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INTRODUCTION

History: Bayer in 1827 has been credited with the first description recognizable of the disease complex now known as lupus erythematosus.(1) His description included merely the typical skin lesions. These were again described by Biett in 1828.(2) Hebra in 1845 called further notice to these findings, and the name "lupus erythematodes" was applied to the disease by Cazenave in 1851.(3) Kaposi in 1872 is credited with the first description of the systemic effects of the disease, and with the classification into discoid and disseminated forms.(4) Osler in the years between 1895 and 1903 added further descriptions of the visceral manifestations. Libman and Sacks in 1924 described the atypical verrucous endocarditis which is now known to be associated with lupus erythematosus.(5) The description of the LE cell by Hargraves in 1948 has probably been the chief stimulus to investigation of this disease. Klemperer's concept of the collagen diseases, including lupus erythematosus, published in 1950, has also stimulated interest. Numerous other investigators have contributed, and medical literature is now replete with articles further contributing to our present knowledge of this intriguing disease.

Definition of the Disease: Systemic lupus erythematosus is a syndrome of great variability which includes cases of

disease having a common pattern of clinical, laboratory, and pathological findings. Presumably, the etiology and pathogenesis are also similar. In a typical case one might see intermittent fever, arthralgia, fatigue, pneumonitis, a "butterfly rash, Raynaud's phenomenon, light sensitivity, weight loss, a false positive serology, hyperglobulinemia, leukopenia, proteinuria, and a positive test for LE cells. The course of the disease usually includes remissions and exacerbations, but is slowly progressive. The disease may be described in great detail, but its limits cannot yet be finally determined because of incomplete knowlege of its pathogenesis, interweaving with other disease entities in many reported cases, and failure of any of the many characteristic findings in the disease to be present in all cases of the disease. Exact criteria for diagnosis cannot be presented. It is questionable, for instance, whether patients with clinical symptoms predominantly of rheumatoid arthritis but with positive LE tests should be said to have rheumatoid arthritis or lupus erythematosus; or whether certain cases of hydralazine toxicity should be regarded as toxic reactions which resemble lupus only by coincidence; or whether lupus erythematosus is indeed present and has been caused by some alteration of metabolism caused by the hydralazine; or even whether this represents a "subclinical" case of lupus erythematosus in which the hydralazine

poisoning has merely brought symptoms to a clinically recognizable level. Thus it is seen that a great deal remains to be determined regarding the "definition" of this disease. It is a clinical syndrome, defined only by the presence of certain characteristic features. These features will be further described in the following pages.

Frequency: It will be impossible to state the incidence of systemic lupus erythematosus until exact criteria can be established for its diagnosis. About all that may prove helpful might be a statement of trends of the medical profession in making the diagnosis. It is stated that prior to 1936 this disease was very rarely reported.(7) Incidence at the 3600 bed Los Angeles General Hospital has been reported as follows:(8)

1948-1949 (prior to use of the LE test)	11 cases
1950-1951 (frequent use of heparinized test)	44 cases
1952-1953 (the same)	35 cases
1954-1955 (use of clotted test also)	54 cases.

These figures are only one indication of the fact that the diagnosis has been applied not infrequently since advent of the LE cell test. Other reports, such as one on 100 cases of lupus seen at the Mayo Clinic between 1948 and 1951, indicate that the diagnosis of lupus is made not uncommonly at medical centers. Similarly, in more recent literature,

it is noted that there are a number of reports of series from 50 to 150 or more lupus patients observed by a given individual or at a given institution. Klemperer, writing in the 1955 edition of Cecil's TEXTBOOK OF MEDICINE, calls lupus erythematosus "a rather common disease".(10)

Methods of Treatment: Much could be said regarding treatment of lupus, but only a few general statements will be made. Of paramount importance is the avoidance of sunlight.(11) This will go far in slowing the progression of the disease.

Adrenal corticoids are quite effective in ameliorating symptoms and probably in prolonging life. Since the progress of the disease is quite variable and there are many natural remissions, accurate evaluation is difficult. Cortisone is more than usually effective in cases where arthritic symptoms are predominant, and also in lupus during pregnancy.(8)(12) It is particularly valuable in the more acute cases where symptoms are rapidly progressive. It may be life-saving here. Massive doses, up to 1000 mg or more of cortisone per day, have been advised for these acute cases.(13) Dosage is then lowered, and may be continued indefinitely at the equivalent of 100 mg of cortisone daily, more or less, or else discontinued.

Antimalarials are effective, particularly against cutaneous manifestations, but also to an extent against

other manifestations of the disease. Chloroquine and atabrine are said to be about equally effective and amodiaquine slightly less effective.(8)

Nitrogen mustard is said to be very good when the manifestations are those of the nephrotic syndrome. Whereas corticoids are the only effective agents in blocking renal damage during the acute attack, the progressive renal damage of chronic lupus is often only poorly controled by the corticoids. Nitrogen mustard has been advocated by some as far the best agent to use in such instances.(8) This drug has been much less extensively used than the corticoids or antimalarials. Many are not enthusiastic about its use because there is already marrow depression in lupus.

Other drugs which have been used, but not really proven effective in a significant number of cases, include: gold chloride,(10) bismuth and PAS,(10) androgens, and conversely even castration,(10) manganese,(14)(15) propylthiouracil,(16) and Vitamin E.(17)

Aim of Thesis: As indicated above, lupus erythematosus is a disease which probably is fairly common, which is yet poorly understood, and which is often very difficult to diagnose. It may resemble a vast number of disease entities, and it should probably be considered in the majority of real

diagnostic problems which arise in the field of internal medicine. There are now available, methods of treatment which will definitely alleviate symptoms and prolong life. While it is true that really accurate diagnosis of many cases will not be possible until more is learned of the pathogenesis, more refinements are made in the LE test, or other new information is garnered; yet, it is also true that the speed with which these advancements can be made is dependent in large part upon as accurate as possible diagnosis of present cases. The ability to separate a disease entity from other similar entities is the first step in learning of its causes and treatment. The aim of this thesis is to delineate criteria necessary for making a diagnosis of lupus erythematosus.

DETAILED DESCRIPTION OF THE DISEASE

Etiology: The etiology of lupus erythematosus is not known. It would be extremely helpful to learn this as a guide both to diagnosis and treatment. There are several theories, and each has both supporting and conflicting evidence.

The original concept of Klemperer that lupus erythematosus was a collagen disease[6] has gained much support and is presently widely held. This helps categorize the disease, but presently furnishes only limited insight as to its etiology. Features common to collagen diseases include

the following:

A. Increase in ground substance.
B. Fibroblast proliferation.
C. Inflammatory reaction.
D. Presence of mononuclear cells.
E. Necrosis and fibrinoid deposit.
F. Widespread involvement.
G. Involvement especially of endothelium, mesothelium, and synovium.
H. Response to corticoids.
I. Unknown etiology.
J. Rise in blood of: mucopolysaccharides, a nonspecific hyaluronidase inhibitor (perhaps heparin), alpha globulins, fibrinogen, and other components derived apparently from injured mesenchyme.
K. A fall of blood albumin and collagenase inhibitor.
L. An increased production of abnormal globulins and of plasma cells.(18)(19)

Thus it seems likely that all of the so-called collagen diseases may have a related etiology, that the above named factors which are common to all are probably directly related to an underlying defect, and that as knowledge is accumulated about one of these diseases it will aid in understanding the others.

It is significant that there are several reports of a familial incidence of lupus erythematosus. One family with eight cases and another with four cases of lupus have been reported.(20) Several other instances have been variously referred to. Reports of placental transmission are not uncommon and may result in a dead fetus with pathological findings confirmatory of lupus erythematosus, or a live baby having many positive LE cells at birth but not having either the LE cells nor symptoms at a later age.(21)(22)(23)(24)

Although a placental transmission of the LE factor is thus demonstrated, there have been no proved instances of actual congenital lupus, since in those cases so far described, the infants which have survived have gradually become asymptomatic and have lost their positive LE cell tests.

An endocrine influence in the disease is suggested by the following facts; that lupus is much more common in women than in men, that it is much more common during the reproductive age than at ages either above or below this, and that there are frequently exacerbations of the disease during pregnancy.

Another striking factor noted regarding incidence of the disease is its frequency in attacking persons of fair skin. All races are susceptible, including negroes;[7][25] but certainly the preponderance of cases occurs in those with a light-sensitive complexion. Furthermore, exposure to sunlight considerably accelerates the disease process.

Some type of immune reaction has been seriously considered as the underlying cause of lupus. It is noted that patients with lupus have a much higher incidence of drug sensitivities and other allergic reactions than do normal persons.[20][26][27][28][29] Furthermore, many of the pathologic changes seen in lupus and the other collagen diseases may also be seen in allergic responses. This theory was first proposed by Klinge in 1933 when he maintained that

those diseases characterized anatomically chiefly by fibrinoid connective tissue damage (lupus erythematosus, periarteritis nodosa, dermatomyositis, malignant nephrosclerosis, and thromboangiitis obliterans) were due to hypersensitivity (he noted this change in rabbits made sensitive to foreign protein).[30] The false positive tests for syphilis and the positive direct Coombs tests, which are not infrequently seen in lupus, have also been interpreted as suggestive of an abnormal antibody. Positive complement fixation to homogenized, assorted nuclei was reported in 22 of one series of 30 patients with positive LE tests. This included all those cases in which the test was strongly positive; yet, was found in none of 15 normals, 21 rheumatoid arthritics, 5 cirrhotics, 3 macroglobulinemias, and 2 multiple myelomas.[31] These findings suggest the presence of antibodies against some component of human tissue. It has also been reported that a marked fall in complement activity of the blood may occur in lupus;[32] thus suggesting that some type of antibody-antigen reaction may have occurred which lowered the available supply of complement. It has been reported that the LE cell phenomenon can be induced with antileukocytic serum.[33] It has also been demonstrated that the LE cell phenomenon can be inhibited by rabbit antisera against serum from patients with disseminated lupus erythematosus.[34] It has been suggested that the

beneficial action of cortisone in lupus is due to its known activity in destroying plasma cells, thus halting antibody production.(35) Various attempts have been made to isolate the so-called LE factor, that is, the supposed substance which causes formation of the LE bodies which are seen in the tissues or in the LE cell. There is general aggreement that such a factor can be demonstrated in the gamma globulin portion of the serum of a patient with lupus. Thus it is seen that there are many reasons to suspect that a hypersensitivity reaction is the cause of lupus. This concept would also be compatible with the evidence that endocrine activity might be influential; although it does not explain why this hypersensitivity would be so greatly increased under the endocrine status existing in the reproductive woman. Dameshek, supporting an auto-immune etiology for lupus, suggests "antigen development may take place in menstruating endometrium".(36) He thus explains that the degenerating endometrium may be an especially fruitful area for development of the auto-antibody, and women in menstruating age correspondingly more susceptible to lupus. This, however, would not seem to adequately explain the tendency for exacerbations during pregnancy. The factor of photosensitivity in lupus is poorly explained by assuming that lupus is due to an immune antibody. Other antigen antibody reactions are not particularly affected by sunlight; whereas certain metabolic

conditions may be so affected. The few reports of a familial tendency are also poorly explained by assuming existence of an immune antibody. Even though susceptibility to allergies is an hereditary factor, susceptibility to only a single antigen is not recognized as being hereditary. Patients with lupus erythematosus are known to show increased incidence of drug and other hypersensitivities, but these apparently develop after onset of lupus more often than before. No reports were noted of increased allergic entities as asthma or hay fever in existence before development of lupus. So the arguement is not settled.

Others believe that lupus is the result of a metabolic derangement, most likely of congenital origin. An increasing number of diseases, formerly of unknown etiology, are now believed due to a congenital defect in enzymatic machinery with a resultant metabolic defect which appears at varying later periods during life. There is much in the clinical behaviour of lupus which would suggest such an etiology. The remissions and exacerbations with yet a slowly progressive course seen in many, the more rapid course seen in some, the aggravation during periods of strain such as during pregnancy, the effect of adrenal corticoids which markedly influence protein and carbohydrate metabolism, the variability of symptoms and yet similarity of pathological change seen in affect tissue all are quite compatible with a basic defect

in metabolism. This, in a given individual, would be manifest in his weakest system, and would progress slowly or rapidly according to his ability to compensate; but it would be similar in process to the disease in other individuals. The occasional instances of familial incidence suggests an hereditary basis, and the great preponderance of cases in females may be interpreted as evidence in favor of an etiological relationship to chromosomal transmission. The hydralazine toxicity syndrome also favors a metabolic etiology because its appearance and severity behave more as though due to a metabolic interference than a hypersensitivity. This will be further described in the discussion on the LE cell test. The chief deterrent to this theory is the demonstration of the LE factor in the gamma globulin portion of the blood of lupus patients. It has been demonstrated that this factor will cause in vitro disintegration of other cell nuclei. The fact that mothers with active lupus may give birth to babies exhibiting LE cells and even histologic tissue changes typical of lupus, and that if the babies survive they later show no evidence of lupus, might be interpreted as evidence of in vivo destruction of normal cells by the LE factor. This would discourage the idea that the active substance in the gamma globulin might be a "normal" response to abnormal body cells. Even should it subsequently be proved, however, that the damaged tissues of the lupoid patient were normal

before contact with the LE factor, it would still seem that the derangement of the cells producing this LE factor could be due to an inborn error of metabolism, and not to later transformation of normal cells on a hypersensitivity basis. Thus it is seen that while hypersensitivity is probably yet the most popular choice for a tentative etiology in lupus, there is also good evidence that a congenital metabolic error may be the real cause.

Some have gone so far as to propose to explain just wherein such a defect may lie. Thus manganese metabolism has been implicated.(15) An aberrant metabolism wherein pantothenate is poorly utilized has also been suggested.(17) Although a few workers feel they have suggestive evidence along those lines, there is at present no really conclusive evidence of a metabolic derangement.

Other theories have also been proposed from time to time, and several of these have not yet completely fallen by the wayside. Around 1900 it was widely believed that there was an association with tuberculosis. Enthusiasm over this theory has subsided although the increased incidence of tuberculosis is noteworthy and a factor to remember before blindly initiating cortisone therapy. This increased incidence is apparently seen before, as well as after, cortisone therapy of lupus. In 1932 Stokes postulated that lupus might be due to hypersensitivity to bacterial products,(37) and in

1934 O'Leary narrowed this to streptococcal products.(38) Both rheumatic heart disease and glomerulonephritis, which are believed to have this etiology, are noted to have certain resemblances clinically, laboratory-wise, and especially histologically to lupus; however, this idea is also out of vogue, mainly because there is no evidence relating development of lupus to a preceding infection. It is mentioned that lupus will occasionaly be noted in conjunction with infection,(11) but in view of the small number of cases thus beginning it would seem that the infection was probably incidental. The idea of a responsible micro-organism is not extinct, however, for a viral etiology must also be considered. Viruses, too, are rather popular these days, and an increasing number of bizarre syndromes and certain types of cancer have been rather definitely shown to be associated with viruses. The beneficial therapeutic effect of nitrogen mustard in lupus is consistent with the viral theory. The beneficial effects of nitrogen mustard might also be due to suppression of production of an auto-antibody since anti-metabolites usually show greatest effects on cells with the most rapid turnover-rate, and since an auto-antibody must surely have a short "life". The beneficial effect of cortisone is certainly not consistent with a viral etiology.

In summary the etiology is unknown. The hypersensitivity

theory is probably most widely held, but the metabolic defect theory also has a number of points in its favor, and a viral etiology is not at all improbable. Many arguments for and against each of the theories may be constructed. Promising fields of study regarding the pathogenesis of lupus concern biochemical studies of the LE body and its formation, and studies of hydralazine toxicity. Both of these will be discussed in more detail in the pages to follow.

Pathological Findings: Lupus erythematosus perhaps has as many different characteristics, each sufficiently specific to be considered diagnostic, as any other disease. While each of these is commonly seen; none is universally seen. Thus there are a number of criteria available for ruling in the diagnosis of lupus, but not one for ruling it out. Among the pathological findings which, if present, are generally considered diagnostic, one might include: (1) demonstration of an LE cell or the LE phenomenon in either bone marrow or blood, (2) presence of Libman-Sacks endocarditis, (3) demonstration of so-called "onion-skinning" of the penicilliary arteries of the spleen, (4) so-called "wire loop" glomeruli and presence of "hyaline thrombi" in the kidney, (5) a characteristic group of changes occurring in areas of the skin in certain lupus patients, and (6) a group of changes affecting connective tissue anywhere and

consisting chiefly of increase in amount and deep staining of the ground substance, fibrinoid degeneration of collagen fibrils, and presence of LE bodies.

In spite of the multiplicity of characteristic microscopic changes which may occur, the usual findings at the autopsy table frequently show little or no apparent gross anatomical changes. This is particularly striking in those who die a rather fulminating death with striking symptoms of multi-system involvement. Cause of death may be difficult to determine. Two series are presented showing cause of death in groups of lupus patients.

Cause of death in 10 cases of lupus:(39)

A. lupus crisis (2)
B. septicemia (2)
C. thrombosis (1)
D. uremia (1)
E. unidentified (4).

Cause of death in 58 cases of lupus (in descending order of frequency):(8)

A. uremia
B. progressive CNS damage
C. pulmonary tuberculosis
D. perforated peptic ulcer secondary to steroids
E. unknown
F. coronary occlusion
G. carcinoma of stomach
H. hemolytic anemia
I. hemorrhage from bowel lesion
J. agranulocytosis from TEM
K. pancreatitis from arteritis
L. congestive heart failure.

Of the two series listed, it appears that the first must have included mostly acute cases; and the second must have included mostly chronic cases. Persons with lupus are much more

susceptible than the average person to infections.

An orderly, concise presentation of the microscopic findings in lupus is difficult to arrange because of the large number of organs involved and changes incurred. An attempt will be made to list the major changes seen in each system. The LE cell, probably most characteristic of all, will be discussed separately.

Libman-Sacks endocarditis is said to have been first described by Libman in 1911, and to consist of verrucae arranged in a single beadlike chain along the closing edge of the endocardial valves, and sometimes combined with nodules or mulberry-like masses scattered over the valvular surface.(5) They are gray to yellow in color and slightly larger than the verrucae seen in rheumatic heart disease. All the valves may be involved, but the mitral and tricuspid valves are most frequently attacked. Negative blood cultures and a lack of any apparent source of embolization are associated. On closer examination these vegetations are seen to consist of a finely granular eosinophilic matrix with clumps of blue, structureless bodies, segmented neutrophiles, and foci of fibrinoid degeneration of collagen scattered throughout.(40)(41) In most reported series about 25-30% of the cases autopsied show Libman-Sacks atypical verrucous endocarditis.(10)(11)(42)(43) Aschoff bodies have not been described in lupus although superficial

resemblances are not uncommon.

The "onion skin" lesion of the spleen is descriptive of the microscopic appearance of the central arteries of the malpighian lymph follicles. The arteries are characteristically surrounded by conspicuous concentric rings of connective tissue. These rings are apparently formed by slow collagenization of adventitial reticulum fibers which are gradually added to, and which may reach considerable thickness. There is no general agreement as to the frequency with which this lesion is seen, the frequency reported in individual series evidently depending upon the chronicity of the disease in that group of patients, and also upon the degree of thickness which the individual feels must be present in order to call a given case "onion skinning". Although this finding has been included with the list of findings specific to lupus, all persons do not so regard it. For instance Teilum and Poulsen state they have also seen it in sarcoidosis and other conditions associated with plasmocytosis. These authors related it to stimulation of the immune mechanism.(44) Most authors merely content themselves with the statement that "Klemperer considers this specific". As with the LE cell, the specificity of this finding will probably be challenged now and then by persons claiming to have seen one or two instances of it in a disease other than lupus. However, since (1) the challenges are very infrequent,

(2) the majority of examples stated to be present in non-lupoid diseases would not pass the criteria of more exacting examiners elsewhere, and (3) there is no way of proving a given patient does not have lupus regardless of what else may ail him, this finding may generally be considered as specific for lupus erythematosus.

The "wire loop" lesion of the kidney is also quite characteristic. There are no known reports of this finding in any diseases other than lupus erythematosus. There have, however, been reports of its presence in atypical states which appeared to be a conglomeration of lupus and other diseases either mixed together or transforming one into the other. In the typical involved kidney the glomeruli appear irregularly thickened and are deeply stained by eosin. They appear like amyloid, and indeed can sometimes not be distinguished from this condition on an H & E stained slide. However, they have none of the staining characteristics specific to amyloid. Neither do they exhibit the characteristic staining properties of collagen. Sometimes they may appear basophilic or necrotic. Seen under the electron microscope, there is described only a generalized thickening of the basement membrane and a variable degree of endothelial proliferation.(45) Studies carried out with phase microscopy indicate that the wire loops may be seen to lie in the capillary wall between the endothelial and epithelial basement membranes.

They are further described as homogeneous and highly refractile.(46) Also seen may be the so-called "hyaline thrombi". They too are rather specific for lupus and are amorphous eosinophilic intraluminal masses which are often regarded as an end product of "wire looping". Although generally described as being present only in the kidney, some have described seeing them throughout the greater and lesser circulation and regard them to be the result of degraded nucleoprotein floating about in the blood stream.(42) Still others suggest that the hyaline thrombi consist of mucoprotein secreted by the endothelial cells of the glomeruli.(44)

A majority of the writers on skin findings in lupus express the opinion that these may be diagnostic. Others feel that they are only strongly suggestive. Skin lesions in acute lupus are said to show marked atrophy of the epidermis with severe edema in the lower cells of the rete; the lack of infiltrate and the extreme edema in the cutis being characteristic. The chronic discoid type usually shows more hyperkeratosis and plugging and less edema in the epidermis and cutis plus a well-defined small mononuclear and frequently periappendageal infiltrate.(41)(47)

Lymph nodes characteristically show enlargement and patchy areas of necrosis. A few nodes are palpable in the majority of moderately advanced cases. Some persons feel that diagnostic changes may be seen within the lymph node.

They describe a picture of frequent absence of the primary and secondary follicles with lymph sinuses which are swollen and distended with lymphocytes, plasma cells, and histiocytes; swollen and hyperplastic endothelial cells; some perivascular cuffing; and peculiar large neutrophilic to eosinophilic cells three to four times the size of a lymphocyte.(48)

Lesions affecting serous membranes are quite common, but also quite non-specific, and may consist of mere thickening or other changes. Any type of arthritis may be seen. The histologic and radiographic appearance of joint involvement is frequently identical to that seen in rheumatoid arthritis.

Respiratory symptoms are very common in lupus, but again there is no characteristic lesion. Secondary infections, particularly pneumonia and tuberculosis, are quite common. One series of 54 cases of lupus illustrates well the multiplicity of findings but lack of specific changes.

Pulmonary lesions seen in 54 cases of lupus:(49)

A. bronchopneumonia 76%
B. pleural effusion 67%
C. pulmonary edema 56%
D. interstitial pneumonitis 54%
E. atelectasis 44%
F. mucinous edema 17%
G. abscess 17%
H. active tuberculosis 6%
I. healed tuberculosis 11%
J. pulmonary infarct 6%
K. emphysema 4%.

Several characteristic types of lesions may be seen in supporting tissues in scattered areas of the body.

Probably the most prounounced lesion is arterial damage. Non-specific arterial changes may be seen anywhere, and are usually seen in all grades of severity. Mildly involved arteries may show only isolated smudges of eosinophilic material with little or no signs of inflammation. In more advanced lesions there may be severe inflammation with infiltration of many neutrophilic granulocytes, some round cells, and usually few, if any, eosinophiles. Endothelial proliferation is common. In very advanced lesions the intimal, elastic, muscular, and fibrous layers are fused into a homogeneous eosinophilic mass.(42)(43) All elements of the connective tissue show some change. The mucoid ground substance, ordinarily hardly visible, appears as a swollen homogeneous mass surrounding the fibrous elements. Elastic fibers become coated with eosinophilic material and lose their characteristic staining properties. Collagen fibers undergo swelling and irregular thickening with loss of fibrillar structure, and assume a homogeneous eosinophilic nature. Characteristic LE bodies may be seen. They are small, homogeneous, hematoxylin-staining bodies which are quite characteristic for lupus and may be seen in the connective tissue in various areas of the body. As with the other previously described characteristics of lupus they are not seen in every case. In one series of 16 autopsied cases of persons with clinical signs of lupus and positive LE cells

preceding death, LE bodies were found in: kidney 13, heart 11, lymph nodes 10, ovary 9, spleen 6, pancreas 5, uterus 5, skeletal muscle 4, fallopian tube 3, esophagus 3 liver 3, skin 3, breast 2, stomach 2, pylorus 2, intestine 2, adrenal 2, periadrenal tissue 2, marrow 2, bladder 1, testis 1, tongue 1, gall bladder 1, and vagina 1 case.(42) Although presence of the LE bodies cannot be exactly correlated to severity of disease, it is probable that their incidence of appearance would be lower in a series of less severe cases of lupus (one supposes there were rather severe cases since all had positive LE cells and all reached the autopsy table in this series).

The nature and pathogenesis of the LE bodies is presently hotly contested. To quote Klemperer, "Klemperer has made the important observation that another deep purplish staining material may be found in some of the affected areas of connective tissue, which he has identified histochemically as consisting largely of desoxyribonucleic acid, and which must therfore be derived from the enzymatic disintegration of nuclear material. This is apparently the same abnormal chromatin material observed in the so-called "L.E. cells" of the blood and bone marrow in this disease by Harrow, Richmont, and Morton".(10) This theory, if true, would be an aid in the understanding of the pathogenesis of lupus. There has been much evidence presented for and against it. Various investigators have reported on the high amount of DNA (desoxy-

ribonucleic acid) in the LE body, and have decided that this DNA was in a depolymerized state on the basis of the feulgen-methyl green extraction ratio. If one stains a slide with methyl green and measures the amount of extraction of red light (625uu), and if he compares this figure to the figure obtained by decolorizing the same slide and staining it with the feulgen method and then measuring the extraction of green light (550uu), the ratio obtained is called the feulgen-methyl green extraction ratio. It has been said to be a delicate indicator of the state of depolymerization of a substance. By this method LE bodies may give a ratio in the range of 2.6:1 to 8.7:1 whereas normal lymphocyte nuclei will give a range of only around 1.1:1 to 1.7:1.(40) Using these methods, a number of theories have been developed postulating the existence of some type of DNase.(33)(40)(42)(50)(51)(52)(53) The attempt has thus been made to link together the findings of cellular destruction, LE bodies, LE cells, and hyaline thrombi by postulating that cell nuclei are destroyed by an enzyme and that the remains float away to be deposited randomly or else are ingested by an LE cell. There is a DNase in the serum of normal individuals, and it has been reported to be slightly increased in the serum of individuals with lupus; however, formation of LE cells is not impeded by heat destruction of this enzyme and thus it seems unlikely that this is significant.(54) It has been reported

that DNase inhibitors are found in normal granulocytes[51][53] so that the possibility arose that the inhibitors might be diminished in lupus. It is also reported, however, that well-designed experiments have failed to demonstrate any inhibition of this inhibitor in lupus erythematosus.[42] The DNase theory yet has a few die-hard adherents, but received its worst blow when reports began appearing that the DNA in LE bodies was not depolymerized and that the change in feulgen-methyl green extraction ratio was due to protein interference and could be reversed by acetylation of basic protein groups present. Further studies now reveal that there is a marked loss of histone and a marked increase in protein in an LE body. Postulation has been made that an abnormal protein may displace histone from its combination to DNA and form a complex with DNA, that the resulting mass is extruded from the parent cell and becomes an LE body, and that it may be ingested to form an LE cell, or it may even combine further with carbohydrate and undergo gradual depolymerization of the DNA and thus form a hematoxylin body.[54][55][56] It may thus be seen that the LE body is an amorphous mass, usually taking hematoxylin stain but occasionaly eosinophilic, which is found in the connective tissue of various organs in certain people with lupus erythematosus; that it appears to be formed of DNA plus an unidentified protein material; and that it is probably of the same origin whether found in

an LE cell or lying free in the connective tissue. Its pathogenesis is being actively investigated.

Signs and Symptoms: The signs and symptoms of lupus form a complex array. A group of findings, any one of which is quite suggestive of lupus, blends into a much larger group of nonspecific findings which may be seen in occasional cases. Indeed, nearly any system in the body may be the first to show symptoms, and nearly any symptom may be seen. The following three series are illustrative of the multitude of ways in which lupus may present itself.

Initial manifestations in 25 cases:(26)

A. purpura 3 cases
B. false positive serology 2
C. Raynaud's phenomenon 2
D. albuminuria 2
E. pericarditis 1
F. arthritis 8
G. fever 3
H. rash 4.

Initial manifestations in 35 cases:(29)

A. joint involvement 19 cases
B. dermatitis 2
C. pyuria and hematuria 2
D. malaise 2
E. chest pain 1
F. alopecia 1
G. chills 1
H. anemia and jaundice 1
I. Raynaud's phenomenon 1

Initial manifestations in 105 cases:(28)

A. acute migratory arthritis 34 cases
B. fever 24
C. erythematous eruption 21
D. fatigue and malaise 18
E. arthralgia 16
F. weight loss 7
G. anorexia 6

H. nephritis 5
I. false positive serology 5
J. pleurisy 5
K. dyspnea 4
L. cough 4
M. nausea 4
N. anemia 4
O. urticaria 4
P. Raynaud's phenomenon 3
Q. drug reactions 3
R. menorrhagia 3
S. lymph node enlargement 2
T. shaking chilss 2
U. pigmentation 2
V. sweats 2
W. phlebitis 2
X. bruising and bleeding 2
Y. pneumonitis 1
Z. epistaxis 1
AA. numbness 1
BB. tingling 1
CC. diplopia-ptosis 1
DD. retinal vein occlusion 1
EE. headaches 1
FF. irritability 1
GG. orthopnea 1
HH. vague chest pain 1
II. substernal pain 1
JJ. pericarditis 1

As indicated, symptoms may begin precipitously or insidiously but often are not those which would raise immediate suspicions of lupus. A variety of other initial symptoms have been reported individually.

Age of onset is most often young adulthood, but this is not invariable as indicated in at least one series.

Age of onset of 163 cases:(8)

0-9yrs	5.5%
10-19yrs	30%
20-29yrs	27.6%
30-39yrs	19%
40-49yrs	10%
50-59yrs	5.5%
60-69yrs	1.8%

Another series is presented showing the signs and symptoms which developed at one time or another during the disease in 44 cases of lupus seen over a 15 year period at Columbian Presbyterian Medical Center.(28)

Symptoms:
- weight loss 100%
- malaise 100%
- joint symptoms 77%
- GI complaints 36%
- abdominal pain 22%
- vomiting, diarrhea 18%
- GU symptoms 18%
- Raynaud's 16%
- psychoses 9%
- convulsions 7%
- hemiplegia 2%.

Signs:
- females 98%
- fever 95%
- skin rash 68%
- cardiac manifestations 70%
- enlarged hearts 34%
- murmurs 55%
- pericardial effusion 16%
- hypertension 18%
- pleural effusion 39%
- pneumonitis 20%
- hepatomegaly 29%
- splenomegaly 27%
- peripheral edema 25%
- facial edema 12%
- eyeground changes 20%

It should be emphasized that these series have been presented more to portray the variability which exists than to serve as too exact a guide of the things one ought or ought not consider as being possibly representative of lupus. The series from Columbia obviously represented only advanced and rather typical cases. Many of the findings listed there would probably be only infrequently noted in mild cases. The disease is also probably more common in males than would be judged from their figure of 98% occurrence in females. As discussed previously, the number of minor and subclinical cases of lupus which may be in existence is only a guess, and present-day ideas about findings which ought to be present in a "typical" case may

be based upon a rather small selection of the total actual cases. Thus in clinical as well as histological findings, it is unwise to discard lupus on the basis of negative evidence. An attempt will be made to describe the manifestations of lupus which may be seen in the various organ systems.

The cardiovascular system is involved frequently, but the resultant symptoms and clinical signs are often far less severe than would be anticipated from the apparent histologic involvement. Hypertension is very notable for its absence. In a disease where damage to arteries, and particularly those of the kidney, is the most prounounced histologic change, and where the patients typically hyper-react to many stimuli, it appears more than coincidental that hypertension is no more frequent. Most reports make no mention of this. The report from Columbia,[28] which has been noted to list apparently advanced cases only, lists 18% with hypertension but does not mention criteria. Klemperer states that the blood pressure is usually normal but sometimes is only slightly elevated.[10] Jager states that significant hypertension develops in less than 20% of cases.[11] It should be noted that there is no apparent correlation between degree of renal damage and presence of hypertension in clinical cases of lupus. It is remarkable that these patients, with so many reasons for developing hypertension, develop it only slightly more frequently than

the general population.

Cardiac signs occur somewhat more frequently; some degree of dilatation and insufficiency with their typical signs and symptoms develop not infrequently. Pericarditis is not infrequent, but clinical evidence of it is not a prominent feature according to most writers. However, one series, composed of 108 cases, included thirteen in which a clinical diagnosis of pericarditis could be made. In all, symptoms were compatible with a dry, fibrinous type of inflammation.(57) Arrhythmias frequently develop during acute febrile episodes. Murmurs, particularly systolic murmurs, are quite common and are frequently associated with Libman-Sacks endocarditis.

Respiratory findings are common, and, in contrast to the situation with the cardiovascular system, the symptoms are often more pronounced than are the evidences of histologic damage. As discussed in the section on pathology, a non-specific pleuritis and evidences of secondary infection are usually about the only anatomic signs of pulmonic involvement. Pleurisy, pleural effusions, and patchy areas of pneumonia are quite common. There is great susceptibility to secondary respiratory infections. It has been reported that a common and most annoying symptom has been a chronic pain in the chest wall, which, however, is unrelated to pleuritis, has no x-ray or auscultatory findings, responds well to salicylates, and is

thought due to a periosteitis or perichondritis.(58) It has been emphasized that all instances of pleuritis should be investigated because of the frequency with which this is an early symptom of lupus.(59)(60)

The renal system is also commonly involved and may be the only system to show symptoms for long periods. The usual clinical presentation is that of the nephrotic syndrome, with marked edema, proteinuria, and hypoproteinemia. In fact, no reports were seen of any cases resembling acute glomerulonephritis or acute pyelonephritis either clinically or laboratory-wise. Apparently the only renal diseases mimicked by lupus are those which cause a nephrotic syndrome. Terminally, of course, any renal disease may present a similar picture which is predominantly that of renal failure. Renal failure is one of the more common causes of death due to lupus. As mentioned, renal hypertension is not a feature of lupus.(7)(10)(11)(20)(26)(27)(28)(56)(61)(62)(63)(64)

There are a number of typical changes in the blood system, and these will be discussed with laboratory findings.

A variety of skin manifestations have been noted. Best known is the characteristic "butterfly" shaped area of erythema stretched over the bridge of the nose to the malar aspect of the cheeks. This lesion is usually raised and indurated, and its surface covered by numerous telangiectatic vessels which may sometimes be obliterated with firm pressure. When long-

standing, these lesions frequently become covered with tightly adherent silvery scales, which, when removed, are seen to have long, horny projections on their under surfaces which had formerly been fitted down into the pilosebaceous follicles. This lesion is usually accompanied by burning and itching, but is not painful. It is also seen on the exposed area of the upper chest, on the tips of the fingers and especially around the nails, on the palms, or on the feet. In rare instances it may even become generalized. During periods of remission of the disease these skin areas diminish, but often leave behind a scarred area of brown pigmentation. After long periods the affected skin becomes atrophic and, where the scalp is involved, permanent baldness develops. In addition to this characteristic skin lesion, a number of more non-specific changes may be seen including areas of telangiectasia, petichial or purpuric hemorrhage, pigmentation, macular or papular or urticarial eruption, scaling, erythema nodosum or erythema multiforme, or of superficial or even moderately deep ulceration. In the Senear-Usher syndrome, a syndrome seen in certain cases of lupus, one sees erythematous scaly lesions over the face and neck, and bullous lesions over the remainder of the body, resembling pemphigus.(10)(11)(41)(64)(57) In one series of 108 patients the following types of skin lesions were seen:

A. "typical" skin lesions 64 persons
B. desquamation 39
C. pigmentation 38
D. hyperkeratosis 18

E. atrophy of skin 24
F. telangiectasia 10
G. purpura 11
H. depigmentation 10
I. vesicles 7
J. crusts 5.

Changes in hair pattern are also typical. Alopecia was said to have been present in some form in 47% of one series but this seems high. Also described was "L.E. hair", this characteristic being the presence of short rather than full length hairs at certain areas, particularly the anterior hair line, due to slow growth, and giving a characteristic disheveled appearance to the individual. This was described in 21 of their series of 108 lupus patients.(56)

The unusual sensitivity to sunlight is seen in several other diseases, such as pellagra or porphyria, but is still very strongly suggestive of lupus.

Raynaud's phenomenon, though perhaps most typical of scleroderma, should always cause one to consider lupus.

Arthritis is a symptom which is seen more commonly than any other as the initial manifestation of lupus, and which eventually appears in the majority of cases of lupus. Typically it is a polyarthritis, and is manifest as transitory swelling and tenderness of several joints at a time. Subcutaneous nodules may or may not be present. It may exactly resemble the type of joint involvement seen in rheumatic fever, or may exactly resemble the type seen in

rheumatoid arthritis. In fact there has been some debate whether certain patients, long thought to have rheumatoid arthritis who developed a positive LE cell test, really had lupus or rheumatoid arthritis. This will be discussed further in sections to follow.

A manifestation of lupus which is frequently overlooked is its effect on the central nervous system. Such symptoms are quite frequently seen, and it is not at all unusual for these to be the first manifestations to appear. Since a not uncommon early effect is to cause a sort of neurosis, the appearance of later rather non-specific symptoms may well be overlooked by the busy practioner who sees many more cases of hypochondriasis than of lupus erythematosus. The following series is a review of 100 randomly selected cases of diagnosed lupus seen at the Mayo Clinic.(9)

Neurologic signs and symptoms:

A. convulsions 14 persons
B. hemiplegia 4
C. double fision 4
D. choked discs 3
E. polyneuritis 3
F. subarachnoid hemorrhage 2
G. nystagmus 2
H. vertigo 2
I. monoplegia 2
J. choreiform movements 2
K. paraplegia 1
L. quadriplegia 1
M. aphasia 1
N. intention tremor 1
O. Bell's palsy 1
P. cortical blindness 1
Q. decerebrate state 1

total 24

Psychiatric symptoms:

A. anxiety, personality change, mental deficiency 7
B. emotional lability 3
C. mental deterioration 2
D. depression 2
E. obsessive trends 1
F. paranoid reaction 1
G. hallucinations with fever 1

total 17

About 30% of cases are stated to show the typical eye signs.(7)(10)(11) Lesions seen are conjuctivitis, episcleritis, embolic petichiae, and corneal erosions. The typical fundoscopic changes are exudate, hemorrhage, papilledema, central vein occlusion, and cytoid bodies. Cytoid bodies are white patches which may be seen in the fundus and are believed to be ganglioform degeneration of nerve fibers. These, in the absence of hypertension or diabetes, are said to be very highly suggestive of systemic lupus.

Symptoms or signs of liver involvement are notably unusual although they do occur. Jaundice is rare except from hemolytic anemia. Mild hepatomegaly is not infrequent, however. Association of liver disease and lupus will be further discussed in Part III.

In unusual circumstances, lupus may cause acute abdominal symptoms, usually through vascular involvement sufficient to cause either a pancreatitis or a peritonitis. This will be further discussed in the last section.

Innumerable other symptoms of a mostly non-specific nature suchas fever, weight loss, malaise, drug hypersensitivity,

occasionaly palpable spleen and lymph nodes, etc., are also frequently seen.

In summary, nearly any signs or symptoms may be seen in lupus. Unexplained signs of disease in any system, and particularly unexplained signs in more than one body system should suggest the diagnosis of lupus. The following list includes circumstances which should particularly call ones attention to the possibility of lupus:

A. Arthritis plus symptoms in another body system.
B. Prolonged unexplained fever.
C. Ill-defined multi-system involvement, particularly in reproductive female.
D. Endocarditis not responding to antibiotic treatment.
E. Recurrent chest pains with no obvious etiology.
F. Recurrent respiratory infections.
G. "Butterfly" skin rash.
H. Photosensitivity.
I. Unexplained skin pigmentation or depigmentation.
J. Raynaud's phenomenon.
K. Bizarre unexplained neurological findings.
L. Retinal findings of cytoid bodies.
M. False positive serologies.
N. Unexplained hemorrhages.
O. Nephrotic syndrome.
P. An atypical "toxemia of pregnancy".

While the above findings may usher in the typical case of lupus, the atypical cases may show any variety of other findings, and diagnosis of such cases is likely to be late.

Laboratory Tests: Characteristic laboratory findings are said to be almost as numerous as characteristic clinical or pathological findings in lupus erythematosus. A variety have been described, some quite extensively. A list is given of tests

which have been proposed to be of diagnostic value in lupus:

A. Positive LE cell test.
B. Leukopenia.
C. Anemia.
D. Thrombocytopenia.
E. Elevated erythrocyte sedimentation rate.
F. Circulating anticoagulants.
G. False positive serology.
H. Cryoglobulins.
I. Positive Coombs test.
J. Urinary red blood cells, white blood cells, albumin, hyaline, and granular casts.
K. Cold agglutinins.
L. Elevated BUN and NPN
M. Decreased glomerular filtration and tubular transport rate tests.
N. High globulin.
O. Low albumin.
P. Positive cephalin-cholesterol-flocculation and thymol turbidity tests.
Q. Near normal BSP test.
R. Nonspecific electrocardiographic changes.
S. Hemolysins.
T. Low urinary 17-ketosteroids.
U. High urinary mucopolysaccharides.
V. Positive complement fixation to assorted nuclei.
W. Positive para-toluene-sulfonic acid test.
X. Low bound and high free serum pantothenic acid.
Y. Positive anti-globulin test.

The LE cell test conveys the most meaning of any of the laboratory tests and will be discussed separately later.

Leukopenia is very characteristic. It is of particular value during exacerbations where most other conditions under consideration would be associated with a leukocytosis. The white count in lupus rarely gets very low, but usually runs between 4000 to 6000 cells per cubic millimeter. Occasionaly it may undergo mild elevation, and may reach 12,000 or so with severe infections. While not low enough to be hazardous

under ordinary conditions, the failure of leukocytes to increase to meet stress situations may explain part of the increased susceptibility to infection.

Anemia is a feature of lupus, and like the leukopenia, appears in a large percentage of cases but does not reach such a serious degree as to cause symptoms. Typically it is normocytic and normochromic.

Thrombocytopenia is also rather common and not infrequently reaches sufficiently severe stages to cause hemorrhage. This is most common in advanced cases, but occasionaly such hemorrhage may be the initial manifestation of lupus.

An elevated sedimentation rate is common but is so non-specific as to be of no diagnostic value.

Circulating anticoagulants are seen occasionaly. Those so far reported have been anti-thromboplastins and located in the gamma globulin portion of the serum.(17)(26)(66)(67)

The false positive serologic test for syphilis is seen frequently and is of great diagnostic help. It has been said to be present in one-fourth or more cases,(10)(68) but this figure may be a little high. Its greatest value lies in the fact that it is not infrequently present before any other signs or symptoms of lupus are apparent, and that a significantly high percentage of false positive serologys are due to lupus. For instance in on reported series of 51 false positive serologys it was found that 4 had positive LE cell tests and 21 more had

strong evidence of some type of collagen disease.[69] In another series of 148 false positive serologys, 10 were proved to have lupus, 7 had symptoms sufficient to classify as rheumatoid arthritis, and 45 had assorted symptoms and blood findings consistent with lupus.[27] Thus it should be emphasized that persons with false positive serologys should be followed for later signs of lupus.

Cryoglobulins are said to exist fairly commonly.[10][70][71]

Cold agglutinins are reported.[10][71]

Positive Coombs tests, usually direct, but sometimes indirect as well, are seen occasionaly, although not in the majority of cases.[10][26] Lupus should be considered when a positive Coombs is seen in an adult.

The urine may show a variety of findings. There are often a few red blood cells, white blood cells, and hyaline and granular casts seen microscopically. Where there is more marked renal involvement, one sees the typical nephrotic syndrome with marked proteinuria. As renal failure develops, and this is a frequent terminus in severe cases of lupus, the BUN and NPN rise and those tests reflecting glomerular filtration and tubular transport indicate decreased function.

Characteristically the serum albumin is decreased and the serum globulin is increased with the total serum protein remaining about normal. Serum albumin and total serum protein may be markedly reduced in presence of the nephrotic syndrome, and sometimes independently of it during an acute lupus crisis.

If electrophoretic patterns are made, lupus like the other collagen diseases, shows only nonspecific changes. The usual change is a slight decrease in albumin and a moderate increase in gamma globulin. This gamma globulin appears as a wide band (therefore heterogeneous) group of related proteins which appears to be qualitatively similar to gamma globulins in pooled sera of normal persons. If the nephrotic syndrome becomes prounounced, the same changes are seen which are specific for the nephrotic syndrome regardless of cause; that is: albumin is markedly reduced, alpha-1 globulin is reduced, alpha 2 globulin is elevated 3-4 times and frequently is fused with beta globulin, gamma globulin is extremely reduced, alpha lipoprotein is usually decreased, and beta lipoprotein is greatly increased.(72) The LE factor appears to be in the gamma globulin fraction, but is not of sufficient quantity to be readily detectable by electrophoresis.(73) On the basis of these findings, one would suppose that the blood level of the LE factor should be lowered considerably in the presence of a marked degree of the nephrotic syndrome, and that if the hypersensitivity theory of lupus is true in its assumption that body tissues are normal in lupus unless altered by the abnormal antiglobulin, then one should have diminution both of symptoms and of positivity of the LE cell test in this circumstance. Such a relation has never been commented upon.

turbidity tests are usually mildly to moderately elevated in fully developed cases of lupus; whereas a positive BSP test is less common and when present shows less change. It would appear probable that the former tests are commonly positive due to abnormal proteins, but that liver damage is not frequently great enough for other associated tests to be positive.(71)

Electrocardiographic changes are usually present in advanced cases but are non-specific and of no diagnostic value.

Hemolysins have been reported but are unusual.(10)(35)

Although it has been reported in one series that 82% of 28 cases had urinary excretion under 4 mg per 24 hours, 17-keto-steroid determinations are not presently considered of great diagnostic help.(57)

It has been reported that whereas the normal urinary mucopolysaccharide excretion runs between about 2.7 to 5.4 mg per 24 hours, that readings of 5-15 mg per 24 hours were found in five patients with lupus erythematosus.(74) This has been suggested for used as a diagnostic test. It has not received enough use for evaluation of its indications.

Another investigator has found that bound patothenic acid tends to be low and free pantothenic acid tends to be high in serum of persons with lupus.(17) The ratio of bound to free forms was thus found to be 2.4 to 7.4 with a mean of

4.3 in 20 normals, 0.4 to 3.6 with a 1.9 mean in a group with discoid lupus, and 0.2 to 2.9 with a 1.3 mean in patients with systemic lupus erythematosus. This was therefore suggested as a possible diagnostic test. No mention was made of whether or not there was close correlation between severity of symptoms and aberration of the ratio. Again, this test has not had sufficient use to evaluate its indications.

Positive complement fixation to mixtures of assorted nuclei has been noted by several. One report suggests that this test be used as the basis for a diagnostic test, and report that using their method they found positive tests in 27 of 30 patients with lupus, (including all those who had strongly positive LE tests) and found it negative in 15 normals, 21 rheumatoid arthritics, 5 cirrhotics, 3 with macroglobulinemia, and 2 with multiple myeloma.(31) This test appears to have possibilities, and is used occasionaly but has not been well-standardized so that interpretations of individual results are uncertain.

A test for lupus erythematosus has been reported which was supposedly discovered accidentally.(75) To perform, one adds 0.1 cc of serum to 2 cc's of p-toluene-sulfonic acid (Eastman 984) 12% in glacial acetic acid; the tube is then shaken, left 20 minutes, and reshaken; presence of a precipitate is a positive test. This test was found to be

positive in 13 patients with active lupus, negative in 11 of 17 with lupus in remission, absent in 3 with polyarteritis nodosa, 3 with generalized scleroderma, 2 with dermatomyositis, 25 with rheumatic fever, 6 with diabetes mellitus, 15 with advanced tuberculosis, 14 with syphilis, 18 with degenerative joint disease, and negative in 70 and positive in 6 patients with rheumatoid arthritis. It was also positive in 1 of 66 apparently healthy persons and in 4 persons with hepatitis. This test would appear to have possibilities of being of diagnostic value, but will need more study before reliability can be placed in its interpretation.

Tests have been described wherein the presence of anti-globulin to cell nuclei has been demonstrated by causing the antiglobulin to fluoresce so as to be visible, or by combining it with I^{131} and recording its presence with a geiger counter. One can then measure residual amounts of gamma globulin on cell nuclei which have been first brought in contact with lupoid or normal serum, and then washed to remove all "free" antiglobulin.(76) This would appear to hold promise of being an extremely valuable test, in that it would be extremely sensitive and would permit one to obtain quantitative as well as qualitative results. Again, however, this test will have to be further developed and used awhile before its results may be interpreted.

The LE Cell Test: The LE cell is a phagocyte, usually a

neutrophilic granulocyte but occasionaly an eosinophile or a monocyte, which contains an LE body. The LE body varies in size from less than that of a red blood cell to several times its size, is round or oval in shape, is a purplish-blue color with Romanowsky stains and lighter staining than the adjoining cell nucleus, lies within the cytoplasm of the phagocytic cell displacing the relatively smaller nucleus, and is characterized by the fact that it is completely homogeneous with no visible traces of chromatin strands. Occasionaly these inclusions are multiple.

It becomes confusing to speak of the "LE cell", the "LE body", and the "LE factor", and to speak of the LE body whether referring specifically to the engulfed body in an LE cell or specifically to the small amorphous homogeneous smudges typically found free in the connective tissues of patients with lupus. The LE body which is found in the LE cell is thought by most people to be of identical origin to the LE body which is found free within the connective tissues, and was described in the section on pathological findings. There is not, however, complete agreement on this. The LE factor is considered to be the entity responsible for the formation of an LE body. The nature of this LE factor is highly debated. Many have hypothesized that it is an antibody, more specifically an antibody against DNA or against the cell nucleus or against the cell membrane. Others have

hypothesized that it is an abnormal enzyme or enzyme inhibitor, or even inhibitor of an inhibitor, and have likewise named various sites of action. Its nature is unknown. It does appear to be evident, however, that there is a protein or protein-bound substance in certain people with clinical manifestations of lupus erythematosus, and that this substance may be found in all body fluids, and that while in the blood it appears to be associated with the gamma globulin fraction. In its presence, nuclei from normal neutrophilic granulocytes swell and become homogeneous with loss of normal chromatin markings, the nuclear membrane ruptures, and the nuclear remnants burst forth, forming a histologically and biochemically identifiable LE body. This body may then be ingested by another normal granulocyte to form a typical LE cell. Furthermore, neither of these two phenomena may occur in the absence of this factor.(33)(77)(78)(79)(80) This series of reactions has been observed in time lapse microcinematographic studies.(78)

This LE cell is typical of the disease, lupus erythematosus, and this finding is relied upon more than any other for establishment of such diagnosis. The cell may be seen in the peripheral blood but is more likely to be seen in the bone marrow. In many patients with clinical symptoms of lupus, but no LE cells naturally occurring, the development of the cell may be initiated by various

procedures. These procedures comprise the various LE cell tests. Three ingredients are required for a positive test: (1) a source of nucleoprotein, (2) the LE factor which will cause alteration of this nucleoprotein, and (3) a phagocytic cell. A number of individual tests have been proposed, and no attempt will be made to enumerate them. A few general principles only will be mentioned regarding mechanics of the tests. It appears that "dead" traumatized cells are slightly more effective than "live" healthy ones to furnish the nucleoprotein, and consequently those tests which include some sort of physical trauma to the cells us usually give slightly greater positive results. Heparin and the other anticoagulants decrease the tendency to form LE cells; consequently clotted blood gives better results than does preserved blood. This may be accomplished by running clotted blood through a sieve or else by defibrinating blood. Two to two-and-one-half hours is about the maximal incubation time, and most tests require about this period. Although some tests appear to give slightly better results than others, invariably there are instances where the supposedly less sensitive test is positive while the other is negative, so that most reports comparing several different methods conclude that one should probably use three or four different modifications in an effort to get a positive test.(55)(57)(80)(81)(82)(83)(84)(85)(86)

The LE rosette is another characteristic of lupus. This is a figure consisting of an LE body surrounded by a cluster of encircling phagocytic neutrophilic granulocytes which have supposedly been attracted by some chemotaxis-like force. If the formation of LE cells is being watched microscopically, it may be seen that the granulocytes surround the LE body in this manner before one of them finally phagocytizes it and becomes an LE cell.(80) It is seen under the same circumstances as the LE cell and has nearly the same significance.

If an LE cell test is negative, there is general agreement that little real information has been gained. Persons with very long-standing, very far-advanced, active lupus will usually have a positive test, but then they are not a diagnostic problem anyway. Unfortunately, the finding of an LE cell is often a fairly late development of lupus, and the majority of mild cases will fail to show LE cells. In certain instances, the presence of LE cells may serve as a guide to the activity of the disease, being present in greatest number during exacerbations and being scarce or absent during remissions. Occasionaly the LE cell is seen before any definite symptoms, and again it may never be found, so rules are difficult to establish.

Much has been said and written about so-called false-positive LE cell tests; many saying there is no such thing, most saying they have never seen one, a few saying they have

seen one, and a very few claiming they are common. Thus one may read: "LE cells have been demonstrated in cases of hemolytic anemia, multiple myeloma, amyloidosis, active chronic viral hepatitis, penicillin hypersensitivity, and during treatment of hypertension with hydralazine".(44) Another reports: Positive LE tests have been seen in 9 rheumatoid arthritics, 1 scleroderma, 1 polyarteritis nodosa, 1 dermatomyositis, 1 Hodgkins, 1 hemolytic anemia, 2 after a reaction to phenylbutazone, and 1 after a reaction to hydralazine".(87) Another report states that of 6 consecutive patients in their care who had penicillin reactions, 3 were found to have positive LE tests.(88) From these reports one would judge that little reliability could be placed in this test. Another reports, however, that in 7000 consecutive LE tests he has found no false positives except for 12 cases of hydralazine poisoning.(58) Yet another states that of 514 patients tested over a 4 year period, 495 were decided to have diseases other than lupus, and only 2 of these had positive tests. Of these, one did on one occasion only and then had but one cell. The other had portal cirrhosis and some symptoms of both hypothyoidism and Cushings disease; thus was a diagnostic problem.(77) Upon further reading, then, one must then modify his view by saying that it seems remarkable that coincidence could load the scales so heavily as to give one group a 50-50 incidence of false positives, and the other group no false

positives in 7000 tests with the exception of hydralazine toxicity. One notes that various other persons verbalize their opinion that there is no such thing as a false positive test, except, perhaps, sparing the hydralazine induced ones.(8) (11)(26)(33)(58)(77)(88)(89) One may say that opinions mean little, and that if someone has seen LE cells in a non-lupoid patient, this has much more significance than the report of someone else who says he has not seen them. This is not entirely true, however, because unfortunately there is a certain amount of subjective opinion in the interpretation of whether or not a given cell is an LE cell. This has prompted the addition of yet another term, that of the "pseudo LE cell", which designates a cell which someone, somewhere has called an LE cell, but which really isn't according to the more exacting criteria of someone, somewhere else. Thus reports come in such as the following: "A patient with symptoms typical of scleroderma was said to have had positive LE cells, but the author on studying the slides sees much nucleophagocytosis and therefore says this was another case of the pseudo LE cell phenomenon and there never was a truly positive LE cell preparation".(33) "The LE phenomenon has been recorded in single cases of polyarteritis nodosa, leukemia, Hodgkins, dermatitis herpetiformis, miliary tuberculosis, and pemphigus without a convincing illustration of an LE cell".(77) It is well to briefly consider some of

the pitfalls encountered in determining whether or not an LE cell is present.

Four other entities have been described as being possible to confuse with the LE cell. The first is platelet aggregations. These are rarely ingested, are more blue than purple, are slightly granular, and should really never be mistaken by an experienced investigator. The second is amyloid inclusions. These would be quite unusual also, and may be differentiated by appropriate stains. The third and fourth are the Tart cell and the nucleophagocytic cell, and these may create a serious problem in diagnosis. These two are considered either together or as being more or less synonomous by most, although the tart cell, as originally described by Hargraves,[19] was a histiocyte whereas nucleophagocytic cells may also be neutrophilic granulocytes. These cells have phagocytized some particulate nuclear matter and may be seen in a very large variety of circumstances and even in normal persons, although their most frequent occurrence is in hypersensitive states of all kinds. The nucleophagocytic cell is differentiated by the fact that the ingested nuclear material still shows strands of chomatin within it, whereas the LE cell inclusion is completely homogeneous. However, partial digestion and homogenization of phagocytized nuclear matter may occur gradually, and the cell is then difficult to differentiate from an LE cell. For this reason, it has been recommended that if many examples of

nucleophagocytosis are seen, and only one or two cells resembling LE cells are seen, and these are at all questionable, that the preparation must be considered as being negative for LE cells.

The chief problem, then, in detection of an LE cell is to determine whether the phagocytic cell has ingested a homogeneous LE body, or whether it has merely ingested a piece of nuclear material and subsequently partly digested it. The cardinal deciding point is whether or not chromatin strands may be seen in the inclusion body. Of aid is the fact that the LE cell is usually a neutrophilic granulocyte, (but may be a histiocyte or eosinophile) and that a nucleophagocyte is usually a histiocyte (Tart cell), but may not infrequently be a neutrophilic granulocyte. As with other blood cells, an unknown cell is partly distinguished by the company it keeps, and thus if only one or two questionable cells are seen, the presence or absence of numerous examples of nucleophagocytosis in surrounding areas should be taken into consideration. Of further aid, would be presence of any rosettes. A sort of rosette formation may be seen around either an LE body or a nuclear fragment, but if a rosette formation is seen around a homogeneous body, this would be of great aid in verifying that an otherwise questionable cell might truly be an LE cell.(79) (91)(92)

It would appear that certain criteria ought to be

followed in the enumeration of cases which may be considered as possible false positives. The following are proposed:

1. Occurrence of a positive LE cell test in a person diagnosed to have a condition other than lupus.

2. Absence of sufficient clinical, histological, or laboratory (exclusive of LE cell test) evidence for the diagnosis of lupus.

3. Disappearance of the positive LE cell test following successful therapy in those conditions which are curable;

   -or-

   In progressive non-curable conditions:

   A. Positive LE cell test must occur in that disorder much more frequently than in a group from the general population of similar age and sex and otherwise similar circumstances.
   B. The group in which the positive LE cell tests are found must not differ in any significant respect from the average case of this condition in persons without LE cells.

4. At least a five-year follow-up to ascertain that no findings of lupus subsequently appear in the patient.

5. Publication of photographs of the LE cells so that other investigators may confirm that they do not appear to be nucleophagocytic cells.

If all the above criteria are fulfilled, the case qualifies as a possible false positive test. From this point, one should determine how many of these false-positives have been reported. One should then compare this to the number of cases reported in which the same presentation was seen, but in the follow-up other symptoms or signs of lupus appeared. It should be remembered also that a waiting period of even five years may be too short.

If one now re-examines the case for the existence of so-called false positive LE cell tests, and if one attempts to count the number of such cases in those conditions other than lupus in which LE cells have been reported, one finds only two conditions in which a significant number of positives have been reported, these are hydralazine poisoning and rheumatoid arthritis. In all other conditions where "false-positives" have been reported, one may conclude that many of these reports were based on the finding of nucleophagocytosis rather than LE cell formation, and that the remainder are best considered as instances where a sublinical case of lupus, during a period of aggravation, exhibited a few LE cells. This may be an injustice to those who propose that false positives exist. On the other hand, since lupus is so difficult to diagnose, since the number of proposed cases of false positives which fulfill all the above criteria is so small relative to the total number of cases of lupus in the United States, and since there are so many reasons for believing that the LE test is specific, then it would certainly appear that the burden of proof should rest on those who would prove the existence of false positive tests and not those who would refute them. This would mean that it would be necessary to prove that lupus was not present in these cases. There is no known way to prove that lupus is not present. Therefore, in all conditions except rheumatoid arthritis and hydralazine toxicity,

it is believed that existence of false-positive LE cell tests must be denied until either many more cases are reported, or until enough is learned of the pathogenesis of lupus that a test may be devised which, if negative, will rule out lupus.

The reported instances of false positives in rheumatoid arthritis and hydralazine poisoning now deserve consideration. Of those persons having diagnosed rheumatoid arthritis and developing positive LE cell tests, most will gradually develop a picture resembling lupus more than rheumatoid arthritis. The remainder will usually show at least a few findings typical of lupus.[10][11][77][92][93][94][95] This problem is difficult because of the facts that rheumatoid arthritis has many variants, that arthritic complaints are the commonest form of presentation for lupus, and that in a number of cases lupus seems to sort of gradually emerge from a developed case of rheumatoid arthritis. The differentiation of these diseases will be discussed in Part III. The LE cell tests reported in persons believed to have rheumatoid arthritis are believed not to be false positive tests, because if the five-year waiting period is observed other findings more characteristic of lupus than of rheumatoid arthritis develop so frequently.

In regard to hydralazine toxicity, many cases of positive LE cell tests have been reported.[10][11][15][86][87][96][97][98][99][100][101][102] This appears to be a true toxicity response rather than a hypersensitivity because the incidence

of development of the LE cells and the severity of the reaction bear a direct relation to the total amount of the drug ingested (allergic or idiosyncratic responses would be less dependent on amount of the drug). Indeed, in dogs, administration of large doses of hydralazine in one rather small series of 8 dogs evoked positive LE cells in seven and typical kidney histologic changes in the eighth.[100] Such a universal response suggests a metabolic interference and not a hypersensitivity. It is noteworthy that in those persons showing positive LE cells on the basis of hydralazine toxicity, there is often seen the early development of a syndrome exactly resembling rheumatoid arthritis which gradually transforms into a syndrome which may show all the findings typical of systemic lupus erythematosus. These observations are of value in interpreting the positive LE tests both in rheumatoid arthritis and in hydralazine toxicity. The only demonstrable difference between the syndrome ordinarily described as lupus erythematosus, and that seen with hydralazine poisoning is that the latter is reversible upon cessation of hydralazine therapy while the former is not presently reversible. Even this difference may be argued against since: (1) lupus in absence of hydralazine poisoning may still be expected to become worse upon its administration and become alleviated by its subsequent withdrawal, (2) hydralazine is too new a drug for evidence accumulate to show whether or not persons showing an

increased susceptibility to hydralazine poisoning will have an increased incidence of lupus in later years, and (3) if other aggravants, such as sunlight and all energizing rays could be completely removed, this might also reduce symptoms to a sub-clinical level in certain lupoid patients. While the mechanism by which hydralazine causes this syndrome is not known, and may be different from the mechanism (or mechanisms) causing lupus, the mechanism causing lupus is also unknown and may differ from one case to another just as well. Since hydralazine toxicity may show all the other pathognomonic findings of lupus, and cannot on the basis of present evidence be said to not be lupus, it cannot be said that the LE cells seen are false positive ones. That is to say, that a case of hydralazine poisoning must be regarded as lupus erythematosus, since it meets the description of the syndrome, and since etiology, being unknown in lupus, may not be used as a criterion upon which to base a diagnosis. It is believed that this hydralazine syndrome is a strong bit of evidence for a metabolic etiology of lupus. The finding that it can be readily induced in such a large percentage of persons on moderate dosage suggests that there may be many subclinical cases of lupus. In neurophysiology, some of the greatest advancements in understanding were achieved through use of such poisons as strychnine, curare, and nicotine. Hydralazine may likewise prove useful in the understanding of

lupus. More study in this field is indicated.

In summary of the LE cell test: (1) numerous methods are available and one should chose two or three of those currently reported to yield the best results, (2) it is necessary to distinguish the LE cell from the nucleophagocytic cell, (3) many cases of lupus will not exhibit LE cells, (4) for purposes of this discussion, false-positive LE cell tests are considered non-existent, those reported in rheumatoid arthritis being believed to designate patients having lupus, those seen in hydralazine poisoning believed to serve as further proof that hydralazine poisoning may be considered as a form of lupus, and other reported instances having so few well-documented cases that they are believed best explained as being patients with subclinical lupus coincidental to or aggravated by another disease. The question of false-positive tests is presently debated, and, judging from reports seen, it would appear that a majority of investigators believe there are no false positives, but would except hydralazine toxicity from consideration.

DIFFERENTIAL DIAGNOSTIC POINTS

Routine Laboratory Tests: It is believed that the following tests should be done in all cases where the diagnosis of lupus is under consideration: (1) complete blood count, (2) urinalysis, (3) repeated LE cell tests, (4) chest x-ray, and (5) serology.

The complete blood count is of value in the evaluation

of other diagnoses as well as lupus. A leukopenia is strong supportive evidence of lupus and extremely valuable when other conditions considered in the differential are associated with a leukocytosis. A leukocytosis militates against the diagnosis of lupus, and if it is over 15,000 to 20,000 very nearly excludes the possibility of lupus. A mild anemia is consistent with lupus though certainly extremely non-specific.

Urinalysis typically shows a multitude of findings including a few red blood cells, a few white blood cells, and a few hyaline and granular casts in any of the collagen diseases. In lupus a common but not invariable finding is the presence of the nephrotic syndrome with varying degrees of albuminuria. Lupus should be considered in all cases of the nephrotic syndrome.

Repeated LE cell tests should be performed when lupus is suspected. The exact number which one should obtain depends, of course, on the clinical picture. It is noteworthy, however, that a number of attempts are often necessary before a positive result is obtained. No single method of testing is particularly recommended since improvements are constantly being reported and the method used in different localities may vary. Generally speaking, however, clotted blood techniques are usually more sensitive; and it is often wise to try two or three different methods where possible. As discussed previously, a positive test is considered specific

for lupus, but negative tests never exclude lupus, The test will most likely be positive at times when clinical symptoms are at their height.

A chest x-ray should be obtained in all cases suspected of having lupus; not because there are any specific findings in lupus, but because there are specific findings in other diseases which should be included in the differential with lupus, and because there is an increased incidence of other lung disease in presence of lupus. It must be emphasized that the presence of other diseases, such as tuberculosis or pneumonia, in no way excludes lupus. These diseases are much more common in persons having lupus than in persons not having lupus, and in the presence of combined disease one will obtain much better results by treating the lupus, as with corticoids, in addition to chemotherapy for the associated disease, even if it be tuberculosis, in which case corticoids are ordinarily contraindicated. Indications for future chest x-rays must be determined carefully; balancing the marked predisposition of a person with lupus toward development of tuberculosis, against the known aggravation to lupus of actinic rays.

A routine serology is believed a worthwhile test to perform on all persons suspected of having lupus. This test is quite simple to perform, and although not specific, is highly suggestive of lupus if a false-positive result is

obtained. A false positive serology is quite commonly seen in lupus and is seen only occasionaly under other circumstances. One should make a determined effort to arrive at an explanation for all false-positive serologies.

Special Laboratory Tests: Other tests to be obtained will depend upon the clinical circumstances and upon other conditions in the differential to be ruled in or out. Biopsies are indicated in certain circumstances. Skin biopsies are said to be disappointing in many instances, but would still be thought worthwhile in cases with striking skin involvement and little else upon which to make a diagnosis.

Liver biopsy is not worthwhile except where indicated for other reasons. Although cases of hepatitis and cirrhosis associated with lupus have been reported, liver biopsy would not be helpful even in these instances, since there are no specific histologic changes to be seen. The usual findings in such cases are either a viral hepatitis or post-necrotic cirrhosis.

Kidney biopsy is very helpful in cases with marked renal involvement, and will often establish a diagnosis whether the disease present be lupus or whether it be one of several other causes of the nephrotic syndrome. This method has been advocated by several as being very useful.(25)(45)(61)(103)(104) It is probably worthwhile where the diagnosis cannot be made by

other means and where there is moderate to marked involvement of the kidneys. It is probably not worthwhile where there is only slight renal involvement since the chance of hitting an area showing involvement would be much less.

Lymph node biopsy is a worthwhile procedure in those cases where there are large nodes detectable by palpation. Under these circumstances there will be other conditions in the differential which of themselves would require that a biopsy be taken. It has been said that a diagnosis of lupus can be made on the basis of a lymph node biopsy, but most persons would not consider the changes that specific. It is not thought worthwhile to do a lymph node biopsy where there are no obviously enlarged nodes available unless there are reasons other than consideration of lupus for doing so.

Muscle biopsies may be attempted, and may occasionaly show sufficient evidence of involvement in the connective tissue for a diagnosis of lupus to be established. Usually, however, no positive findings are obtained by muscle biopsy of lupoid patients.(105) Findings observed in biopsy of various lupoid tissues are described in the section on pathological findings.

Those laboratory tests previously described and based upon urinary mucoplysaccharide excretion, upon postive c complement-fixation reactions to cell nuclei, upon the ratio of bound to free serum pantothenic acid, and upon the reaction

of serum with the Eastman 984 reagent all may prove to be of value and all merit further study, but presently are not a reliable guide because of insufficient experience with their use. Use of an antiglobulin labeled with I^{131} appears to hold unusual promise of becoming a valuable test, but again has not been adequately evaluated. These tests were described in the section on laboratory tests.

The Differential Diagnosis: No complete list can be made which would include all the conditions one should consider in an individual in whom lupus is suspected. This is because lupus may present itself in an extremely variable manner. The following list includes conditions which may and have been confused with lupus, but in each individual case there will likely be additional illnesses that ought to be considered:

scleroderma
dermatomyositis
polyarteritis nodosa
rheumatoid arthritis
rheumatic fever
sarcoidosis
tuberculosis
amyloidosis
syphilis
porphyria
bacterial endocarditis
glomerulonephritis
lipoid nephrosis
brucellosis
hypersplenism
cirrhosis & hepatitis
infectious mononucleosis
acute surgical abdomen
pellagra
drug reaction
psychoneurosis
pyelonephritis
bartonellosis
coccidioidomycosis
histoplasmosis
hemochromatosis
amyloidosis
renal vein thrombosis
uridione toxicity
diabetic neuropathy
lymphosarcoma
Hodgkin's disease
psittacosis
periodic neutropenia
subleukemic leukemia
Stevens-Johnson syndrome
trichinosis
epilepsy
toxemia of pregnancy
multiple myeloma

Because of the extreme variability of the disease, no set rules may beestablished for making a diagnosis, and procedures will vary from case to case. A few of the conditions causing particular difficulty in differentiation will be briefly discussed.

Acute Surgical Abdomen: Whereas involvement of abdominal viscera is a common occurrence in lupus, acute abdominal symptoms are not often reported. Pollak et. al. report on 14 cases, however, in which abdominal symptoms caused by lupus were sufficiently severe to call in surgical consultation.(25) Diagnoses made on these 14 patients included acute appendicitis, acute cholecystitis, perforating peptic ulcer, volvulus, paralytic ileus, small bowel obstruction, severe gastroenteritis, parametritis, infection of broad ligament, infective peritonitis, and pancreatitis. Ten of the cases were found to have a non-infective peritonitis and four to have a pancreatitis. Twleve of the fourteen were known to have lupus before development of the abdominal symptoms. Of the series of 14, two were men, and four of the women were negroes. The following findings were observed in the fourteen cases:

1. Temperature: about normal in 5; 104° or over in 3.
2. Pulse: roughly proportional to temperature.
3. Pain: Present in all and quite variable, being localized or diffuse; dull, cramplike, or colic-like.

4. Vomiting: in 10.

5. Diarrhea: in 3.

6. Constipation: in 4.

7. Distention: in 13.

8. Tenderness: in 13 and usually marked.

9. Rebound tenderness: in 8.

10. Guarding: in 8.

11. Rigidity: in 4.

12. Bowel sounds: decreased in 3 and absent in 3.

13. Abnormal urine: 12.

14. Leukopenia: 8.

From study of the above list one gathers that he should suspect a lupoid etiology af acute abdominal symptoms when (1) leukopenia is present, (2) abnormal urinary findings typical of lupus are seen, (3) abdominal pain and tenderness are proportionately much worse than consistent with a relatively mild amount of guarding or rigidity. Other findings seem quite compatible with non-lupoid causes of the acute abdomen. It is stated by the authors that the non-operated cases showed very definite improvement 24-48 hours after institution of therapy with large doses of adrenal corticoids.

In the instance of a person presenting with symptoms of an acute surgical abdomen who is not known to have lupus, it is recommended that lupus be suspected if (1) leukopenia is present, (2) urinary findings are typical, (3) other signs

typical of lupus are noted, particularly if there is an exacerbation of them concurrently with the development of the abdominal symptoms. The finding of pain and tenderness out of proportion to minimal guarding and rigidity may occasionaly be suggestive, particularly in borderline cases. However, pain and tenderness show so much subjective variation, and rigidity varies so greatly with location of the inflammation and general condition of the patient, that this ratio isn't thought to be very reliable. If none of the above conditions are fulfilled, one should presently exclude lupus and procede with his diagnostic workup. If any of the above conditions are present, one must then evaluate the possibility of lupus. Handling of the case would then depend upon severity of the patient's condition, and upon the diagnoses receiving chief consideration. If signs appear very likely, as for instance if a definite leukopenia is present, or if an erythematous rash has developed concurrently with the abdominal signs, then one ought to temporize if the patient's condition will permit it. If the patient's condition is not at all serious, one may procede with a full diagnostic workup. If the patient's condition is grave, and a non-surgical condition such as pancreatitis is chiefly considered along with lupus, one should include steroids as a part of the therapy if lupus is seriously thought present. If the patient's condition is severe and a surgically amenable condition such as a perforated

ulcer is suspected, one should procede with surgery, but should begin the patient on adrenal steroids preoperatively if he feels the evidence for lupus to be very strong. In any event, it will be worthwhile to make a routine check for lupus and to follow the patient after recovery with an eye toward development of further symptoms.

In the instance of a person known to have lupus, one should always suspect that acute abdominal symptoms may be either lupoid or non-lupoid in origin. One should particularly suspect they are lupoid in origin if the white blood count falls instead of rises, or if there is a concurrent increase in any manifestations of lupus previously present in the patient, of if there is development of any new lupoid symptoms. One should immediately place the patient under large doses of adrenal steroids whether surgery is contemplated or not. If symptoms resemble a condition amenable to surgical treatment, surgery should be performed if such a condition ordinarily demands rather prompt surgical intervention. This is true even though there be other evidence (for example a decreasing white count) that lupus is in exacerbation. If such haste is ordinarily not really necessary, then one should wait out the 24-48 hour period for evaluation of the effect of the cortisone.

Amyloidosis: Amyloidosis is an uncommon disease which bears

certain resemblances to lupus. In this disease, a protein of variable composition but usually associated with a material similar to chondroitin-sulfuric acid is abnormally deposited in tissue. Four types of amyloidosis are commonly recognized: (1) primary amyloidosis, (2) secondary amyloidosis, (3) amyloidosis associated with multiple myeloma, (4) localized amyloid tumors.

Primary amyloidosis is a relatively rare disease and is seldom seen before the age of 40; thus while considered in passing, it would not often be a serious diagnostic possibility in most cases of lupus. Cardiac, smooth, and skeletal muscle are the most commonly involved sites, but liver, kidney, and spleen are also not infrequently involved. This entity most commonly presents as an insidiously developing congestive heart failure or nephrotic syndrome, and should be considered in the differential with lupus in cases so beginning. It may occasionaly be identified by the congo red test, but since this type of amyloid often does not take the stain well, early cases and even many well-advanced cases of amyloidosis will not be diagnosed by this method. Macroglossia is said to be present in one-half the cases, and if noted, is a very valuable diagnostic sign. Polyneuropathies may be seen in either lupus or amyloidosis. Amyloidosis would be expected to be associated with a more steadily progressive course than lupus, which is noted for its remissions and exacer-

bations. It is said that there is often abnormal serum proteins and that these may sometimes be seen with the aid of electrophoretic patterns, but this change is so subtle as to rarely be readily apparent, and so is not presently of real diagnostic help(77) In otherwise doubtful cases, lupus may be diagnosed if there is a positive LE cell test; or primary amyloidosis may be diagnosed if a positive biopsy can be obtained. Muscle biopsy is usually most fruitful although skin lesions (present in form of xanthelasmic plaques in about 25 per cent of cases) are also suitable. One should recall that amyloid and LE bodies are indistinguishable under H & E stain.

Secondary amyloidosis is much more common, and occurs secondary to chronic suppurative or inflammatory processes including tuberculosis, bronchiectasis, osteomyelitis, Hodgkin's disease, chronic ulcerative colitis, regional enteritis, chronic pyelonephritis, and rheumatoid arthritis. Spleen, kidney, liver, and adrenal cortex are most commonly involved; and lymph nodes, pancreas, gastrointestinal tract, prostate, thyroid, and other glands may be involved. Even if extensively involved, glands function relatively normally until very late in the disease, and symptoms are usually those of the underlying disease. The nephrotic syndrome may occur but is usually quite mild. Thus confusion with lupus arises only where the underlying disease might be confused with lupus, or occasionaly where the underlying disease is a common complication of lupus. For

instance, if the underlying disease is rheumatoid arthritis, one might interpret the appearance of a mild degree of the nephrotic syndrome as indicating a diagnosis of lupus instead of the correct diagnosis of rheumatoid arthritis plus secondary amyloidosis. One might similarly confuse tuberculosis with secondary amyloidosis, as being lupus with tuberculosis secondarily developing, since tuberculosis very frequently complicates lupus. In instances where doubt exists, one should attempt to rule out amyloidosis by performing a congo red test, and, if indicated, a liver or kidney biopsy. One or the other of these should be positive in the majority of cases where amyloidosis is sufficiently advanced to cause recognizable symptoms. Differentiation is less important than with some other diseases since there is little difference in treatment of the nephrotic syndrome regardless of whether it is caused by lupus or amyloidosis, since symptoms such as arthritis may be treated about the same whether due to lupus or to rheumatoid arthritis, and since diseases such as tuberculsosis should be recognized regardless of which other entity accompanies it.

Amyloidosis secondary to multiple myeloma, and localized amyloidosis should not be a diagnostic problem in separation from lupus.

Subacute Bacterial Endocarditis(SBE): Oftentimes a very difficult case to diagnose is one which presents with symptoms

which might be due to either lupus or to SBE. The frequency with which Libman-Sacks endocarditis occurs in lupus, and with which congestive heart failure may be a prominent symptom has already received comment. SBE simulates Libman-Sacks endocarditis in the cardiac manifestations, such as heart murmurs and symptoms of congestive failure, but also in other ways. SBE not infrequently begins as a fever of undetermined origin, sometimes steady but often intermittent and accompanied by very vague symptoms of anorexia, weight loss, slight nausea, easy fatigue, and malaise exactly such as one would likely observe in an early case of lupus. Joint inflammation is said to occur in about 25% of cases of SBE. Emboli to the kidney are very common in SBE setting up a focal glomerulitis so that there is commonly microscopic hematuria, and may be albuminuria. The spleen is said to be palpable in about 50% of the cases of SBE, and skin pigmentation, usually a light tan color, is seen occasionaly.(10)(11) These findings are all ones which have been mentioned previously as being very strongly suffestive of lupus. One might expect that the classic embolic phenomena described for SBE (Osler's nodes, splinter hemorrhages, Roth spots, petichiae in various locations) would be much less common in the Libman-Sacks endocarditis since in SBE the emboli are believed to break off from the clumps of bacterial growth rather than from the endocardial lesion itself, and in the Libman-Sacks

type of endocarditis there are no bacterial clumps. It is true that there are fewer emboli in the lupoid endocarditis than in SBE, but the "embolic" phenomenon may be seen regardless. In SBE the bacterial emboli do not assume new growth in their peripheral location, but only block tiny blood vessels, stopping flow, causing necrosis of the wall, and a tiny hemorrhage. This cannot be readily detected from minute hemorrhages originating from other causes, and in lupus there may be petichial hemorrhages related to platelet deficiency. Apparently, in Libman-Sacks disease, the peripheral petichial hemorrhages are even more common than in other lupoid presentations. Perhaps there is a degree of embolization from platelet aggregations upon the endocardial lesions. At any rate, signs of embolic phenomena prove little as to a lupoid or a bacterial etiology. Indeed, the classic triad described by Libman consisted of fibrinous pericarditis, white-centered petichiae in the skin, and constitutional symptoms.(7)

The laboratory may be of considerable help. A positive blood culture for streptococcus viridans, which is said to be obtainable in around 80% of cases of SBE, would clinch the diagnosis for SBE. A positive LE cell preparation would be positive proof of lupus. A false positive serology would be strongly suggestive of lupus. The white count may be normal, but is usually moderately elevated in SBE so that a leukocytosis would be strong evidence of SBE and a leukopenia

strong evidence of lupus. Because SBE may cause a focal glomerulonephritis, minor urinary findings would not be of great significance; but the presence of a full-blown nephrotic syndrome would strongly suggest lupus, and in cases where there appeared to be marked renal involvement and yet diagnosis was still uncertain, renal biopsy might be very helpful. Cases of SBE presenting as renal insufficiency have been reported.(107) The renal involvement as a consequence of emboli, may be moderate. One must always remember that a given finding, as kidney damage, is not always related to primary conditions considered. It may be only an incidental finding, particularly in older persons.

The test of therapy may also be of diagnostic aid and may be resorted to for the answer. Although scorned by some as "sloppy" procedure, it is greatly preferable to its alternative of diagnosis by autopsy. In doubtful cases one would proceed to emply antibiotic therapy. If this were of no avail, and lupus were suspected, one would attempt a short course of corticoid treatment. There are few cases of SBE or of Libman-Sacks endocarditis which would not show some clinical improvement under appropriate therapy. It may be borne in mind that a bacterial endocarditis may develop on valves damaged by Libman-Sacks disease as well as by rheumatic fever, but this would be a very rare circumstance.

Brucellosis: Brucellosis is a disease which should not pose a real problem in differentiation from lupus. It will be mentioned briefly, however, since it has been reported to be misdiagnosed for lupus on occasion,[28][58] and since the clinical picture may show many resemblances. The following signs and symptoms were noted in a series of 94 cases of brucellosis diagnosed at the University of Minnesota and well portray the non-specific, widespread involvement which is characteristic of both brucellosis and lupus.[10]

Symptoms:

A. weakness 91% of cases
B. sweats 76%
C. chills 75%
D. anorexia 70%
E. generalized aches 69%
F. headache 64%
G. rigors 56%
H. nervousness 52%
I. backache 51%
J. joint pain 44%
K. depression 40%
L. insomnia 38%
M. pain back of neck 36%
N. cough 30%
O. abdominal pain 21%
P. constipation 12%
Q. visual disturbance 12%
R. nausea and vomiting 10%
S. diarrhea 10%
T. GU disturbances 7%
U. neuralgia 5%

Signs:

A. fever, 98% of cases
B. lymphadenopathy 46%
C. palpable spleen 45%
D. palpable liver 26%
E. abdominal tenderness 9%
F. skin lesions 9%
G. neurologic changes 8%
H. cardiac abnormalities 8%
I. tenderness over spine 6%
J. fundoscopic changes 3%
K. orchitis 2%
L. pain over hip 2%
M. jaundice 1%
N. pain over sacroiliac 1%

Although the clinical picture can thus resemble lupus, and although brucellosis is usually accompanied by a normal white count or a leukopenia which may further confuse the examiner, the two diseases can be differentiated if both are carefully

considered and adequate tests are done. The diagnosis may not be made the same day the patient is first seen, however. Brucellosis is now chiefly either an occupational disease or a geographic disease and in the average city dweller in the United States its acquirement is very unlikely. Further, chronic brucellosis is probably very uncommon, and anyone who has had these vague symptoms for a period of over six months probably does not have brucellosis although some cases do so exist. These two factors may be kept in mind to guide in estimating the likelihood of brucellosis.

Wherever brucellosis is suspected, the proper screening test is the agglutination reaction. Agglutinins occur in virtually all cases of brucellosis, appearing during the second or third weeks of the disease. A dilution titer of 1:100 or greater is generally considered as reliable proof of active disease. Lower titers are not significant. A rising titer during a febrile state is very significant. Cross reactions may occur with Pasturella tularensis and Vibrio comma. It is recommended that one attempt blood cultures in those cases where a positive agglutination reaction is obtained. Positive blood cultures have been said to be obtainable in about 50% of the cases. Various other laboratory tests have been proposed, but are generally felt to be not worthwhile.(10)(11)

Thus brucellosis should be suspected when there is

development of non-specific disease characterized chiefly by fever, weakness, and nervousness in a person either engaged in an occupation where he is in contact with animals or animal products, or who has been in an epidemic area. Where suspected, an agglutination reaction should be performed. If the titer is less than 1:100 at a time when the patient is symptomatic and whose original symptoms began at least three weeks previously, it may be concluded that the patient has a disease other than brucellosis. If he has a titer of 1:100 or over, or a titer near this which has been shown to be rising during the period of symptoms, and if he has clinical evidence of brucellosis, and if he does not have a clinical history of Asiatic chloera or tularemia, he may be considered to have brucellosis although an attempt at confirmation through blood culture should be made. Differentiation between brucellosis and lupus is thus made by ruling brucellosis in or out on the basis of an agglutination titer.

Cirrhosis and Hepatitis: Chronic liver disease is an easy condition to diagnose as to presence or absence, but often it is difficult, if not impossible, to determine its original etiology. Liver involvement, although quite common in lupus, does not commonly cause symptoms. Bearne, in 1956, reported on a series of 26 cases of an unusual form of hepatitis occurring in young women.(108) Eleven of these bore symptoms consistent with lupus, and one had a positive LE test, and

he suggested a possible collagen disease etiology in these cases. Eleven other cases, each with a positive LE cell test, were reported by four other investigators, each of whom attempted to minimize the findings consistent with lupus and report the cases as examples of false positive LE tests.[109][110][111][112] However, it would appear that certain findings more consistent with lupus than with hepatitis were present in these cases. Bartholomew et. al. have recently reported on a series of seven patients, all of whom have chronic liver disease, and all have a number of findings characteristic of lupus including repeatedly positive LE cell tests.[113] The liver disease might be an incidental finding or might be associated with the lupus, but was believed by this group to be due to lupus for the reasons that: (1) the patients had lupus, (2) they were mostly young women (four were under 25) in whom cirrhosis is uncommon, and (3) similar instances of lupoid symptoms plus liver disease have been reported in the papers above-mentioned. It is concluded that the cases thus far reported are definitely not false positive tests for LE cells, since lupus was definitely present. It appears likely that development of the liver disease was ficilatated by, if not directly caused by, the lupus, but this point cannot be settled on present evidence and opinions only may be given. In the cases reported, there have been autopsy reports of subacute viral

hepatitis, and of postnecrotic cirrhosis in the involved livers. General symptomatology has been clinically consistent with a post-necrotic type of cirrhosis of insidious development.

There should be no unusual diagnostic probelem related to determination of presence of lupus in a person with liver disease, or vice-versa. Diagnosis as to whether or not the liver disease has been caused by the lupus, when the two are found together, is presently an insoluble problem.

Dermatomyositis: No difficulty will be encountered in differentiating the typical case of dermatomyositis from the typical case of lupus. Difficulty arises, however, in a number of borderline cases in which the patient will appear to have a sort of mixture of the two diseases with clinical, laboratory, and even histological findings typical and even "specific" for each of the two diseases. Scleroderma often behaves similarly, and cases will arise in which no decision can be made as to which of this trio of diseases is the primary disease of that patient. Many observers share the opinion that the etiology of these collagen diseases is very similar if not identical, and that certain instances arise where a patient appears to have a non-specific collagen disease with combined features.(33)(70)(77)(114)(115)(116) It cannot be stated, however, that

these particular patients do not in fact have two or three different diseases with a resultant admixture of manifestations; indeed, one would expect that a person susceptible to one would be more likely susceptible to another than would the average person. Thus, with our present state of knowledge, the best that can be done is to call the disease whichever of the entities seems definitely more pronounced, or, if there is strong evidence of both, one can only say that he is dealing with an "atypical" collagen disease having manifestations of both lupus and dermatomyositis. As knowledge further accumulates regarding the etiology of these diseases, it may later be possible to separate these borderline cases.

Dermatomyositis, as its name implies, manifests itself chiefly through alterations of skin and skeletal muscle. Any skeletal muscle may be involved although the trunk and proximal portions of the extremities usually show the greatest involvement. The patient notes stiffness, tenderness, and loss of strength in these muscles. Atrophy and contractures may make a late appearance. Microscopically the fibers may show proliferation of nuclei, occasional round and giant cells, and varying degrees of degenerative change. The skin manifestations are very non-specific and may take any form, but most commonly are erythematous in nature. Edema is another common feature even though the kidneys and heart are rarely affected. Periorbital edema is especially common,

and it is said that the skin about the eyes not infrequently develops a peculiar heliotrope hue. Laboratory tests usually indicate a slight anemia and a normal white count with an occasional eosinophilia. There may be reversal of the AG ratio. If there is an appreciable amount of muscle involvement there is commonly a creatinuria and a hypocreatininuria. Muscle biopsy is pathognomonic in uncomplicated cases.(105) The course of the disease is most commonly of a slowly progressive nature with an insidious onset and usually a fatal termination.(10)(11) The typical case is thus a definite clinical entity which is not a particularly hard diagnostic problem, but those cases appearing to be an admixture with either lupus or with scleroderma may be quite confusing and often a single diagnosis cannot be reached. Fortunately, there is not a great deal of difference in therapy of these diseases so an ante-mortem separation between them is less important.

Polyarteritis Nodosa: Difficulty is often encountered in the differentiation between polyarteritis nodosa and lupus. Both diseases show many vagaries, and both may be associated with a multitude of manifestations. Polyarteritis is also a collagen disease; its etiology is unknown although many cases seem to be related to hypersensitivity. These two diseases do not merge together to the extent that lupus, dermatomyositis,

and scleroderma may merge; but lupus and polyarteritis may produce about the same clinical picture and occasionaly histologic differentiation may also become confused. The histologic pattern is different for the two diseases, however, in the typical case. Polyarteritis affects small arteries and arterioles, and unlike lupus, the necrosis which occurs is usually accompanied by an intense inflammatory response. Multiple nodular lesions two to four millimeters in diameter occur along the course of the affected artery. It has been described that these can be detected by palpation externally,[117] but this can probably be done only in a minority of cases. The lesion consists of a necrosis, usually beginning in the media, which is accompanied by a non-specific inflammatory response. This in turn may be followed by any of the usual sequelae of necrosis and inflammation of vessels including thrombosis, aneurysm formation, organization, or recanalization. The necrotic area is often eosinophilic and has been said to have a fibrionoid appearance.[41][43][105] This histologic finding, a segmental arteritis with both necrosis and marked inflammatory response, is quite typical for polyarteritis and quite different from the usual vascular involvement seen in lupus in which aneurysms and thromboses are not associated and inflammation is less prominent and not seen in early stages. Unfortunately, the histologic findings have been said to not be specific for polyarteritis, having been reported in such other conditions

as erythema multiforme, erythema nodosum, Weber-Christian disease, rheumatoid arthritis, lupus, scleroderma, dermatomyositis, drug hypersensitivity, and serum sickness. These "false positive" biopsy reports remind one of the similar controversy regarding "false positive" LE cell tests, and somewhat the same sort of situation may exist. Whether or not the occurrence of this finding in the presence of a disease diagnosed as other than polyarteritis, or its appearance and subsequent disappearance in association with a temporary toxic state, can be interpreted to mean that polyarteritis was not present and thus that the finding is not specific for polyarteritis, is debatable. An investigation into this problem would be interesting but is considered beyond the intent of this paper, and for purposes of diagnostic differentiation between lupus and polyarteritis, it is advised that one follow what appears to be the majority opinion in this respect, that the presence of biopsy evidence alone is not presently proof of the disease, but that presence of biopsy evidence plus the usual clinical picture is satisfactory evidence of the disease. This wouldappear a safe and sane middle course, the catch of course being that there is really no typical clinical picture to polyarteritis because of its great variability. Some of the more common manifestations of polyarteritis will be listed; any of them may be the presenting symptom.

Manifestations of polyarteritis nodosa include:

1. Onset: either insidious or abrupt; usually no apparent predisposing factor, but not uncommonly begins with an "incidental" hypersensitivity reaction.

2. Incidence: affects all ages but mostly between forty and sixty years; males affected three or four times more often than females.

3. Course: usually fatal but recovery may occur, particularly with hypersensitivity-induced cases; may be many remissions and exacerbations and course is usually prolonged.

4. Cutaneous lesions: a variety may occur; may be erythematous; may resemble embolic phenomena.

5. Hypertension: said to occur in at least 50%.

6. Neurologic disorders: may be peripheral neuritis, paresthesias, cranial nerve palsies, convulsions, etc.

7. Arthritis: frequently joints are painful, there may be swelling and tenderness; there may be deformities resembling those seen in rheumatoid arthritis; this is usually bilateral and worse in lower limbs.

8. Renal injury: is common; hematuria, albuminuria, and terminal uremia are very common; in presence of kidney damage there is nearly always a related degree of hypertension.

9. Pulmonary symptoms: many have asthma, less frequently one sees cough, hemoptysis, pleurisy.

10. Heart involvement: is common though usually is not grave.

11. Gastrointestinal symptoms: vomiting, diarrhea, and vague abdominal pains are common; occasionaly an acute surgical abdomen may be simulated.

12. General malaise, with some degree of weakness and of weight loss and with intermittent fever is quite common.

13. Anemia: a moderate anemia is usual.

14. Leukocytes: there is a leukocytosis in around 80% of the patients, ranging between 12,000 and 50,000 but occasionaly a leukopenia is seen; eosinophilia may be seen in 20 to 25% of cases.

15. Other findings: Raynau's phenomenon, false positive serologies, and all manner of other manifestations are reported in occasional cases.

In review, one sees that the range of manifestations of polyarteritis is diverse, and will vary according to the particular area in which lesions happen to occur. Overall, there is considerable resemblance to lupus. There is no manifestation characteristic of lupus which might not well be seen with polyarteritis. Presence of leukocytosis would certainly be suggestive of polyarteritis, however, as would also an eosinophilia. A false positive serology occurs much more frequently in lupus than in polyarteritis but may be seen in either. Development of an increasing hypertension in relation to a progressive loss of kidney function would be very suggestive of polyarteritis rather than lupus, but a static hypertension would carry less diagnostic significance because of the commoness of essential hypertension. On the other hand, a progressive loss of kidney function without a progressive hypertension, or the development of a marked nephrotic syndrome, would suggest that lupus would be very much more probable than polyarteritis. A positive LE test, as usual, is considered diagnostic of lupus. If the symptoms could well be due to either diseases, and if the LE cell test

is negative, histologic evidence will be required for diagnosis. Polyarteritis is thus suspected by the clinical and laboratory findings, and diagnosed by biopsy.

Occasionaly one finds histologic evidence of both, and occasionaly one finds histologic evidence of one and then later notes that the clinical findings more and more resemble the other. This, of course, presents a dilemma to the conscientous diagnostician, and at present it is an insoluble one. Opinions would differ as to how such an entity should be classified. It seems safest to consider that such a patient has had both diseases, and not to overstep present knowledge by trying to explain that one turned into the other or that one of the diseases could produce the findings considered typical of the other. Defining a disease by an enumeration of certain findings frequently enough noted, may not be the most ideally correct method, but when the pathogenesis is not known, greater inconsistencies in diagnosis will result if persons attempt to include atypical cases by theorizing thata supposed etiology would really permit one thing to change to another. Diagnosticians and pathologists alike, having their individual compulsions, will often label such a disease as one entity or the other, but it should be remembered there are certain cases in which the two diseases cannot be clearly separated. Polyarteritis is a disease which is quite often not correctly diagnosed

is a disease which is quite often not correctly diagnosed ante-mortem. Since the predominant and often lethal manifestation of polyarteritis and often the lethal manifestaion of lupus is kidney damage, and since treatment is the same for either, and prognosis about the same, an ante-mortem diagnosis between these two is not completely essential.

Hypersplenism: The term "hypersplenism" is used in description of a variety of disorders in which there is excessive destruction of blood cells by the spleen. Primary hypersplenism is said to occur when there is no demonstrable disease process affecting the spleen which would cause it to destroy excessive numbers of cells, and secondary hypersplenism is said to occur when there is an underlying disease such as malaria or portal hypertension which alters the structure of the spleen. Hypersplenism of either type may manifest itself by destruction of excessive numbers of red blood cells, white blood cells, plateles, or even all three. It is a condition occurring not uncommonly, and the usual treatment is either splenectomy or adrenal corticoid therapy; the former being generally preferred for prolonged or rapidly advancing cases, and the latter being preferred for short-lived, milder cases which are still sufficiently severe to require some sort of therapy.(118)

Lupus characteristically has a decreased number of all three blood elements, and not infrequently will present itself in this way, and may show no other findings except for anemia or thrombocytopenia for several years. The thrombocytopenia is often severe enough to result in various bleeding phenomena. The extent to which the spleen is responsible for the cytopenia seen in lupus is not known. In addition, a person with lupus may develop secondary hypersplenism. Cases of lupus developing secondary hypersplenism of considerable degree are usually not a diagnostic problem. Cases of lupus presenting as idiopathic thrombocytopenic purpura cannot be distinguished from that condition until other manifestations develop, and since this may require several years, one can only bear in mind that what appears to be an early case of thrombocytopenic purpura may later turn out to be lupus.

Given time, patients can definitely be catergorized as having either one disease or the other, since hypersplenism per se will not cause symptoms of lupus, and since it is assumed that the natural tendency of lupus is to grow progressively worse and exhibit more and more findings. The diagnostic problem that may arise regards the determination of when splenectomy is indicated and when it is not. Dameshek has observed several cases of lupus which exhibited rapid dissemination and deterioration of the

general condition immediately following splenectomy, and he states, "since the strong possibility of dissemination of the process following splenectomy is present, it is probably best to postphone splenectomy as long as possible".(36) No other similar reports have been noted, but until the matter is more thoroughly studied, and valid conclusions drawn, it is thought wise to keep his observations in mind. Should they be correct, it would probably be wise "never" to perform a splenectomy in a person known to have lupus (except in emergencies such as splenic rupture). It would also be wise to rather carefully review all candidates for splenectomy on the basis of thrombocytopenic purpura, and to temporize if possible particularly in those patients who would be likely candidates to have lupus (as fair-skinned, light-sensitive, reproductive females, etc.) and especially in those who have had symptoms suggestive of lupus (as arthritis, chest pain, etc.).

Rheumatoid Arthritis: Considerable confusion may arise in differentiating between lupus and rheumatoid arthritis. This problem was very briefly noted in the discussion of the so-called "false positive" LE tests. It is frequently noted that cases which appear to be typical rheumatoid arthritis for years may gradually change into a clinical picture incorporating more and more features of lupus and may show a positive LE cell

test. On this basis one might conclude that: (1) the patient has had rheumatoid arthritis and no other disease the entire time, (2) the patient has had lupus all the time and never did have rheumatoid arthritis, (3) the patient had rheumatoid arthritis but this changed into lupus, (4) the patient had rheumatoid arthritis and developed lupus subsequently. Of these four possibilities, there is no justification for claiming that any of them is correct 100% of the time, because in view of present knowledge, or lack thereof, the only honest conclusion that may be drawn is that the patient has exhibited evidence of each entity and their inter-relationship is not known. As discussed under the section on polyarteritis, a disease, of unknown etiology cannot be delineated according to etiology. If its diagnosis is customarily determined on the presence of a certain syndrome of clinical and/or laboratory and/or histologic manifestations, then one must adhere to this system until a better one is found to supplant it. Accordingly, if the lupus syndrome develops in a person with diagnosed rheumatoid arthritis, the person must be said to have lupus. Likewise, if a typical case of rheumatoid arthritis is in existence for a suitable length of time, it must be said to be such and not to be lupus even though lupus develops later. What constitutes a "suitable length of time" is a matter of debate, and will doubtlessly change as our experience with these two diseases increases. Lupus may present only one of its

manifestations for varying lengths of time, and thus may show only arthritic symptoms in the beginning. One hesitates to express an opinion as to just how long a "suitable length of time" is, for fear that his opinion may change radically by next week. The following stand is presently recommended on this problem: (1) if symptoms typical of lupus appear in a person with diagnosed rheumatoid arthritis, the person must be said to have lupus, since classical rheumatoid arthritis does not include findings in the lupus syndrome, (2) if classical rheumatoid arthritis is present for several years or more before development of classical lupus, one should say that the person probably has lupus and likely has had rheumatoid arthritis also, since in the classical lupus syndrome one does not usually see involvement in one system only for a period of more than several years before involvement of another system occurs. It must be borne in mind, however, that the inter-relationship of these two diseases is not known, and that if subsequent knowledge informs us of the pathogenesis of these diseases, that more accurate separation may be possible.

Classical rheumatoid arthritis should probably be defined, and this is not easily done. For purposes of this discussion the classical findings include the typical joint involvement, the associated local muscle atrophy, subcutaneous nodules, and various non-specific laboratory findings such as an

increased sedimentation rate. In addition to these, one notes that it is reported that some degree pf cardiac involvement is very commonly seen at autopsy.(11) Various sources state that such findings as pleuritis and chest pains, pericarditis, and other manifestations also occur commonly. It must be said that there are many variations of rheumatoid arthritis, and that there are probably etiological relationships between rheumatoid arthritis and lupus. Rheumatoid arthritis is a systemic disease affecting connective tissue somewhat diffusely. In acute attacks, it may be associated with fever, malaise, pleuritis, and other symptoms typical of lupus. However, symptoms arising from systems other than the musculo-skeletal system, and particularly if present chronically, are much more suggestive of lupus than of rheumatoid arthritis. It is often difficult to determine whether or not minor involvement of another system is etiologically related to an arthritis, or whether it is incidental to it and caused by a different mechanism. This is why it will be impossible to make highly accurate diagnoses in diseases like rheumatoid arthritis and lupus erythematosus until their etiology is known and until some related test which will prove which category a given patient falls within can be determined. Until then, one must continue to categorize by clinical judgment of the patient's symptoms, and there will be many cases falling between what is considered

classical rheumatoid arhritis and what is considered classical lupus. These cases must be included in whichever group they most closely resemble, or, if it seems unfair to make a choice, then one must fall back onto the diagnosis of "atypical collagen disease".

The sheep-cell agglutination reaction, latex-agglutination, and similar tests have been proposed as an aid to the diagnosis of rheumatoid arthritis. It would appear from results reported to date, that these tests are related to arthritis and to its degree of severity, but that to date they have often shown little difference as to whether rheumatoid arthritis or lupoid arthritis was present.[40][70][119][120][121][122][123]. There is hope that with continued improvement in this type of test, it may be developed into a more useful diagnostic test.

Scleroderma: Another disease which at times may be indistinguishable from lupus is scleroderma. The typical case of scleroderma may show any of the clinical manifestations of lupus, but will predominantly show the characteristic skin changes with a resultant waxy, taut, shrunken, thickened skin. In addition, there is usually some involvement of smooth muscle, especially in the esophagus, stomach, and intestine. Thus there is no problem in differentiating the typical case of scleroderma from the typical case of lupus. The difficulty

arises in that certain patients may exhibit any manner of transition between findings typical of lupus and those typical of scleroderma. As with the other collagen diseases, one is tempted to say that there must be a similar etiology, and that perhaps one can cause symptoms typical of the other in certain instances. In these indeterminate cases, one can only say that an "atypical" collagen disease is present which shows certain manifestations of each disease. These cases cannot be diagnosed to be solely one disease or the other on the basis of present knowledge.

SUMMARY

Lupus erythematosus is a clinical syndrome of unknown etiology and multiple manifestations. One of the collagen diseases, its effects on the body are very widespread. It is probably associated with as many different "specific" clinical, histological, and laboratory findings as any other disease; yet its diagnosis is often very difficult because each case behaves differently. Not uncommonly cases are seen in which lupus and another of the collagen diseases appear to be coexistent. In these instances, there is the temptation to label the case as either one disease or the other. However, since these diseases are defined by their manifestations, and since their pathogenesis is not known, it would seem unwise to attribute typical manifestations of

one to the other, even on the basis of a supposed similarity in pathogenesis. Thus the fact that these diseases must be diagnosed on the basis of the presence of certain findings, which have only empiracally been found to be related, adds to the difficulty of diagnosis. The most widely held theory on the etiology of lupus proposes that it is probably due to an auto-immune hypersensitivity. Evidence is presented, however, that it might equally well be due to an error of metabolism. Other possibilities, for instance a viral etiology, have not been ruled out. As the etiology and pathogenesis become better understood, these will probably serve as a better basis for determining the diagnosis of lupus than its present concept of a clinical syndrome.

Hydralazine toxicity may result in a state exactly resembling lupus. There is no evidence that this state differs in any way from lupus incurred in any other manner. It appears that this should offer tremendous potential as a research tool. This has been poorly utilized up to the present time.

The LE cell test has been subject to wide debate as to its specificity. On the basis of present evidence it is believed to be specific. Criteria for consideration of a possible "false-positive" LE cell test are proposed.

Several newer laboratory tests for lupus have been described, and one, employing I^{131} labelled antiglobulin,

appears unusually promising since it should be extremely sensitive and should permit quantitative as well as qualitative results to be obtained.

Many diseases may be confused with lupus. From a therapeutic standpoint, differentiation is relatively unimportant in some cases but highly essential in others.

These problems are discussed in the body of this thesis, and tentative answers to some questions are proposed.

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