those with RA, lower levels in other diseases
Cytoplasmic Antigens	
Actin (anti-actin)	found in chronic active hepatitis
Golgi apparatus (anti-Golgi)	found in SS & SLE
Lysosomes (anti-lysosomes)	60-70% in SLE ¹⁷
Mitochondria (anti-mitochondrial)	20% in SLE ¹⁷
Ribosomes (anti-ribosomal)	15-20% in SLE ¹⁷

antigen abbreviations are arbitrarily designated; unless otherwise noted info. from ref. #12

Table 8**OTHER AUTOANTIBODIES IN HUMAN SYSTEMIC LUPUS ERYTHEMATOSUS**

<u>Autoantibodies (AA)</u>	<u>Incidence</u>
Rheumatoid Factor	30%
Anti-erythrocyte AA	10-40%
Anti-platelet AA	40-80%
Anti-lympho/thymocyte AA	70-80%
Anti-cardiolipin AA	20%
Anti-liver AA	< 5%
Anti-kidney AA	< 5%
Anti-thyroid AA	10-25%
Anti-neuronal AA	10-30%
Anti-collagen AA	< 5%

definitions of the above tissue types are in the glossary, all information from reference #17

Table 9**DIFFERENTIAL DIAGNOSIS BETWEEN SLE AND RA¹¹**

<u>Factors</u>	<u>SLE</u>	<u>RA</u>
Joint Pain	Present, usually without objective signs	Present, with swelling and perhaps later X-ray changes
Anemia	May be present	May be present
Rheumatoid Factor	Sometimes positive	Usually positive
Facial Rash	Frequent	Non-existent
Sensitivity	Frequent	Rare
Mouth Ulcers	Occasional	Non-existent
Alopecia	Frequent	Rare
Fever	Frequent, very high	Usually low when present
Kidney Probs.	Often present	Not present
ANA Positive	Sometimes positive	
False-positive syphilis test	Occasional	Almost never
Anti-DNA Ab	Usually positive	Negative

Table 10POTENTIAL SIDE EFFECTS OF CYCLOPHOSPHAMIDE & AZATHIOPRINE ²²

<u>Effect</u>	<u>Cyclophosphamide</u>	<u>Azathioprine</u>
<i>Common (more than 10% of patients)</i>		
Gastrointestinal	+	+
Bone marrow suppression	+	+
Suppressed immunity	+	+
Alopecia	+	-
Gonadal suppression	+	-
Hemorrhaging within bladder	+	-
<i>Uncommon</i>		
Cancer	+	+
Bladder cancer	+	-
Hypersensitivity reactions	+	-
Fibrous tissue formation within bladder	+	-
Urinary problems	+	-

ABBREVIATIONS AND ACRONYMS

Ab antibody	MCTD mixed connective tissue disease
ACA antibody to chromosomal centromere	MG myasthenia gravis
ACh acetylcholine	MHC major histocompatibility complex
AChR acetylcholine receptor	MSA mitotic spindle apparatus
Ag antigen	nRNP nuclear ribonucleoprotein
ANA antinuclear antibody	NSAID nonsteroidal anti-inflammatory drug
ARA American Rheumatism Association	PCNA proliferating cell nuclear antigen
CNS central nervous system	PMN polymorphonuclear (leukocyte)
CREST calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia	PSS progressive systemic sclerosis
C3 complement component #3	RA rheumatoid arthritis
C9 complement component #9	RANA rheumatoid arthritis nuclear antigen
DLE discoid lupus erythematosus	RNA ribonucleic acid
DNA deoxyribonucleic acid	SLE systemic lupus erythematosus
DNP deoxyribonucleoprotein	SS Sjogren's syndrome
EAMG experimental autoimmune myasthenia gravis	SSPE subacute sclerosing panencephalitis
HLA human leukocyte-associated (antigen)	Tc cytotoxic T (cell)
Ig immunoglobulin	Td delayed-type hypersensitivity T (cell)
IgG immunoglobulin G	Th helper T (cell)
JCP juvenile chronic polyarthritis	TLI total lymphoid irradiation
LCMV lymphocytic choriomeningitis virus	Ts suppressor T (cell)

GLOSSARY

- Acetylcholine** - a neurotransmitter found in many of the neuromuscular junctions of the body.
- Actin** - a protein found in muscles. It is very important in contraction.
- Action Potential** - the electrical activity developed in a muscle, nerve or the central nervous system during activity.
- Albumin** - a group of water-soluble proteins found in animal tissues.
- Alopecia** - a general loss of hair.
- Anasarca** - generalized swelling throughout the entire body.
- Androgen** - a male sex hormone.
- Anemia** - reduction in the number of red blood cells.
- Antibody** - serum protein formed in response to an antigen not recognized by the immune system.
- Antigen** - any foreign material which can be specifically bound by antibody or T cell receptors.
- Antinuclear Antibody** - an antibody produced against nuclear material (DNA, RNA, etc.) of any kind.
- Aphasia** - defect in the power of speech, writing, or signs, or of comprehending spoken or written language.
- Ascites** - the effusion of serous fluid into the abdominal cavity.
- Atherosclerosis** - the blockage of blood vessels by cholesterol-containing plaques.
- Autoantibody** - antibody produced against one's own tissues.
- Autoimmunity** - immune response to one's own tissues.
- Axillary Lymph Nodes** - the lymph nodes found underneath the arms.
- B Cell** - a type of lymphocyte which originates and differentiates in the bone marrow of an individual.
- Bradycardia** - abnormal slowness of the heartbeat.
- Bronchospasm** - rapid contraction of the walls of the bronchi.
- Bronchus** - a branch of the trachea within the lung.
- Brucellosis** - infection caused by one of the species of *Brucella*.
- Calcinosis** - a condition characterized by formation of calcium deposits in certain tissues.
- Cardiac Rub** - another term for a heart murmur.
- Cardiolipin** - a substance which is present in the heart.
- Cellular Cast** - a complex of protein and different cells types, depending on the cast, which is similar in shape to a kidney tubule.
- Central Nervous System** - the part of the nervous system including the brain and the spinal cord.
- Cerebral Vascular Accident** - a copious extravasation (discharge) of blood with the brain.
- Cervical Lymph Nodes** - the lymph nodes found in the neck.
- Cholinergic Crisis** - an overdose of anticholinesterase drugs, seen in patients with myasthenia gravis.
- Cholinesterase** - a membrane-bound enzyme which degrades acetylcholine.
- Chromosomal Centromere** - the region where the arms of the chromosome meet.
- Colon** - part of the large intestine.
- Complement** - a lytic substance in normal serum that combines with an antibody-antigen complex, producing lysis when the antigen is an intact cell. There are nine known components of complement.
- Corticosteroids** - a type of steroid produced in the adrenal gland (located near the kidneys) often used to suppress the immune system in autoimmune diseases or in organ transplantation.
- Cutaneous** - referring to skin.
- Cytoplasm** - the fluid of a cell not including the nucleus.

Cytostatic - that which inhibits cell growth.

Cytotoxic - that which kills certain cells.

Cytotoxic T Cell - a type of T cell which recognizes, binds, and destroys foreign cells.

Delayed-Type Hypersensitivity T Cell - a type of T cell which secretes substances to influence other attack cells.

Deoxynucleoprotein - DNA with proteins attached to it.

Dermatomyositis - inflammation of the skin, subcutaneous tissue, and underlying muscle.

Diplopia - double-vision.

Discoid Lesions - disk-like lesions characterized by elevated, reddish patches of rough and scaly skin.

Discoid Lupus Erythematosus - an autoimmune disease which affects only the skin of patients. It is somewhat similar to systemic lupus erythematosus.

"Drug-Induced" Lupus Erythematosus - a condition which appears after the use of certain drugs and has many of the same symptoms as systemic lupus erythematosus.

Dyspnea - difficult or labored breathing.

Edema - the accumulation of fluids within tissues.

Electrocardiogram - a graphic tracing of the electrical current produced by contraction of the heart muscle.

Electrolyte - a solution which conducts electricity by means of its ions.

Electromyogram - the record of changes in the electrical activity of a muscle.

Endocarditis - inflammation of the endocardium.

Endocardium - the internal lining of the heart.

Endocytosis - the inclusion of certain particles into the cell.

Enzyme - a protein complex which speeds up chemical reactions.

Epstein-Barr Virus - a type of herpesvirus which is responsible for a disorder called Burkitt's lymphoma (a transformation of B cells resulting in tumors).

Erythema - redness of the skin caused by the congestion of underlying capillaries.

Erythema Multiforme - a complex characterized by numbers of various types of lesions which appear suddenly.

Erythrocyte - a red blood cell.

Esophageal - referring to the esophagus.

Esophagitis - inflammation of the esophagus.

Estrone - a type of estrogenic hormone.

Fasciculation - a small local contraction of muscles.

Felty's Syndrome - a condition characterized by a combination of chronic arthritis, enlargement of the spleen, reduction in leukocytes, and spots on the skin.

Fibrin - an insoluble protein which is responsible for the essential portion of a blood clot.

Fibrous Tissue - tissue having many fibers which often grows between other layers of tissue.

Follicular Plugging - the blockage of hair follicles.

Germinal Center - area in lymphoid tissue where the formation and differentiation of lymphocytes occurs.

Golgi Apparatus - a complex network in the cell's cytoplasm believed to be important in secretion of cellular substances.

Graves' Disease - an autoimmune disease which primarily affects the thyroid gland.

Heart Murmur - a gentle blowing sound heard during heartbeats upon direct examination of the chest.

Helper T Cell - a type of T cell which releases substances to encourage an immune response.

Hemoptysis - bloody sputum

Hepatomegaly - enlargement of the liver.

Hepatotoxicity - a poisonous effect on the liver.

Herpes Zoster - the type of virus which produces chickenpox and shingles.

Histocompatibility - Being matched in regard to organ transplantation.

Histone - a group of proteins which are often complexed with DNA.

Hyperplasia - abnormal growth of normal cells.

Hypertension - increased blood pressure.

Hypoalbuminemia - abnormally low albumin content in the blood.

Hypokalemia - abnormally low potassium content in the blood.

Hypotension - lowered blood pressure.

Ileum - part of the small intestine.

Immunofluorescence Assay - a technique which uses fluorescently-tagged antibodies for the detection of certain antigens.

Immunoglobulins - serum protein, produced by certain white blood cells, which specifically binds to an antigen. The proteins called antibodies are included in this group.

Juvenile Chronic Polyarthritis - a disorder which is very similar to rheumatoid arthritis. Also called juvenile rheumatoid arthritis.

Keratotic Scaling - formation of hard calluses on the skin.

Ketoacidosis - an accumulation of keto acids (chemical compound with a CO group and a COOH group in it) in the blood.

Klinefelter's Syndrome - a congenital disorder which occurs when a male baby picks up an extra X chromosome, thus having an XXY pattern, instead of the normal XY pattern.

Lacrimation - increased secretion of tears.

Leukocyte - a general term for a white blood cell.

Leukopenia - reduction in the number of white blood cells.

Lipopolysaccharide - a compound found in certain bacterial cell membranes which can produce an inflammatory response.

"Lupoid Hepatitis" - a condition characterized by the presence of LE cells, antinuclear antibodies, and active liver disease.

Lupus Profundus - a condition which occurs as deep lesions within the skin appearing as hardened lumps.

Lymphocyte - a type of white blood cell responsible for controlling many of the immune responses.

Lymphocytic Choriomeningitis Virus - a type of virus which have been found to be able to produce a persistent infection because of its becoming dormant.

Lymphoma - cancer of the lymph nodes.

Lymphopenia - a reduction in the number of lymphocytes.

Lysosome - a cytoplasmic vacuole which contains many different types of enzymes for the digestion of material which is engulfed into the cell.

Maculopapular - referring to small, elevated bumps, which are often discolored when compared to other areas.

Malaise - a condition of general body discomfort.

Malar Eminence - another term for the cheek bones.

Membrane Depolarization - the act of transmission of an electric current down a nerve cell or a muscle.

Meninges - the membranes surrounding the brain and the spinal cord.

Meningism - a hysterical simulation of meningitis.

Meningitis - inflammation of the meninges.

Mitochondria - a complex which is responsible for cellular metabolism.

Mitotic Spindle Apparatus - the compound which is responsible for separating the chromo-

somes during mitosis.

Mixed Connective Tissue Disease - an autoimmune disease which is actually a combination of many different types of autoimmune disease, as a result symptoms are wide-ranging. It is also called the "overlap syndrome."

Monoclonal Antibody - an antibody which is produced by a clone of a specific plasma cell

Myalgia - the aching of muscles.

Myasthenic Crisis - an adverse reaction to a removal from or a change of medication, seen in patients with myasthenia gravis.

Myocarditis - inflammation of the myocardium.

Myocardium - the actual heart muscle.

Myoid cell - muscle-like cell located in the thymus.

Myxovirus - the group of viruses which include the influenza and parainfluenza viruses.

Nasolabial Folds - the area between the nose and the lip.

Nasopharyngeal - referring to the part of the throat above the soft palate.

Nephritis - inflammation of the kidney.

Nephrosis - any disease of the kidney.

Nephrotoxicity - a poisonous effect on the kidney.

Neuromuscular Junction - the junction between a nerve and the muscle which it controls.

Neurotransmitter - a specific chemical which plays a role in the transmission of an impulse from one nerve fiber to another.

Nonsteroidal Anti-Inflammatory Drug - a type of drug which does as its name implies, it acts against inflammation and simple pains.

Nuclear Matrix - a protein network found between the nucleolus and the nuclear membrane.

Nuclear Ribonucleoprotein - a type of compound which is thought to be similar in nature to deoxyribonucleoproteins except that it is associated with RNA.

Optic Disk - a white, round disk at the back of the eyeball where the optic nerve enters the eye.

Orthopnea - inability to breathe except in an upright position.

Osteonecrosis - death of bone cells, often associated with bone disintegration.

Osteoporosis - the reabsorption of bone by the rest of the body.

Pancreatitis - inflammation of the pancreas.

Paramyxovirus - the group of viruses which include the mumps, measles, and rubella viruses.

Periarticular Soft Tissue - the tissue situated around a joint.

Pericarditis - inflammation of the pericardium.

Pericardium - the membrane which surrounds the heart.

Peripheral Nerves - the nerves which are not a part the central nervous system.

Peripheral Neuritis - inflammation of the nerve endings.

Phagocytosis - the active process of engulfing particulate matter within a cell.

Phospholipid - a compound which contains a phosphorus and a fatty component. This compound is found in tissues in much of the body.

Plasma Cell - a sensitized B cell which secretes antibodies specific for a certain antigen.

Platelet - a cytoplasmic fragment which takes an active part in the coagulation of blood and formation of blood clots.

Pleura - the membrane surrounding the lungs and lining the thoracic cavity.

Pleurisy/Pleuritis - inflammation of the pleura.

Pneumonitis - inflammation of the lung without gross toxicity

Polyarteritis - inflammation of several arteries at the same time.

Polymorphonuclear Leukocyte - a type of white blood cell that phagocytoses foreign material.

Polymyositis - an inflammatory disorder of the skeletal muscle.

Postsynaptic Terminal - the nerve ending found after the synapse.

Presynaptic Terminal - the nerve ending found before the synapse.

Proliferating Cell Nuclear Antigen - a nuclear protein found most often in cells which are proliferating.

Proteinuria - large amounts of protein in the urine.

Psychosis - any major, severe form of prolonged mental disorder.

Ptosis - drooping of the eyelids.

Purpura - condition characterized by pinpoint, purplish red spots on the skin.

Raynaud's Phenomenon - attacks of paleness and blueness along with numbing of fingers and toes.

Reovirus - a group of viruses against which antibodies have been produced in patients with SLE.

Retina - the back part of the eye which is responsible for the ability to see.

Rheumatoid Arthritis - an autoimmune disorder characterized by severe inflammation of the joints.

Rheumatoid Arthritis Nuclear Antigen - one of the first nuclear antigens which was found to have antibodies produced against it in rheumatoid arthritis.

Rheumatoid Factor - an antiimmunoglobulin antibody directed mainly against IgG molecules.

Ribosomes - a particle which is found in the cytoplasm of a cell composed of protein and RNA.

Roentgenograph - a photograph similar in nature to an X-ray only using roentgens.

Rubella - a virus more commonly known as German measles.

Sclerodactyly - localized scleroderma on the fingers and toes.

Scleroderma - an autoimmune disorder characterized by a hardening and leather-like appearance of the skin.

Sendai Virus - a relative of the mumps virus.

Septicemia - the presence of bacterial toxins in the blood.

Sjogren's Syndrome - an autoimmune disease which is often marked by a drying of the eyes and mouth.

Smith (Sm) Antigen - a nuclear antigen against which antibodies are produced in SLE.

Splenomegaly - enlargement of the spleen.

Subacute Bacterial Endocarditis - inflammation of the lining of the heart caused by a bacterial infection.

Subacute Sclerosing Panencephalitis - a fatal disease caused by a latent measles infection which reactivates to cause disintegration of the brain and the systems which the brain controls.

Suppressor T Cell - a type of T cell which turns off an immune response to a specific foreign antigen.

Synapse - the region of contact between two nerves or one nerve and a muscle.

Systemic Lupus Erythematosus - an autoimmune disease which affects all parts of the body characterized by high levels of antinuclear antibodies.

T Cell - a type of lymphocyte which originates in the bone marrow, but differentiates and matures in the thymus.

Telangiectasia - a disorder where the capillaries and small arteries become dilated.

Tensilon - a short-acting anticholinesterase drug which is used to enhance the effects of acetylcholine on a muscle.

Thrombocytopenia - decrease in the number of blood platelets.

Thymocyte - a lymphocyte in the thymus.

Thymoma - tumor or cancer of the thymus.

Thymus - a gland-like organ which regulates the differentiation and maturation of certain white blood cells (T cells).

Total Lymphoid Irradiation - a possible way to treat autoimmune disease by exposing lymphatic tissues to large doses of radiation.

Treponema pallidum - the organism which causes syphilis.

Uremia - the presence of urinary constituents in the blood.

Urinalysis - a test attempting to detect increased amounts of protein and cells in the urine, which is indicative of kidney problems.

Vasculitic Lesions - lesions which are characterized by being slightly tender to the touch and somewhat hardened.

DRUGS AND CHEMICALS

<u>OTC Name</u>	<u>Chemical Name</u>	<u>Uses</u>
Tensilon	edrophonium Cl	MG diagnosis
Mestinon	pyridostigmine Br	MG treatment
Prostigmin	neostigmine Br	MG treatment
Mytelase	amibenonium Cl	MG treatment
-	prednisone	immunosuppressant
-	azathioprine	immunosuppressant
-	cyclophosphamide	immunosuppressant
Procan/ Pronestyl	procainamide HCl	for hypertension
Apresoline	hydralazine HCl	for hypertension
Dilantin	diphenylhydantoin	for convulsions
Laniazid/ Nydrasid/ Teebaconin	isoniazid	for tuberculosis
Cuprimine/ Depen Titratabs	penicillamine	RA treatment
Tetracycline	-	general antibiotic
Atabrine	quinacrine	for skin lesions
Plaquenil	hydroxychloroquine	for skin lesions
Arahen	chloroquine	for skin lesions

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