Medical Grand Rounds
February 15, 1979

The Clinical Spectrum of Lupus Skin Disease

Lupus Erythematosus, a hard-to-diagnose malady, can imitate heart attack, appendicitis, gynecological disorders — even a brain tumor.

— From Family Weekly, Nov. 26, 1978, "The 'Red Wolf' Disease That Baffles Doctors," by Gloria Hochman

Characterization of a New Cutaneous LE Subset

James N. Gilliam

THE CLINICAL SPECTRUM OF LUPUS SKIN DISEASE: CHARACTERIZATION OF A NEW CUTANEOUS LE SUBSET

I. Introduction
   Overview of advances in LE since 1975

II. Historical Aspects and Classification of Cutaneous LE

III. Morphologic Features of Cutaneous LE

IV. Pathologic and Immunopathologic Features of Cutaneous LE
   A. Pathology
   B. Immunopathology
   C. Proposed mechanism of injury in cutaneous LE - GVH disease

V. Clinical and Serologic Features of Cutaneous LE Subsets
   A. Chronic Cutaneous LE (DLE)
      1. Case I
      2. Summary of Data from 80 patients
      3. Position on LE Spectrum
   B. SLE with DLE (SLE/DLE)
      1. Case II
      2. Summary of Data
      3. Position on LE Spectrum
   C. LE Profundus
      1. Case III
      2. Summary of Data
      3. Position on LE Spectrum
   D. Subacute Cutaneous LE (SCLE)
      1. Case IV
      2. Summary of Data
      3. Position on LE Spectrum
   E. Acute Cutaneous LE (ACLE)
      1. Case V
      2. Summary of Data
      3. Position on LE Spectrum

VI. Immunologic Basis for Variation in the Expression of Cutaneous LE

VII. Conclusion

THE CLINICAL SPECTRUM OF LUPUS SKIN DISEASE: CHARACTERIZATION OF A NEW CUTANEOUS LE SUBSET

I. INTRODUCTION

There have been few major advances in our understanding of lupus erythematosus since the last grand rounds on this subject. I gave a Medical Grand Rounds titled, The Clinical Syndromes Within the Spectrum of Lupus Erythematosus in 1975. At that time, I discussed the role of abnormal immunoregulation which seemed to be an important underlying factor in the development of autoimmunity [2,35]. Since then several investigators have provided evidence that defective suppression of B cell antibody production by regulatory T cells is present in patients with active SLE and in aging NZB/W mice, animals with a lupus-like disease [3,9,26,60,75,129]. The importance of T cell abnormalities in causing B cell hyperactivity and autoimmunity in SLE is still a matter of some controversy [125]. Hormonal effects on immunoregulation have been recognized and sex hormone levels have been found to have a profound modulating influence on the immune response in NZB/W mice [97,118]. Androgen has a protective effect in these animals. This hormonal influence on immunoregulation may have something to do with the striking sex differences in disease prevalence in both human and mouse lupus.

Support for the role of infection as a triggering or aggrevating event in SLE has gained little ground since 1975. Indeed, some have expressed the feeling that the search for an infectious agent in LE should be abandoned [86,87]. On the other hand, there have been several reports of serologic and immunopathologic abnormalities in non-consanguinous household contacts in lupus family members [20,31,67,72,85] and examples of lupus appearing in families with pet dogs having SLE [5]. Papers that describe viral antigens in the kidney [70] and skin [80] of lupus patients have also appeared. Such reports continue to stimulate interest in the concept of an infectious etiology in LE but definite proof for this is still lacking.

Genetic factors in LE have also been investigated [5,9]. The role of HLA in the immune response continues to be of great interest [22,45,94]. A weak association between HLA-B8 and SLE has been described [53,101]. It has also been claimed that patients with DLE who have HLA B8 are prone to develop SLE [73]. Since 1975, more attention has been focused on the D locus of the major histocompatibility complex since it appears to be more closely related to the putative immunoregulatory gene(s) [115]. A recent paper has shown that patients with SLE have a slight, but significant, increase in HLA DW3 and DW4 [93].

The concept of LE subsets, which was the general theme of the 1975 Grand Rounds, has continued to gain in popularity [1,127]. The idea that lupus patients can be divided into groups, or subsets, that share certain clinical, serologic, pathologic and prognostic features is extremely useful in the diagnosis and management of a disease which displays such a wide variety of clinical patterns. Individual patients acquire distinct forms of the disease and, within certain limits, maintain these same clinical features throughout the course of their disease. If indeed immunologic mechanisms play a major role in the expression of LE, one would expect patients within the same clinical subset to share certain immunologic abnormalities which might be identified by a laboratory test. In fact, clinical subsets have been found that do share common immunologic markers. In 1972, Gordon

Sharp reported that antibodies to a nuclear ribonuclear protein (RNP) occurred in high frequency in patients with a more benign connective tissue disease, the MCTD syndrome [40,102]. Dr. Sharp gave a lucid description of this "subset" at a Medical Grand Rounds here last November. The association between severe lupus nephritis and anti-DNA antibodies is well known [14,108] and has served as a useful marker for the lupus nephritis subset. Recent studies have provided information suggesting that the DNA antibody class [117] and subclass [107] give additional information about the severity of the renal lesion. When DNA antibodies are mainly of the IgM class renal disease is less severe [84]. In NZB/W mice the proportion of IgM to IgG anti-DNA can be altered by sex hormones [118]. Endogenous or exogenous androgen appears to prevent the shift from predominately IgM to IgG anti-DNA production in these animals and this appears to be associated with a more benign disease [118]. More recently workers have suggested that a group of ANA negative patients with antibodies to a cytoplasmic antigen (RO) form a distinct subset [30,43,89]. Many of these subsets were discussed four years ago and little new information has appeared since that time. The exact pathogenic relationship, if any, between these antibodies and the associated disease subset remains a mystery.

Also mentioned in my 1975 Grand Rounds was the concept that the cutaneous involvement in LE can be a clue to the nature of the overall disease process. In that discussion I described in detail the clinical features of all types of skin disease in patients with LE, both the LE specific and non-specific skin lesions. These are summarized in the following tables.

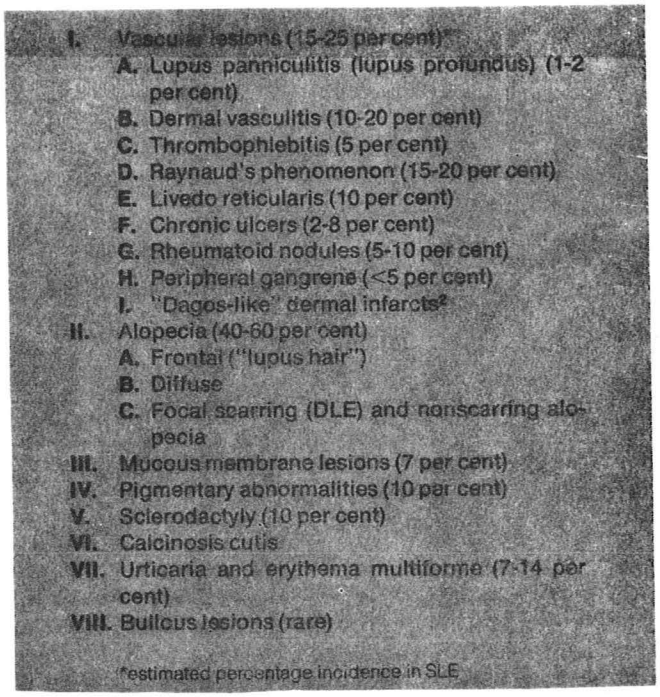
Clinical Features of the Lupus-Specific Or Diagnostic LE Skin Lesions

I. Epidermal and upper dermal lesions
   - A. Chronic cutaneous (chronic discoid LE) (15-20 per cent)*
     1. Scarring and atrophy
     2. Usually confined to the head and neck
     3. Most often without associated extracutaneous disease
     4. Low titers of antinuclear and anti-nDNA antibodies
     5. Subepidermal immunoglobulin common in lesions but rarely present in normal skin
     6. Simultaneous occurrence of lupus nephritis rare
   - B. Subacute cutaneous (15-25 per cent)
     1. Usually widespread
     2. Residual telangiectasia but no atrophy or scarring
     3. Associated with extracutaneous involvement but skin disease may be the major and occasionally the only manifestation
     4. Anti-nDNA variable; subepidermal immunoglobulin in abnormal skin
   - C. Acute cutaneous LE (40-60 per cent)
     1. Transient facial erythema and edema lasting hours to days
     2. Resolution leaving hyperpigmentation but no scarring
     3. Extracutaneous involvement
     4. Correlation with a flare-up of systemic disease
     5. Elevated levels of anti-nDNA antibodies and renal disease
     6. Subepidermal immunoglobulin in abnormal and normal skin

II. Deep dermis and subcutaneous tissue (2 per cent)
   - A. Chronic, nontender, firm, subcutaneous nodules
   - B. Erythematous, possibly sclerotic or ulcerating
   - C. Overt SLE in approximately one half of the cases coexistent DLE in 70 per cent
   - D. Skin
     1. Normal—variable; if present, indicative of occult systemic disease
     2. Abnormal—vascular deposits of immunoglobulin usually present

*approximate percentage incidence in SLE

Clinical Features of the Nonspecific LE Skin Lesions



Today I will focus my discussion on five LE subsets identified by characteristic LE specific skin lesions. I will briefly review the salient clinical and laboratory features of four of these. Then I will present a more detailed analysis of a newly recognized subset of cutaneous LE. Finally, I will speculate on the relationship between cutaneous and systemic LE based upon our current concepts of the immunopathology of this disease.

II. HISTORICAL ASPECTS AND CLASSIFICATION OF CUTANEOUS LUPUS ERYTHEMATOSUS

Lupus was for many years recognized as a disease solely involving the skin. In 1851 Cazenave introduced the term lupus erythematosus to distinguish patients with a nontuberculous form of lupus from those with lupus vulgaris [13,56]. Kaposi is generally regarded as being the first to recognize the systemic component of LE in 1872 [56]. It then became clear that this generalized systemic disease did not emanate from the condition of the skin as was believed earlier. Indeed, to many investigators the skin seems to bear little relation to the severity or extent of the systemic disease -- a most important but largely ignored concept. On the other hand, some continued to hold the opinion that a close relationship existed between the skin and visceral lesions, and that some toxic product(s) originated in the skin and was dispersed throughout the body [44]. This idea was substantiated by the common observation that exposure to ultraviolet light was often accompanied by an increased intensity of both the cutaneous and systemic symptoms. Despite this, increasing numbers of patients with SLE were identified during this period

with visceral symptoms that anti-dated their cutaneous manifestations by weeks or years, and increasing numbers of patients were also found who had little or no cutaneous disease [7]. These observations added to the confusion regarding the relationship between cutaneous and systemic LE [58,81,100,130]. The failure to recognize that the severity of the disease process in visceral sites such as the kidneys might be inversely related to the process in the skin has perpetuated the confusion.

It has long been recognized that skin lesions in patients with systemic LE usually do not scar or cause atrophy [44]. The morphologic differences between this superficial, acute or subacute cutaneous lesion and the classic scarring and atrophy of the chronic discoid type led many observers to conclude that SLE was a separate and independent disease. The concept that SLE and DLE were two different diseases was strengthened by the observation that patients with the more transient and superficial skin lesions consistently had a more severe disease than those with discoid LE (chronic scarring cutaneous LE). However, several observations still linked these morphologic variants into the single disorder, lupus erythematosus. These observations are as follows:

1) Gradual and progressive transitions between subacute and chronic discoid expressions were occasionally seen [56].

2) Some patients with typical chronic destructive skin lesions (DLE) later developed systemic disease [6,61].

3) Patients with acute systemic LE (SLE) were observed to develop chronic scarring discoid skin lesions during the course of their disease or with remission of systemic symptoms [35].

4) The histopathology of LE skin lesions in different phases of development showed similar changes suggesting a common pathogenesis [15,25].

The lack of a widely accepted system of classification for the morphological varients of cutaneous LE has been another source of confusion. This has made it impossible for dermatologist, rheumatologist, nephrologist and other physicians with an interest in LE to communicate intelligently about the skin involvement in this disease. The classification that seems most useful and the one that I will use in this discussion is a modification of the classification suggested by Brocq in 1925 [56] and O'Leary in 1934 [78].

In this classification cutaneous LE is divided into three types based strictly upon the clinical appearance without consideration of systemic aspects of the disease. The three forms of LE specific skin disease are as follows: 1) chronic scarring or discoid LE (Brocq's "fixed" type), 2) subacute cutaneous LE (Brocq's symmetrical erythema centrifugum), and 3) acute cutaneous LE (exanthematous cutaneous LE according to Brocq). Subtypes of these major categories are listed in the following table:

CLASSIFICATION OF CUTANEOUS LE

I. Chronic Cutaneous LE (DLE)

- A. Localized DLE
- B. Generalized DLE
- C. Hypertrophic DLE
- D. Lupus Profundus (Lupus panniculitis)

II. Subacute Cutaneous LE

- A. Localized (Erythema perstans faciei of Kaposi)
- B. Generalized (Symmetrical erythema centrifugum)
  1. Papulosquamous
  2. Annular - Polycyclic

III. Acute Cutaneous LE

- A. Localized - malar erythema
- B. Generalized - diffuse erythema (exanthematous)

III. MORPHOLOGIC FEATURES OF CUTANEOUS LE

Chronic cutaneous LE (DLE) is characterized clinically by erythema, atrophy, telangiectasia, scaling and both hyper- and hypopigmentation. The lesions are sharply circumscribed, pink to violacious in color and have central scarring with peripheral areas of active inflammation. They usually persist for months or years. Upon healing, telangiectasis may be the most prominent feature, but areas of atrophy and scarring are invariably present. Hyper- and hypopigmentation are especially pronounced in black skin and follicular dilation with keratin plugging is usually seen. These lesions are frequently found on the malar areas, nose, forehead, scalp and ears, and other areas of light exposure. Occasionally they are scattered widely over the body resulting in severe disfigurement. These widespread lesions are referred to as generalized or disseminated DLE [78]. A hypertrophic type of DLE is occasionally seen [51,126]. This variant of DLE is elevated and extremely hyperkeratotic often resembling lichen planus, psoriasis or a keratoacanthoma [126]. Another closely related type of cutaneous LE is lupus profundus or lupus panniculitis [52]. The clinical features of this form of cutaneous LE will be discussed separately.

The lesions of subacute cutaneous LE (SCLE) are more ill-defined and superficial. These lesions are non-fixed, non-scarring, erythematous, telangiectatic and often extend over the face, upper back, shoulders, neck, extensor arms and backs of the hands. Their distribution is widespread and symmetrical often coinciding with areas of light exposure. With time, superficial scaliness develops and the eruption may then resemble psoriasis or pityriasis rosea [56].

Acute cutaneous LE has been described as a "butterfly rash". It is marked by edema and erythema. Such lesions may appear urticarial but they are more persistent than true urticaria. They commonly affect the malar area, are abrupt

in onset, and last for several hours to a few days. The appearance of such lesions commonly coincides with flares of the systemic disease. On examination, the patient's entire face may be involved sparing only the eyelids and peri-orbital regions, or the eyelids may be involved in a manner similar to that seen in dermatomyositis. In occasional patients, upper dermal edema is so intense that subepidermal blisters develop and subsequently rupture to leave crusts and small erosions. Hyperpigmentation commonly occurs and this may be the most obvious finding when a patient is seen.

IV. PATHOLOGIC AND IMMUNOPATHOLOGIC FEATURES OF CUTANEOUS LE

A. Pathology

The pathologic target is skin, as in many other tissues, is the epithelial-mesenchymal interface, where the basal lamina (Type IV collagen) is synthesized [66]. The most distinctive pathologic change occurs along the dermal epidermal junction [15,25,66]. Morphological changes noted by light, fluorescence, and electron microscopy suggest that the basal cell or germinal portion of the epidermis is the primary site of injury whether the lesion is acute, subacute or chronic [15].

In the lesions of chronic cutaneous LE hyperkeratosis and follicular plugging are prominent. The nucleated portion of the epidermis is generally atrophic and mononuclear cells infiltrate periappendageal and perivascular areas in the dermis. The density of this lymphocytic and histiocytic infiltrate varies considerably but is often related to the age and destructiveness of the lesion. The most characteristic changes are at the basal layer of the epidermis. These consist of:

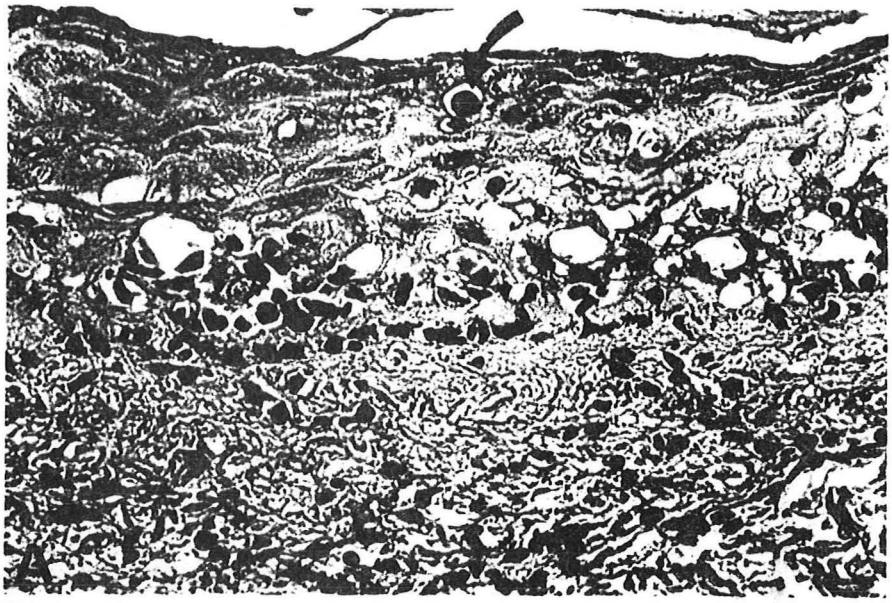
1) loss of the normal organization and orientation of basal cells,

2) edema with vacuole formation between and sometimes within basal cells,

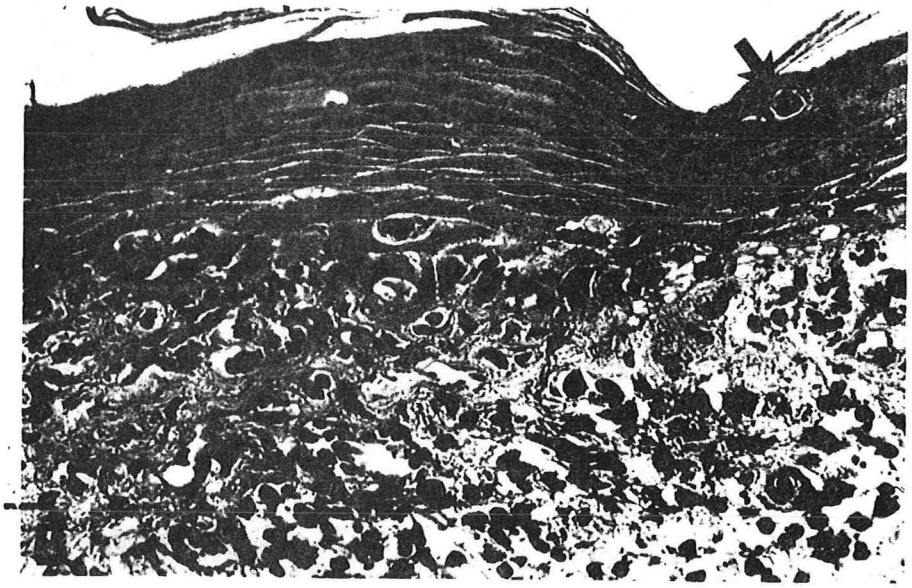
3) partial obliteration of the dermal epidermal junction by a mononuclear infiltrate.

Increased melanogenesis and interruption of pigment transfer is indicated by the accumulation of melanin in macrophages beneath the epidermis (incontinence of pigment). In older lesions thickening of the PAS positive epidermal basement membrane occurs. These rather characteristic changes in the germinal layer of the epidermis are also seen in a seemly disparate assortment of disorders, including animal [112] and human [50,65,104] graft-versus-host disease, lichen planus [66], dermatomyositis [15,55] poikiloderma of Jacobey [66], certain drug reactions (arsenicals [66], hydroxyurea [57], busulfan [62]) and vitamin B-12 deficiency [39]. These disorders all of which produce lichenoid or poikilodermatous cutaneous reactions have been reviewed by Pinkus [88]. The common denominator for these changes seems to be basal cell injury.

The histopathologic changes of subacute cutaneous LE (SCLE) cannot be reliably distinguished from DLE. Follicular plugging, hyperkeratosis and cellular infiltration are less prominent but the overall pattern is esentially the same.



A. Subacute cutaneous LE Vacuolar changes along the D-E junction and satellite cell necrosis (arrow).



B. Chronic cutaneous LE D-E junction obscured by mononuclear infiltrate. Cellular infiltrate more dense than in SCLE (A).

In this form the lymphohistocytic infiltration is largely confined to the papillary dermis and upper dermal edema may be a prominent feature. Similar histologic changes may be seen in biopsies taken from the maculopapular erythematous lesions of patients with dermatomyositis and, as will be discussed, in patients undergoing a graft-versus-host reaction.

The pathologic change in acute cutaneous LE may be quite subtle. The initial impression when looking under low power is that the skin is virtually normal. At higher magnification the distinctive changes along the dermal epidermal interface are seen. A few lymphocytes are present and a series of small vacuoles may be noted within and deep to the basal layer.

In general, the only histologic difference between chronic, subacute and acute cutaneous LE is the intensity and duration of the inflammatory process. Otherwise, the general histologic pattern of injury at the dermal epidermal junction is identical. Chronic, scarring, discoid lesions have the most dense cellular infiltrate which usually persists for months or years. In contrast, the evanescent butterfly rash of SLE has a sparse almost imperceptible, lymphocytic infiltrate. Thus, the pathologic changes in cutaneous LE define a spectrum extending from the chronic, scarring, discoid lesions at one end to the acute, evanescent, butterfly rash at the other with subacute cutaneous LE occupying an intermediate position.

B. Immunopathology of Cutaneous LE

Immunopathologic studies of tissue from LE skin lesions have shown that a majority have immunoglobulin deposits along the dermal epidermal junction [124]. Since this site corresponds to the principal area of cutaneous injury it has been suggested that antibody or antigen-antibody complexes play a primary role in the pathogenesis of these lesions [76]. However, several findings indicate that antibody or immune-complex mediated injury at this site is unlikely [37]. It is known that subepidermal immunoglobulin deposits are frequently present in clinically normal skin of patients with SLE [11,48,54,77,83] and that the presence of these "normal skin" deposits is inversely related to the presence of chronic LE skin lesions [38]. Furthermore, the appearance of subepidermal immunoglobulin deposits follows the inflammatory response in experimentally induced lesions by several weeks [17]. There is also evidence which suggests that antibody is produced locally in these chronic lesions which may contribute to the formation of subepidermal deposits [63]. In contrast, deposits in normal skin appear to be a result of circulating antibody to DNA [84,110]. Preliminary evidence suggests that DNA:anti-DNA complexes form in the skin and are localized along the dermal epidermal junction because DNA, released from the epidermis, binds to subepidermal connective tissue [42,78]. In addition to the lack of evidence for antibody related injury in LE skin lesions the histologic appearance of cutaneous LE, as described above, is more consistent with cell mediated immune injury.

C. Proposed Mechanism of Injury in Cutaneous LE

The earliest experimental evidence suggesting a primary role for cell mediated immunologic injury in cutaneous LE came from the studies of Stastny, Stembridge, and Ziff in 1963 [112]. These workers studied the cutaneous pathology of homologous disease in rats and demonstrated that the early skin lesions had prominent hydropic degeneration along the basal layer, remarkably similar to the changes in cutaneous LE. The more chronic lesions showed dermal sclerosis and replacement of hair follicles as seen in scleroderma. Several recent papers have described similar pathologic and clinical changes in the skin of patients with graft-versus-host disease following bone marrow transplanatation [50,65,98,104,133]. As shown in the figure, a characteristic lupus-like pattern of epidermal cell injury has been observed in skin biopsies from these patients [133].

Lerner, K.G., et al. Histopathology of Graft-vs-Host Reaction in Human ... Transplantation Proc. 6:367, 1974.

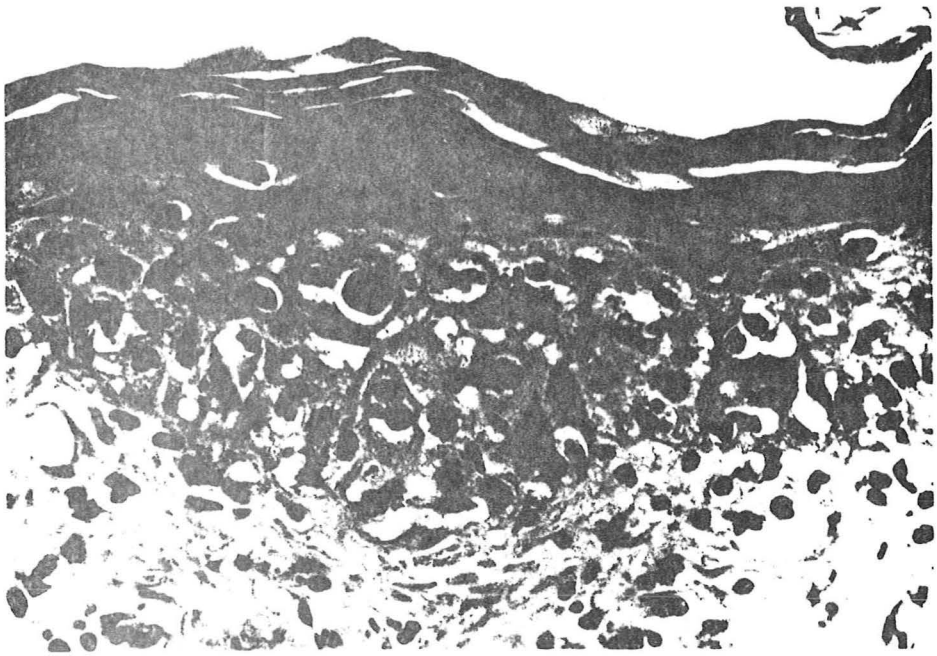
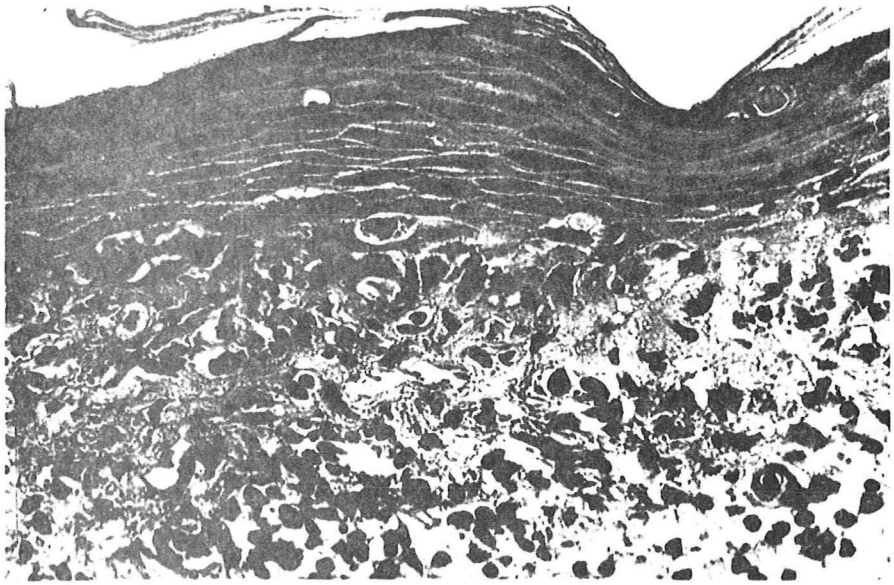


Fig. 1. Skin biopsy (×200) from 12-year-old male 37 days after marrow allograft for acute lymphocytic leukemia showing grade-II GvHR with basal vacuolar degeneration and necrosis, spongiosis, dyskeratosis and eosinophilic necrosis, and moderate dermal and epidermal lymphocytic infiltration.



Chronic Cutaneous LE D-E junction obscured by mononuclear infiltrate. Cellular infiltrate more dense than in SCLE. The histopathologic picture is strikingly similar to that shown in the above figure of the GVH reaction.

Listed below are the morphologic varieties of skin lesions that have been described in patients with GVH disease.

SKIN LESIONS IN PATIENTS WITH GRAFT-VERSUS-HOST DISEASE

1. Toxic epidermal necrolysis [8,82]
2. Poikiloderma vasculare atrophicans [50,104]
3. Lichen planus [99,104,120]
4. Discoid lupus erythematosus [46]
5. Scleroderma [29,46,64,104,111,128]

Lesions resembling drug induced toxic epidermal necrolysis may be seen in the acute GVH reaction of both humans and animals [8,82]. In chronic GVH disease skin changes which suggest a diagnosis of poikiloderma, lichen planus, discoid LE or scleroderma have been observed. Gratwhol and coworkers have reported a Sjögrens-like syndrome following allogeneic bone marrow transplantation with scleroderma skin lesions in one patient and DLE lesions in another [46]. These observations suggest that "activated" or "aggressor" lymphocytes may be responsible for a range of lupoid skin lesions. Local GVH reactions in animals have been found to produce striking angiogenesis (new vessel formation) which has been attributed to a lymphocyte derived angiogenic factor presumably from "activated" lymphocytes [105]. Such a factor could explain the prominent telangiectatic changes which serve as important clues for the clinical diagnosis of LE skin lesions.

Several recent observations have raised questions about the role of antibody in the genesis of these LE-like GVH skin lesions. Studies by Spielvogle, Ullman and Goltz [111] and Tsoi and coworkers [121] have demonstrated cutaneous immunoglobulin deposits (principally IgM) at the dermal epidermal junction and in dermal blood vessel walls. Merritt, Mann and Rogentine described a complement fixing IgM antibody specific for epithelial cells in serum from human subjects undergoing graft-versis-host reactions [71]. This antibody could be directed to minor histocompatibility antigens on epidermal cells (Langerhans cells). Alternatively, viruses might alter surface antigens on epidermal cells and provoke an antibody and/or cell mediated immune response resulting in similar pathologic and immunopathologic changes. Whether these recently discovered immune deposits or serum antibodies play a primary role in the genesis of GVH skin lesions or whether they appear as secondary phenomena following epidermal cell damage is not known. In any event both cellular and humoral systems seem to contribute to the immunopathology of GVH skin lesions resulting in a change that is very similar to cutaneous LE. The gross and microscopic similarity between the skin lesions of GVH disease and the collagen disease group is fascinating and suggest a common mechanism of injury.

V. CUTANEOUS LE SUBSETS: CLINICAL AND SEROLOGIC FEATURES

A. Chronic Cutaneous LE (DLE)

Studies of the immunologic derangements in patients with chronic cutaneous LE (DLE) have yielded variable results [6,23,69,95,96]. Differences of opinion regarding both the clinical course and laboratory findings in these patients reflect two basic difficulties: 1) failure to strictly define the group being studied and 2) failure to use standardized and carefully controlled tests. When patients are selected by the presence of chronic cutaneous LE (DLE) excluding all those with evidence of visceral involvement by history or physical examination only a small number will have detectable immunologic abnormalities [91,92,95]. The clinical and laboratory findings from 80 patients that met the above criteria are summarized in the following tables:

CLINICAL FEATURES OF 80 PATIENTS WITH DLE [92]

Head and/or neck involvement	96%
Generalized DLE (lesions above and below the neck)	42%
Photosensitivity	60%
Mucous membrane lesions	4%
Nail fold changes (periungual erythema and/or telangiectasia)	0%

LABORATORY FINDINGS IN DLE PATIENTS [92]

Erythrocyte sedimentation rate (< 20mm/hr)	56%
Anemia (HB < 11g/100 ml)	2%
Leukopenia (WBC < 4500 per mm^3)	7%
Biologic false positive VDRL	3%
Positive LE cell preparation	0%
Positive antinuclear antibody test	
Rat kidney substrate (norm. 0 pos.)	4%
KB cell substrate (norm. 12% pos.)	30%
Native DNA antibodies	0%
Rheumatoid factor	1%

As illustrated in the above tables, DLE patients without manifestations of visceral involvement have little underlying hematologic or immunologic abnormality. The skin lesions are generally located above the neck although a number of patients may have lesions both above and below the neck therefore fitting O'Leary's definition of generalized DLE [78]. A few patients have extensive lesions involving the neck, back, shoulders, forearm and occasionally the legs. Some writers believe that patients with such widespread lesions are

more likely to develop systemic disease, however there is no evidence to support this concept and others have denied it [68,79,116]. The term disseminated DLE has frequently been used for this widespread variety of chronic cutaneous LE. However, this term should probably be avoided since disseminated LE has also been used for the systemic (or acute, generalized) variety. Here constitutional symptoms, multiple-system involvement and laboratory abnormalities are the main findings and skin manifestations may or may not be present. In contrast the skin lesions are the main and generally the only findings of chronic, cutaneous LE, both in the localized and generalized forms. The following case history illustrates some of the above points.

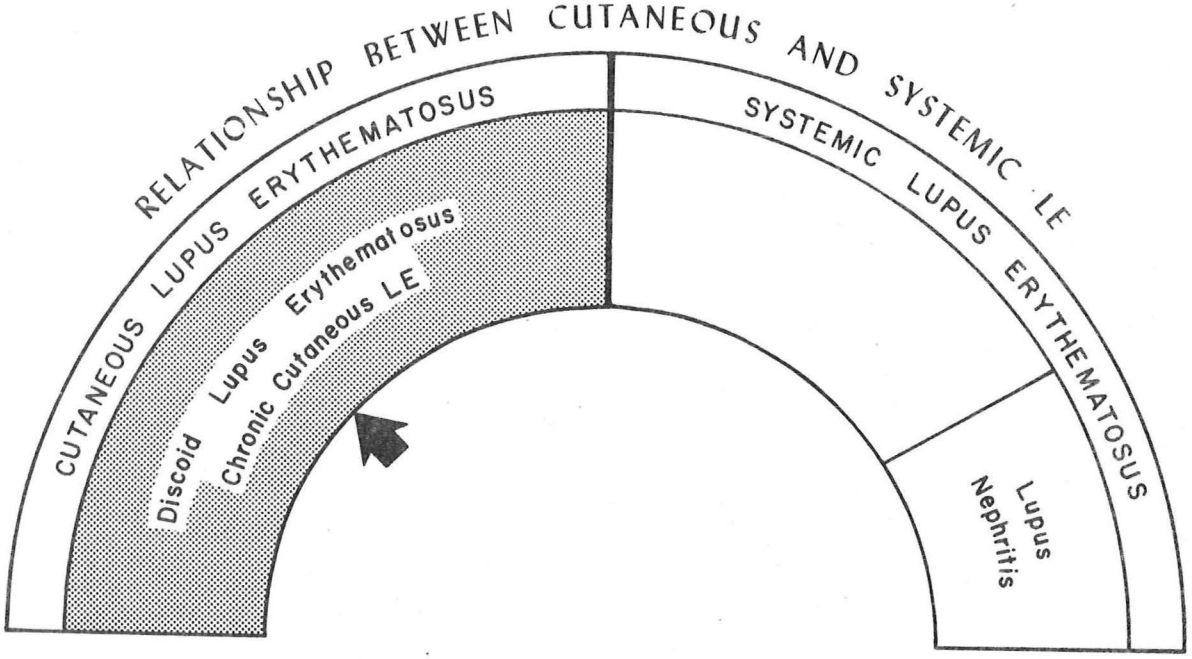
> Case I, PMN # 20-36-09: P. W. first developed erythematous, scaly, atrophic well-demarcated plaques on her face and scalp in 1961 when she was 46 years old. The lesions slowly spread to involve the entire scalp producing total scarring alopecia. She had no history of joint pain, fever, or other evidence of systemic involvement. Antinuclear antibodies, serum complement levels, VDRL and rheumatoid factor tests were all negative. Eleven years later, in December of 1972, she was referred to the Parkland Clinic after the onset of weight loss, cough, general malaise and dissemination of the cutaneous lesions over her trunk and upper extremities. A complete evaluation at the time failed to demonstrate any evidence of systemic LE. However, the chest x-ray revealed a density in the left lower lobe, which proved to be adenocarcinoma. In May of 1976, four years after diagnosis and resection of her lung cancer, evidence of recurrent adenocarcinoma with metastasis to the right lung was detected. She received cobalt therapy to the chest and mediastinum and afterward her antinuclear antibody test became postitive in a significant titer for the first time. In March, 1977, at age 62 (16 years after the initial diagnosis) she died of metastatic carcinoma without any evidence of systemic LE.

As indicated above a search for abnormal laboratory values in cases of DLE is generally unrewarding. Some workers have reported a relatively high incidence of abnormal laboratory findings [23] but this discrepancy can be explained by a lack of uniformity in patient selection and laboratory techniques. Most cases of discoid LE do not present difficulty in diagnosis. In doubtful cases histopathologic examination is usually definitive enough to allow a diagnosis.

The prognosis in patients with DLE is excellent. It is quite rare to see any of these patients acquire systemic lupus erythematosus. The incidence of transition from either localized or generalized discoid LE to SLE is less than 5% [100]. On the other hand, a small percent of patients with SLE have discoid LE for periods up to 25 years before developing multisystem disease [134]. The frequency of discoid LE as the presenting feature of patients with SLE varies from 8 - 16% in several large published series [24,28,119,123,132]. These SLE patients with DLE skin lesions have a milder form of systemic disease, as will be discussed later. One should keep these points in mind when the

diagnosis of DLE is made since patients are often frightened when their physician fails to alert them to the fact that DLE, unlike SLE, is almost always a local and self-limited disease process [103,116].

In summary, discoid LE is a benign though sometimes disfiguring skin disease which is rarely associated with visceral involvement. The diagnosis can usually be made clinically and confirmed on the basis of characteristic histologic and immunopathologic findings. Chronic cutaneous LE (DLE) occupies the most benign end of the LE spectrum as shown in the figure below.



B. SLE with DLE Skin Lesions (SLE/DLE)

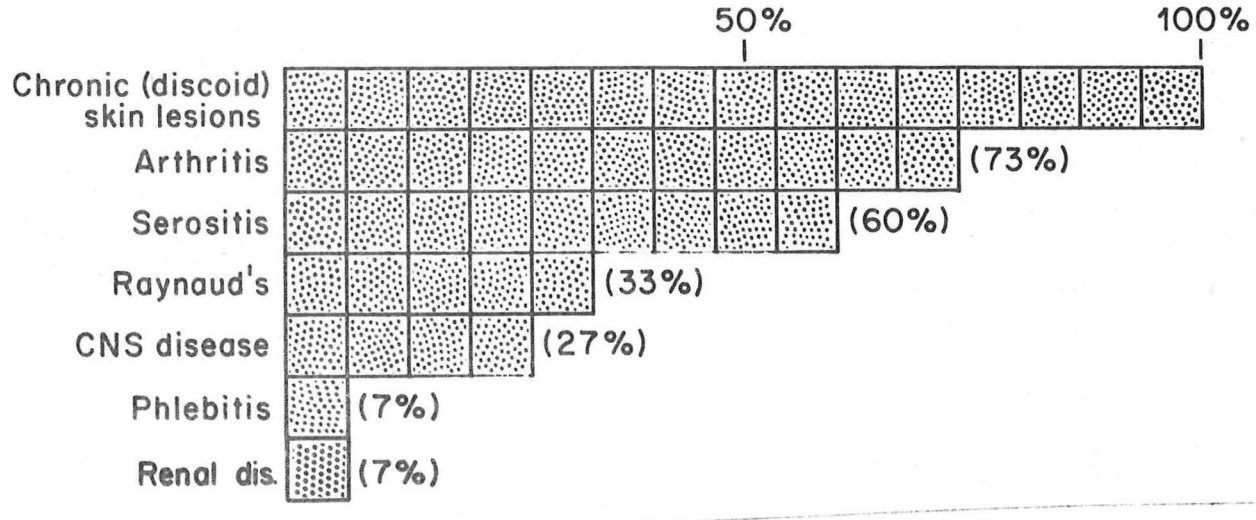
Case II, PMN # 12-72-94, J. D.: This 38 year old black woman developed discoid lupus erythematosus at the age of 26. Ten years later she developed symmetrical polyarthralgias, involving primarily the wrists and many MCP and PIP joints. A skin biopsy was taken and the histologic diagnosis of cutaneous LE was made. The RA latex test and the sensitized sheep cell agglutination

tests were both strongly positive and the antinuclear antibody test was negative. There was no history of Raynaud's phenomenon, serositis, seizures, prolonged fever, mucous membrane ulcerations, alopecia or renal disease. Physical examination revealed scattered, inactive, sharply marginated, scarred lesions on the face, scalp, ears, palms and soles. There was moderate joint tenderness with some synovial thickening of the wrists and several MCP and PIP joints. The lungs and heart were normal. There was no adenopathy or hepatosplenomegaly.

During the next several months her arthritis remained active. Subsequent laboratory evaluation disclosed a positive ANA test in high titer (speckled pattern) and a total gamma-globulin level of 3.4 gm/dl. Direct immunofluorescence staining of skin biopsies showed immunoglobulin deposits at the dermal epidermal junction in lesional but not normal skin. The following year (1974) she began to complain of episodic pain and discoloration of the tips of her fingers when exposed to cold and had findings typical of Raynaud's phenomenon. Widespread lymphadenopathy was also detected. The antinuclear antibody test was persistently positive in a high titer (speckled pattern) and the anti-DNA test was negative.

This patient demonstrates a transition from chronic cutaneous or discoid LE to systemic disease. As mentioned, such transitions are uncommon (occurring in no more than 5%) but data from large series of SLE patients indicates that approximately 15 to 20% have discoid skin lesions [95]. The chronic cutaneous lesions in these SLE patients are histologically and clinically identical to those seen in patients with uncomplicated DLE. Prospective analysis of such patients has suggested that as a group SLE patients with discoid lesions (SLE/DLE) have a more benign clinical course with less severe renal disease [26,33]. The clinical manifestations of 15 Parkland patients with systemic lupus erythematosus and discoid skin lesions is shown in the figure below [90].

CLINICAL MANIFESTATIONS OF SLE PATIENTS WITH DISCOID SKIN LESIONS



The most striking clinical feature of this patient group is the low incidence of clinically apparent renal disease. One patient had profuse proteinuria and a renal biopsy that showed histologic changes consistent with membranous glomeruonephritis. During a four year follow-up period she continued to have moderate proteinuria without evidence of deteriorating renal function. She was treated intermittently with steroids in moderate doses and hydroxychloroquine. As shown in this figure, arthritis and episodes of serositis (pleurisy and/or pericarditis) were the most common extracutaneous manifestations in this group of patients. Raynaud's phenomenon was present in five of the 15 patients (33%) and central nervous system involvement occurred in the same proportion seen in unselected SLE patients [24,119].

Antinuclear antibodies were present in 93% when tested during periods of active disease as shown in the table below [90]. This is similar to the incidence of ANA positivity in other active SLE patients [91] but vastly different from the low incidence in DLE patients without systemic disease [92].

FLUORESCENCE ANTINUCLEAR ANTIBODY (FANA) TEST
NUCLEAR STAINING PATTERNS IN PATIENTS WITH DLE AND SLE/DLE

Group	No. Tested	Positive FANA Test*		
		No.	%	
DLE	80	3	4	
				$p < .001$
SLE/DLE	15	14	93	
Healthy controls (blood bank donors)	100	0	0	

* Positive FANA test using rat kidney sections as the nuclear substrate at serum dilutions of 1:16.

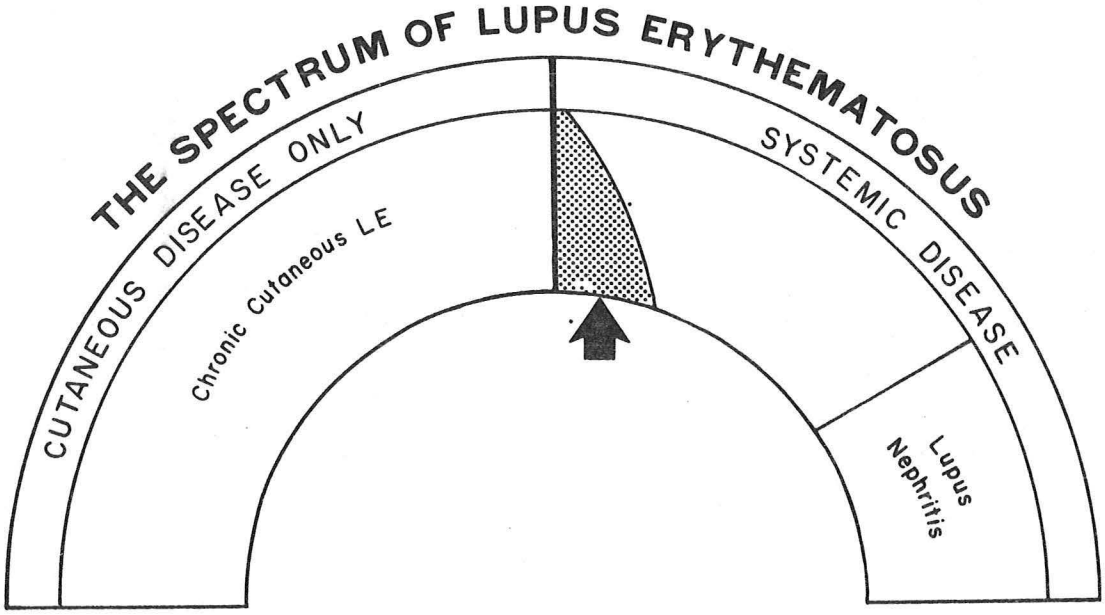
Subepidermal immunoglobulin deposits in apparently normal volar forearm skin was demonstrated in three of the 15 SLE patients with discoid skin lesions. Such deposits are not found in the normal skin of patients with uncomplicated discoid LE but are frequently observed in skin from patients with severe systemic LE and high serum concentrations of antiDNA antibodies.

SUBEPIDERMAL IMMUNOGLOBULIN DEPOSITS IN VISIBLY NORMAL (VOLAR FOREARM) SKIN

Study Group	No. Tested	Subepi Ig Deposits No.	Subepi Ig Deposits %
DLE	27	0	0
SLE/DLE	15	3	20
SLE (unselected)	42	23	55
Hospitalized controls	20	0	0

As in patients with chronic cutaneous LE, the patients with SLE and discoid skin lesions did not have significant elevations of anti-DNA antibodies or low serum complement levels [90].

These findings add support to the concept that SLE patients with chronic scarring discoid skin lesions (SLE/DLE) have a relatively benign disease. SLE/DLE patients generally do not produce large amounts of anti-DNA antibody which may explain the relatively low incidence of deposits in normal skin and the rarity of severe renal disease. This SLE/DLE subset is characterized by chronic skin and musculoskeletal complaints with little tendency to develop the usual life threatening complications of SLE. The figure below illustrates the position these patients occupy on the LE spectrum.



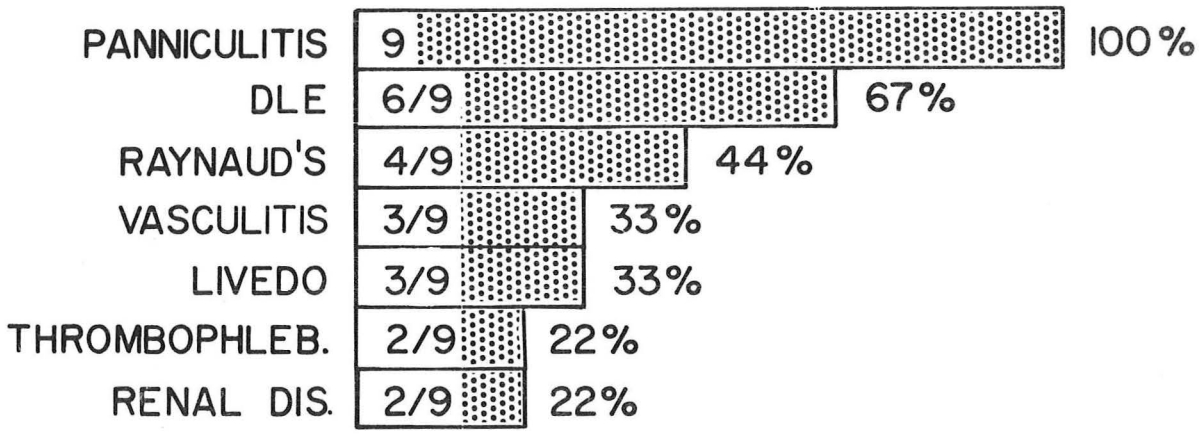
C. LE Profundus or Lupus Panniculitis

Case III, PMN # 05-90-78: D. E., a 59 year old black woman has had a twenty year history of polyarthritis and a positive serologic test for syphilis. In 1962, at age 35 she was diagnosed as "possible SLE" following an episode of pleuritis and pericarditis. A weakly positive antinuclear antibody test was detected at that time. She continued to complain of arthritis over the next two years, however, her ANA was positive at a low titer only occasionally. When seen in November 1962 she had alopecia, easy fatigability and mild arthritis. Her serum gammaglobulin level was increased (3.3 gm/dl), the erythrocyte sedimentation rate was 80 mm/hr and her total white count was 3,500 per mm^3. A urinalysis was within normal limits. Throughout this period (1962-1964) numerous LE preparations were negative. In May, 1966, four years after the initial diagnosis of "possible SLE" she was reevaluated in the arthritis clinic. In the absence of further episodes of pleurisy, fever or other symptoms of SLE it was decided that she probably had mild rheumatoid arthritis. In 1970, the patient developed erythematous, scaly and scarring lesions on the face. Several months later scattered, ill-defined, erythematous nodular facial lesions appeared at sites that were not involved by the discoid skin lesions. A biopsy of one of these nodular lesions revealed dense collections of lymphocytes in the deep dermis and epidermis. Biopsies from the sites of superficial scaling, erythema and atrophy revealed changes typical of discoid LE. Over the past seven years (1971-1978) the patient has continued to have intermittent arthritis, arthralgias, leukopenia and antinuclear antibodies at a titer of 1:160. ENA and DNA antibody tests have been consistently negative. The erythematous nodular skin lesions as well as the discoid skin lesions have improved with antimalarial therapy. She has not developed evidence of renal disease and her arthritis is nondeforming and nonerosive.

Persistent subcutaneous nodules have been recognized as a feature of LE for almost 40 years [52]. This form of cutaneous LE known as lupus profundus or lupus panniculitis has been dealth with almost exclusively in the dermatologic literature [74,122]. The relationship between lupus profundus and other clinical presentations of lupus erythematosus is still only partially understood. Data from a review of the literature suggests that approximately 40 to 50% of patients with LE panniculitis have or will develop manifestations of systemic disease [49,59,122,135]. This is in striking contrast to patients with simple DLE. The lesions of lupus profundus begin as firm, non-tender, deep nodules which evolve in time to produce atrophic depressed areas with attachment of the overlying skin. Such lesions are commonly located on the scalp, face, deltoid and subdeltoid areas, buttocks, thighs and breast. Firm nodular lesions in the breast may simulate carcinoma as emphasized recently by Harris and Winkelmann in an article entitled "Lupus mastitis" [57]. Soft tissue x-rays of these lesions may show subcutaneous calcification and the histologic picture may be diagnostic [32]. However, skin biopsies and other surgical procedures should be approached with some caution since they may produce chronic, non-healing lesions which are quite difficult to manage. The

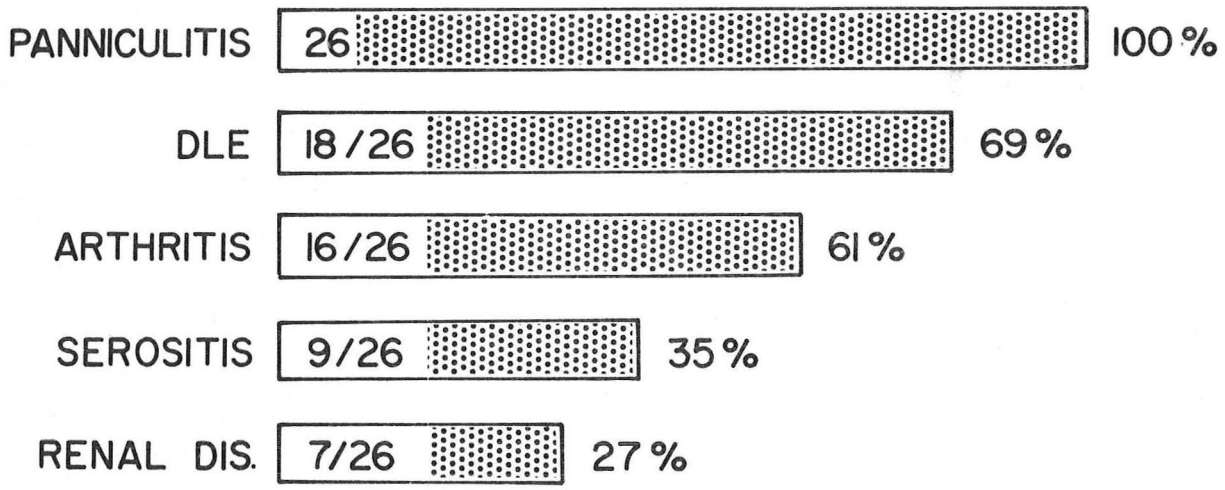
lesions of lupus panniculitis or lupus profundus may also spontaneously ulcerate leaving deep ulcers which penetrate the subcutis to the fascia. The figure below gives the incidence of the more common clinical manifestations in nine patients with lupus panniculitis.

CLINICAL MANIFESTATIONS OF PATIENTS WITH LUPUS PANNICULITIS (LUPUS PROFUNDUS)

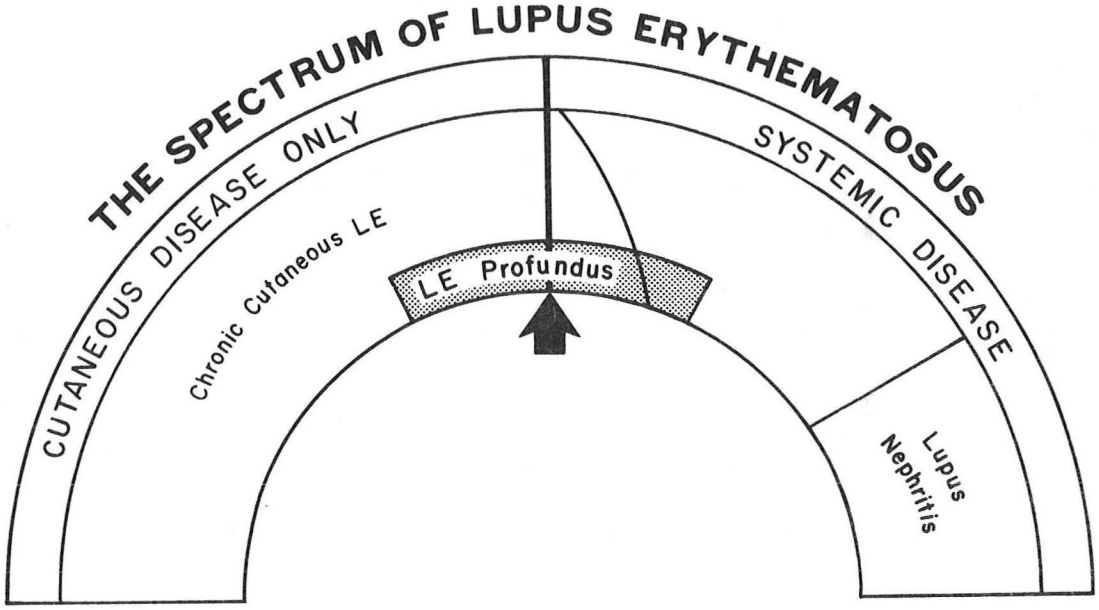


This data was derived from a report of six cases [21] plus three patients followed in the Parkland Clinic. A constant and well recognized feature of this subset is the frequent association of DLE. The incidence of vascular involvement of various types is also impressive in this small group. Renal disease is present in a minority of cases and death from renal failure appears to be uncommon [135]. Data from a larger number of patients reported by Zweiman [135] are summarized in the figure below.

CLINICAL MANIFESTATIONS OF PATIENTS WITH LUPUS PANNICULITIS (LUPUS PROFUNDUS)



Again the most striking feature is the high incidence of chronic cutaneous LE and the relatively low incidence of renal disease. In general, patients with LE panniculitis appear to have relatively benign form of SLE similar to that seen in other SLE patients with chronic scarring or discoid type skin lesions. Thus, patients with chronic cutaneous LE of the discoid type who have in addition lupus profundus will more often show evidence of systemic disease. Based upon this information patients with lupus profundus also appear to occupy an intermediate position on the LE spectrum as illustrated in the figure below.



D. Subacute Cutaneous LE (SCLE)

Case IV, PMN # 48-73-89: L. B., a 20 year old white man was well until May, 1974, when he developed a widespread, red scaly rash over the exposed parts of his body. This eruption was initially diagnosed as psoriasis. In July, 1974, bullous lesions appeared following sun exposure and he was referred to a dermatologist. A diagnosis of lupus erythematosus was made on the basis of a skin biopsy and two positive LE preparations. During the summer of 1974, he had intermittent episodes of fever to 103° orally. He developed lymphadenopathy, polyarthritis and marked fatigability.

In September, 1974, he was referred to the Parkland Special Dermatology Clinic where the following was observed: a diffuse, erythematous scaly eruption over the face, upper chest, back, shoulders, and extensor aspect of both arms with sparing of the axilliary areas and the medial portion of the arms. There was diffuse scalp hair thinning. A fundascopic examination revealed cytoid bodies. A large superficial erosion was present on the hard palate. There was marked cervical axilliary and inguinal lympadenopathy. Cardiac and chest examination were unremarkable. The

spleen was palpable. There was slight tenderness to palpation over the right ankle and left knee and decreased range of motion of these joints. The left knee showed a moderate efusion. The neurologic exam was normal.

The total white blood count was 3,700 per mm^3 (750 lymphocytes per mm^3) and the erythrocyte sedimentation rate was 120 mm per hour. The hematocrit and hemoglobulin were low (Htc 29 vol %, Hgb 10 gm/dl). The Coombs test was positive. The blood urea nitrogen was 23 mg/dl with a creatinine of 0.9 and a creatinine clearance of 87 cc/min. Protein excretion in a 24 hour urine specimen was 2.1 grams. The antinuclear antibody test was positive with a peripheral pattern at 1:640 and a speckled pattern at 1:1280. An LE prep was positive. The serum complement level was depressed, the antinative DNA test and the RA latex test were positive. A serum protein electrophoresis revealed a decreased albumin and a polyclonal increase in gammaglobulin. A skin biopsy was interpreted as showing changes consistent with lupus erythematosus. Immunofluorescence staining of normal (flexor forearm) and lesional skin revealed deposits of IgG, IgM and IgA at the dermal-epidermal junction. A renal biopsy was considered but deferred after an IVP revealed a congenital fusion of the kidneys.

The patient was placed on 60 mg of prednisone per day in divided doses, and during the next two to three months he experienced marked improvement in his symptoms with disappearance of the fever, arthritis and lymphadenopathy. The complement and anti-DNA levels returned to normal and subsequent examination of his urine revealed a normal sediment and only a trace of protein. With normalization of his laboratory studies and disappearance of his symptoms, the prednisone was gradually reduced and within six months (March, 1975) he was on 35 mg per day. On this dose his skin disease reappeared and has been persistently present since that time. Hydroxychloroquine (Plaquenil) was added without benefit and after four months discontinued.

Two years after the onset of his disease (May, 1976) he was readmitted following a grand mal seizure. Except for transient EEG abnormalities an extensive seizure workup was entirely normal. In spite of negative lupus serological test and absence of clinical features to suggest SLE activity it was assumed that the seizure was a manifestation of the systemic LE. During the past two years serologic studies have shown positive (speckled pattern) anti-nuclear antibodies in high titer, positive antibodies to the RNAase insensitive component of ENA by hemagglutination (anti-Sm), negative anti-DNA antibodies, normal complement levels, normal BUN and creatinine. Renal function has been stable and in the normal range. The major problem has been the extensive persistently active skin disease which has failed to respond to intensive topical therapy, prednisone in moderate (30 mg) to large (60 mg) doses, hydroxychloroquine and immunosuppressive agents.

This patient has widespread, non-scarring subacute cutaneous LE (SCLE) with moderately severe systemic disease. This variety of LE skin disease has not generally been regarded as a distinct form of cutaneous LE separate from DLE [109]. This histologic and clinical pattern is similar to DLE, but there are distinct differences between subacute cutaneous LE and locallized or generalized DLE. SCLE is non-scarring, less persistent and well-fixed than DLE. SCLE lesions are usually widespread, have a tendency to coalesce and most importantly, appear to be commonly associated with overt systemic manifestations of LE [109]. Subacute cutaneous LE corresponds with the symmetrical, non-fixed, non-scarring, superficial eruption classified as symmetrical erythema centrifugum by Brocq in 1925 [62]. Neither this term nor the concept that it represents a distinct form of cutaneous LE has been accepted. For this reason many different names have been used for this variety of cutaneous LE (see table below). General physicians frequently call it the photosensitive or systemic "lupus rash" [28]. Most modern dermatologists use the term disseminated discoid LE. Unfortunately, the name "disseminated discoid LE" blurs the distinction between SCLE and the true generalized scarring DLE as defined by O'Leary [78] and illustrated by Case I. Since the pathologic changes in this diffuse superficial form of cutaneous LE seem intermediate between the chronic destructive variety (DLE) and the transient acute malar rash we feel that the term subacute cutaneous LE is appropriate.

ALTERNATE TERMS FOR SUBACUTE CUTANEOUS LE

Symmetrical erythema centrifugum (Brocq)

Disseminated discoid LE

Generalized DLE

Superficial lupus rash

Photosensitive lupus rash

Systemic lupus rash

Subacute disseminated cutaneous LE

Psoriasiform LE

Autoimmune annulare erythema

Erythema annulare centrifugum

Over the past seven years 27 patients with this form of cutaneous LE have been identified from patients seen at Parkland and the private referral clinic. During this same interval almost 300 patients with either discoid or systemic LE have been seen suggesting an incidence of approximately 10%. The sex, age and racial distribution and duration of disease are listed in the table below.

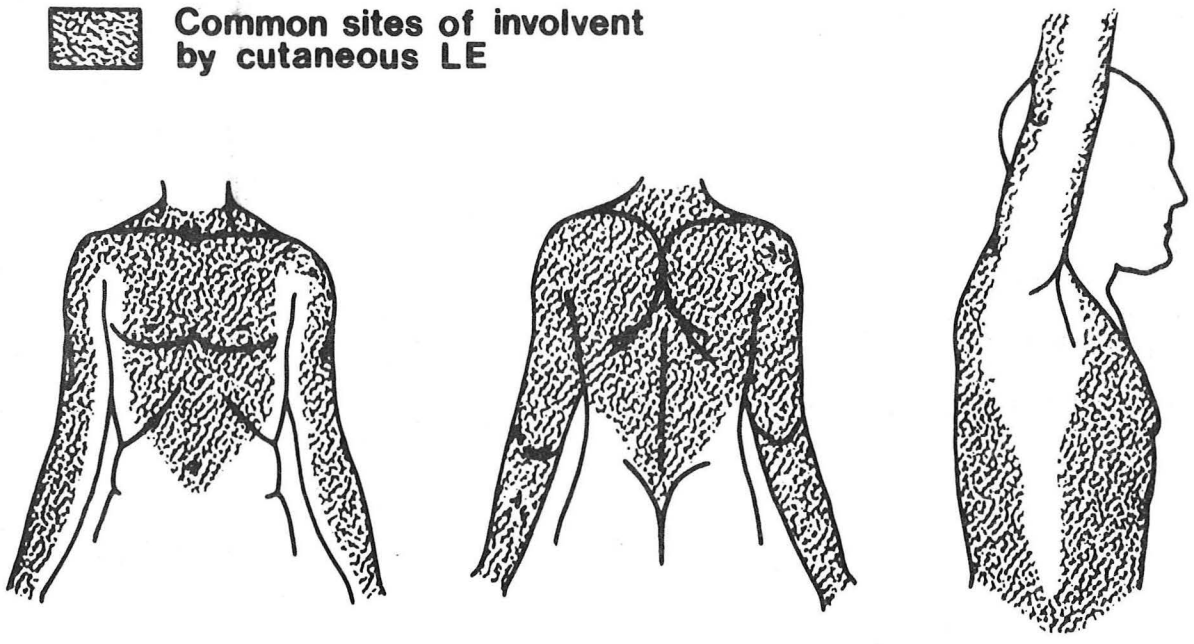
SEX, AGE, RACIAL INCIDENCE AND DISEASE DURATION IN PATIENTS WITH SCLE

	Sex	Age (Yrs.)		Race (No. of Pts.)			Disease Duration (Yrs.)	
	No. of Pts. (%)	Mean	(Range)	W+	B++	LAm+++	Mean	(Range)
FEMALES	19 (70)	44.3	(19-59)	16	3	-	5.3	(.08-32)
MALES	8 (30)	41.0	(17-67)	7	-	1	2.9	(1-4)
TOTAL	27 (100)	43.3	(17-67)	23	3	1	4.5	(.08-32)

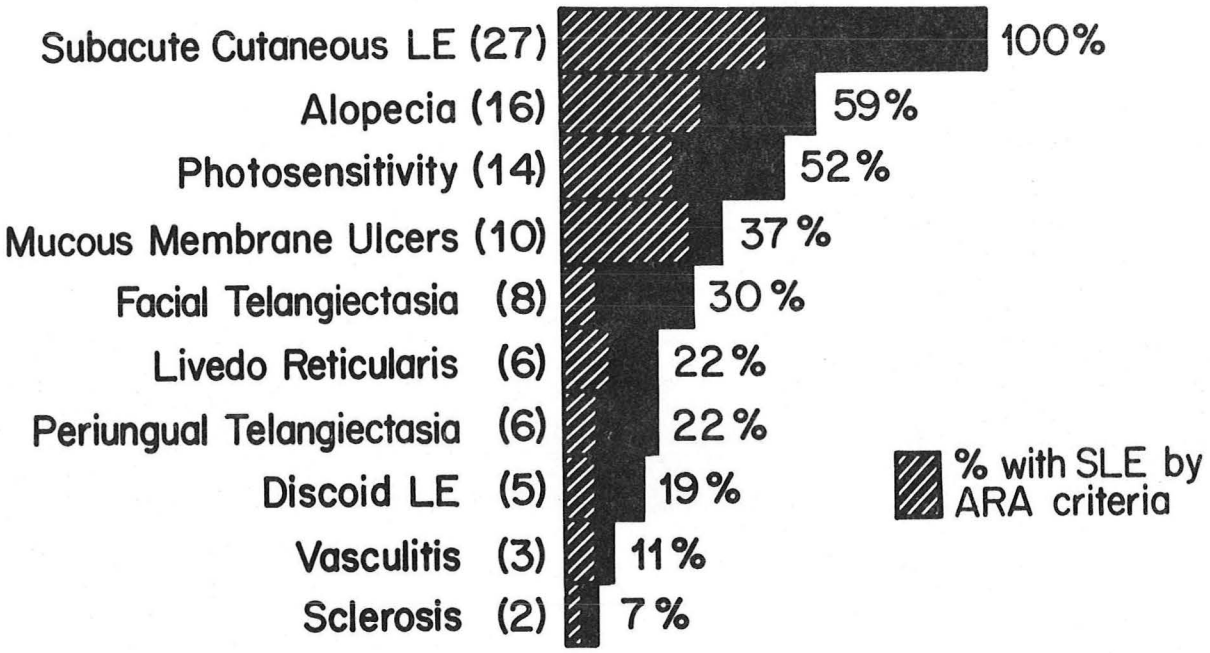
\+ White ++ Black +++ Latin American

Nineteen (70%) of the patients were female and eight (30%) were male. The mean age of the entire group was 43.3 years with a range of 17 - 67 years. Twenty-three were white (85%), three were black (11%) and one was Latin American (4%). The mean duration of skin disease for the entire group was 4.5 years, ranging from one month to 32 years.

Two morphological varieties of SCLE have been seen with one or the other usually predominating. A papulosquamous or psoriasiform pattern was present in some patients as demonstrated by the above case. Others had annular lesions which tended to coalesce, producing polycyclic gyrate configurations. Occasionally both patterns were present in the same patient. The lesions spare the knuckles, inner aspect of the arms, axillia, and lateral trunk as shown in the figure below.

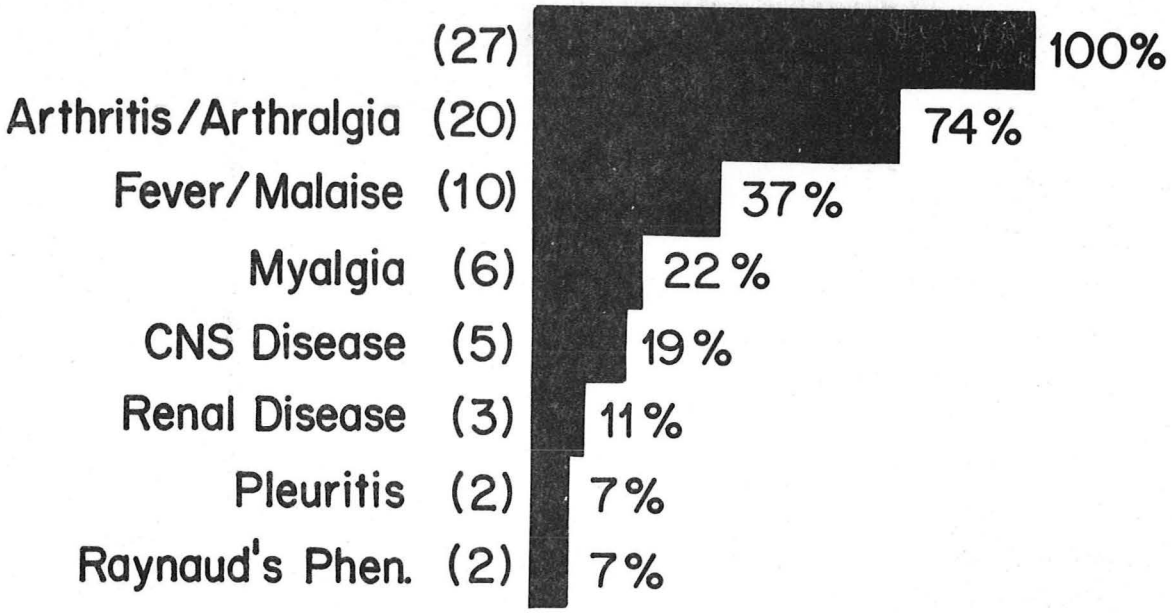


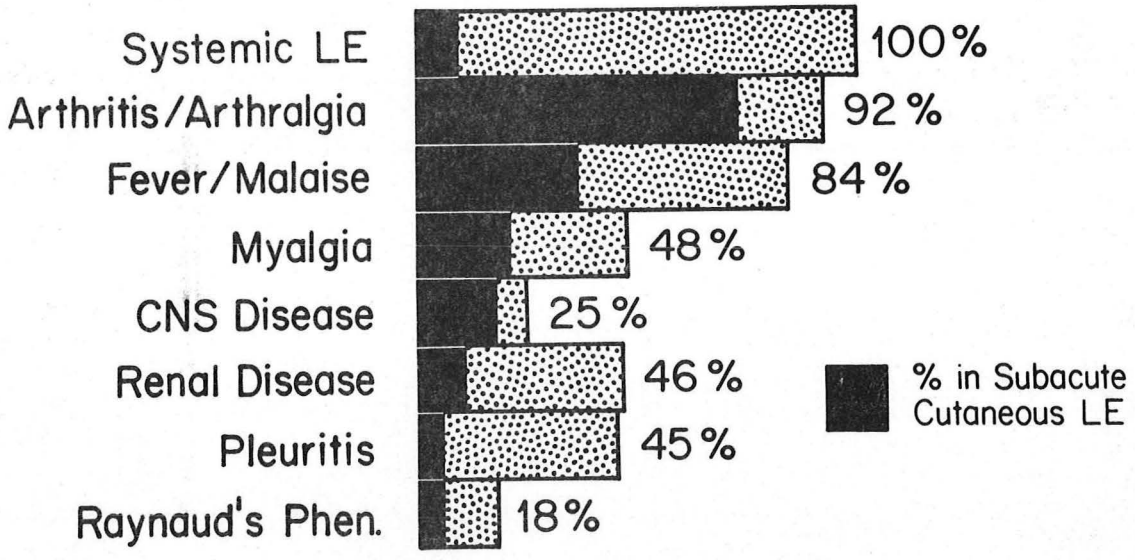
SCLE lesions are rarely seen below the waist. Subtle greyish hypopigmentation and telangiectasis are frequently seen in the center of the annular lesions which are bordered by erythema and a superficial scale. Follicular plugging and adherent hyperkeratosis are uncommon features of SCLE and scarring with dermal atrophy is absent. The disease has an exacerbating and remitting course often lasting for several years. As individual lesions resolve, hypopigmentation and telangectasia may become more evident. The dyspigmentation will usually persist for many months but eventually fades. The telangiectatic changes occasionally remain indefinitely. Other dermatologic features of this group are illustrated below.



Diffuse non-scarring alopecia occurs in 59%, photosensitivity in 52%. Mucous membrane ulcers often involving the hard palate were seen in 37%. These occurred most often in patients with ARA criteria for SLE [16]. Livedo reticularis and periungual telangiectasia were observed in about one-fifth of the SCLE patients. Nineteen percent had localized DLE skin lesions. The DLE usually occurred on the scalp as a single lesion and often preceded the onset of SCLE by many years.

Forty-eight percent of the patients with SCLE had at least four or more ARA criteria for SLE [16]. The figures below illustrate the incidence of different systemic manifestations in SLE patients with SCLE and compare these findings with the manifestations in a large published series of SLE patients [24].

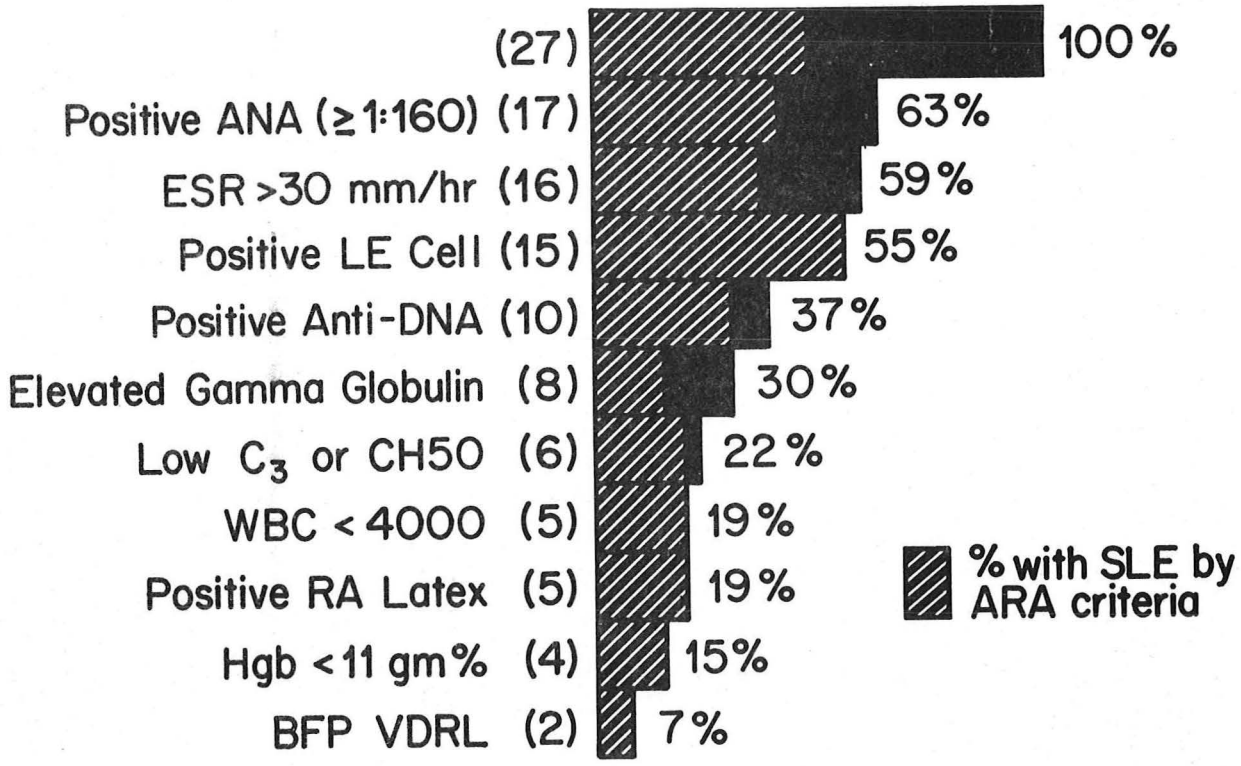




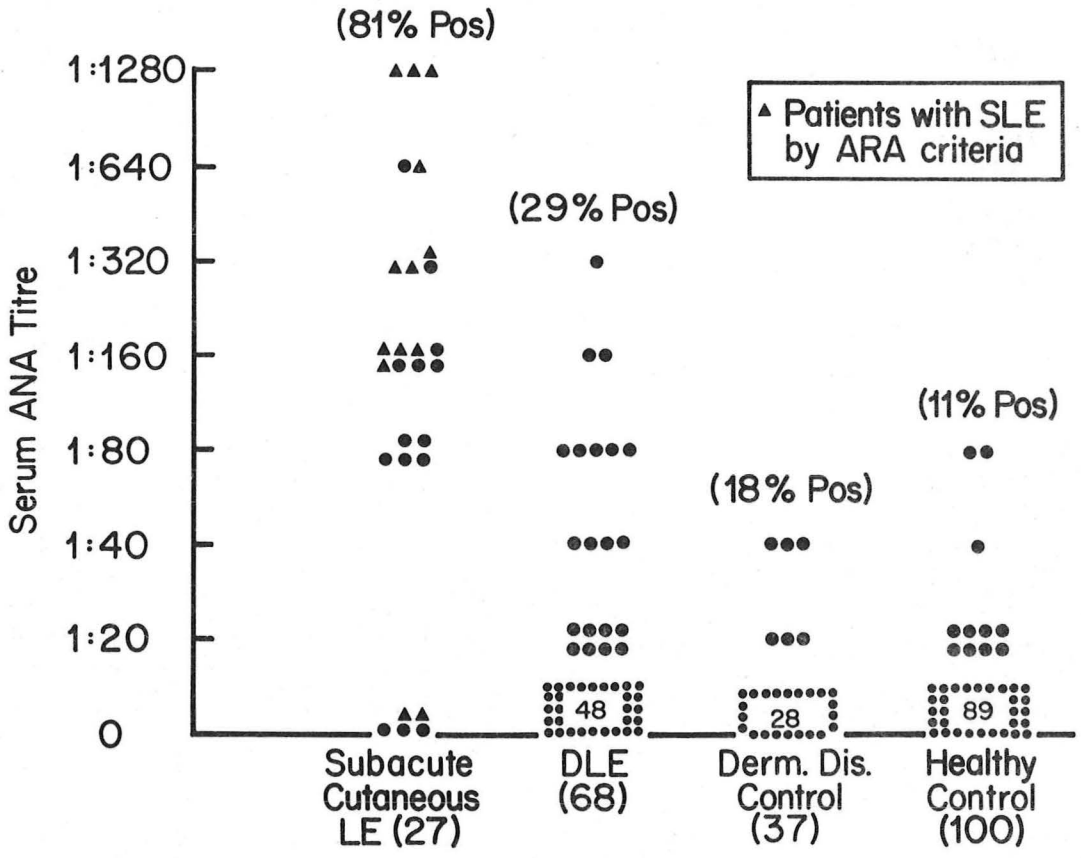
Dubois, EL Tuffanelli, DL: Clinical Manifestations of SLE JAMA 190: 104-111, (Oct. 12) 1964

Arthritis or arthralgia was the most frequent extracutaneous manifestation occurring in 74% of the patients. Fever and malaise were seen less often, occurring in 37% of the group. Central nervous system involvement occurred in about one-fifth of the patients; however, severe CNS disease was not seen. Three patients had thought disorders and one (Case IV) had an unexplained seizure disorder. Renal disease was seen in only three (11%) of the subacute cutaneous LE patients. Two had renal biopsies. One showed focal mesangial glomerulitis and the other had diffuse proliferative glomerulonephritis with mesangial and endothelial cell proliferation. These two patients have been followed for three and six years, respectively, and both have normal renal function at the present time. The patient with the diffuse proliferative lesion was treated for 18 months with cyclophosphamide and prednisone. The patient with mesangial glomerulitis received prednisone alone in moderate dosage.

The laboratory findings in the SCLE patients are summarized in the figure below. Erythrocyte sedimentation rates and ANA tests were abnormal in slightly more than half of the patients. LE cell preparations were also frequently positive. All the patients with positive LE preps had ARA criteria for SLE. DNA antibodies were present in low levels in ten of the patients. Eight of whom had four or more ARA criteria for SLE. Depressed complement levels, leukopenia, and positive rheumatoid factor tests occurred in about one fifth of the patients.



Eighty-one percent of the SCLE patients had detectable antinuclear antibodies using a relatively sensitive (KB epithelial cell) nuclear substrate (see figure). With same assay 29% of the patients with DLE were positive in low titers. Sixty-three percent of the SCLE patients had ANA titers equal or greater than 1:160, the range often found in SLE sera. Only 4% of patients with DLE have ANA titers in this range [91,92]. The SCLE patients with SLE by ARA criteria had the highest ANA titers ranging from 0 to 1:1280 with a mean of 1:160.



Note: ANA tested with KB cell substrate

The ANA fluorescence patterns were homogenous and particulate in all with the exception of two peripheral patterns. The following tables and figures compare fluorescence antinuclear antibody tests, subepidermal immunoglobulin deposits in visibly normal skin, anti-native DNA and total hemolytic complement levels in patients with DLE, patients with SLE and DLE (SLE/DLE), SCLE patients and patients with SLE and nephritis. Notice that the patients with SCLE and SLE/DLE have disease manifestations which are intermediate when compared to DLE and LE nephritis.

FLUORESCENT ANTINUCLEAR ANTIBODY (FANA) TEST *
AND NUCLEAR STAINING PATTERNS

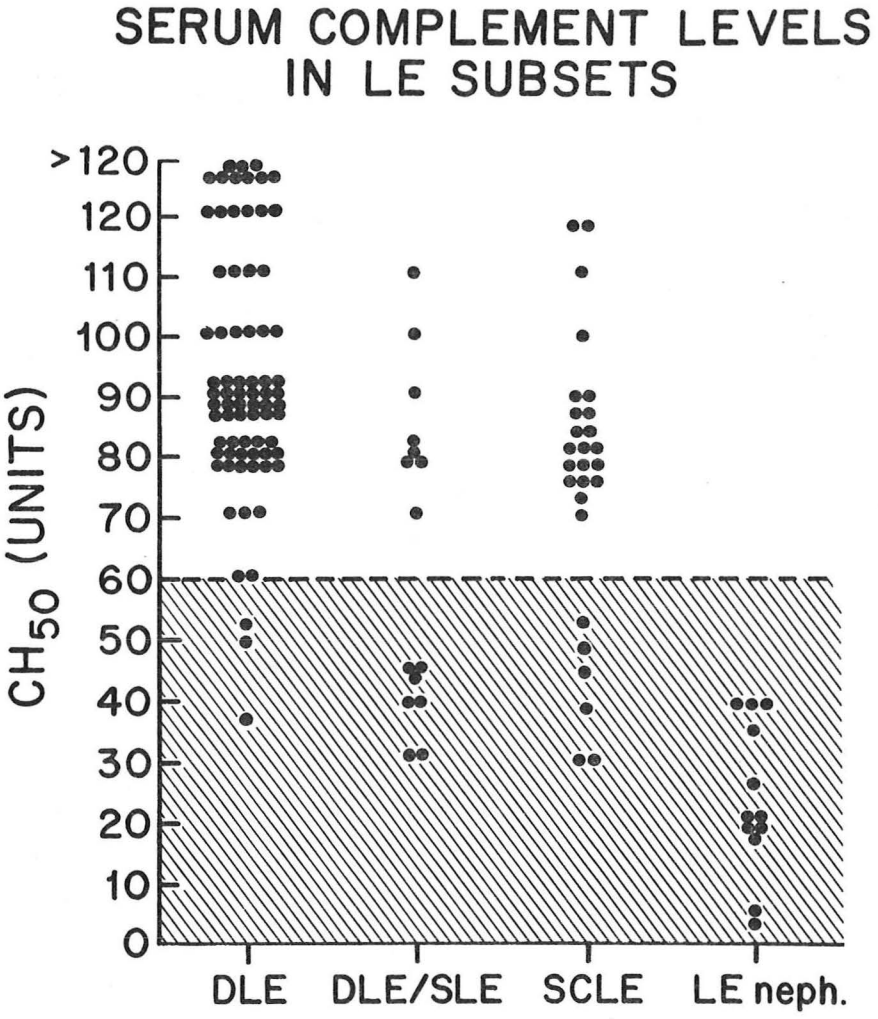
GROUP	NO. TESTED	POSITIVE ** FANA TEST		PATTERN		
		NO.	%	P	H	S
DLE	80	3	4	...	...	3
SCLE	27	17	63	2	10	12
DLE/SLE	15	14	93	...	9	5
SLE NEPH.	13	13	100	6	5	2

* ANA test using rat kidney sections (RKS) as substrate. This test is 10 fold less sensitive than ANA test using KB cell substrate.

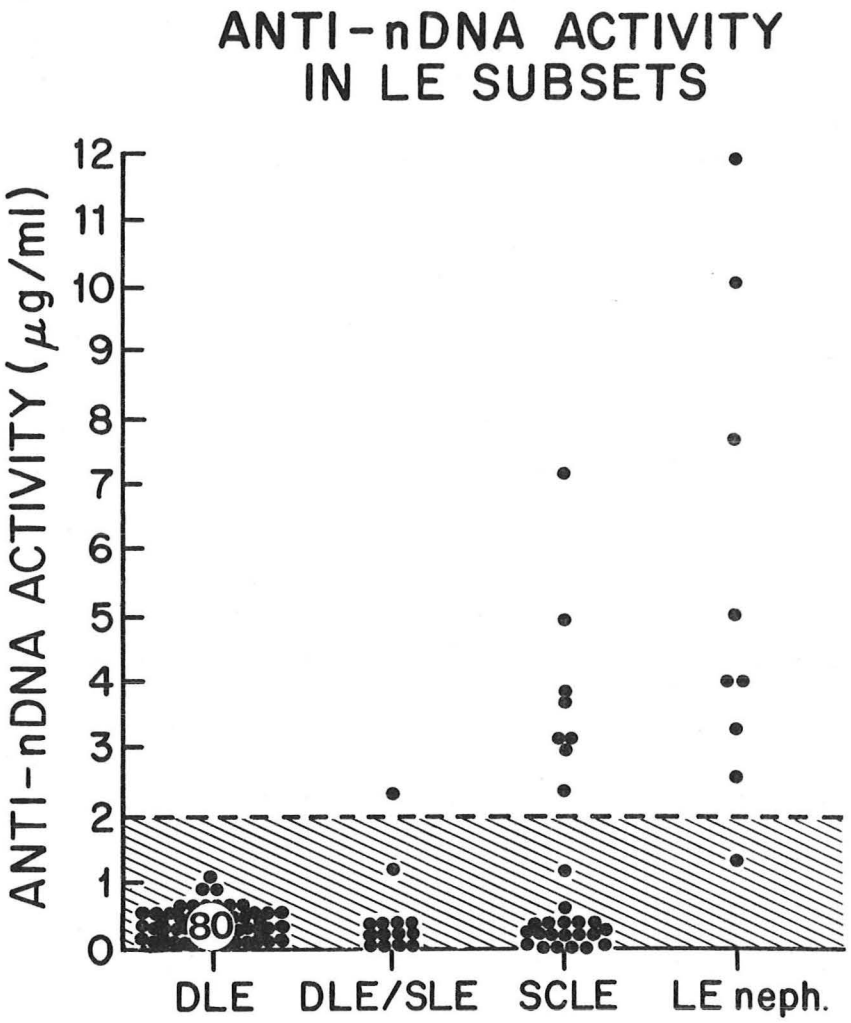
** Positive at a titer of 1:16 or greater (1:16 RKS ≃ 1:160 KB)

SUBEPIDERMAL IMMUNOGLOBULINS DEPOSITS IN VISIBLY NORMAL SKIN

GROUP	NO. TESTED	POSITIVE LUPUS BAND TEST	
		NO.	%
DLE	27	0	0
DLE/SLE	15	3	20
SCLE	23	6	23
SLE NEPH.	13	13	100



Total hemolytic complement (CH_{50})
levels determined during times of active disease.



DNA binding measured by the nitrocellulose filter binding assay using calf thymus DNA.

Therefore a subset of patients with SCLE can be identified with a relatively benign form of SLE marked by musculoskeletal symptoms and a low frequency of nephritis and severe CNS disease. The SCLE and the SLE/DLE groups are clinically quite similar. Although SCLE patients may have no overt systemic manifestations, approximately half have definite evidence of systemic LE by ARA criteria [109]. In contrast, patients with true generalized or disseminated DLE rarely have systemic manifestations or develop systemic LE [92]. The most common laboratory abnormality in the SCLE patients was a positive antinuclear antibody test in 63% compared to only 4% in DLE patients using the same assay system.

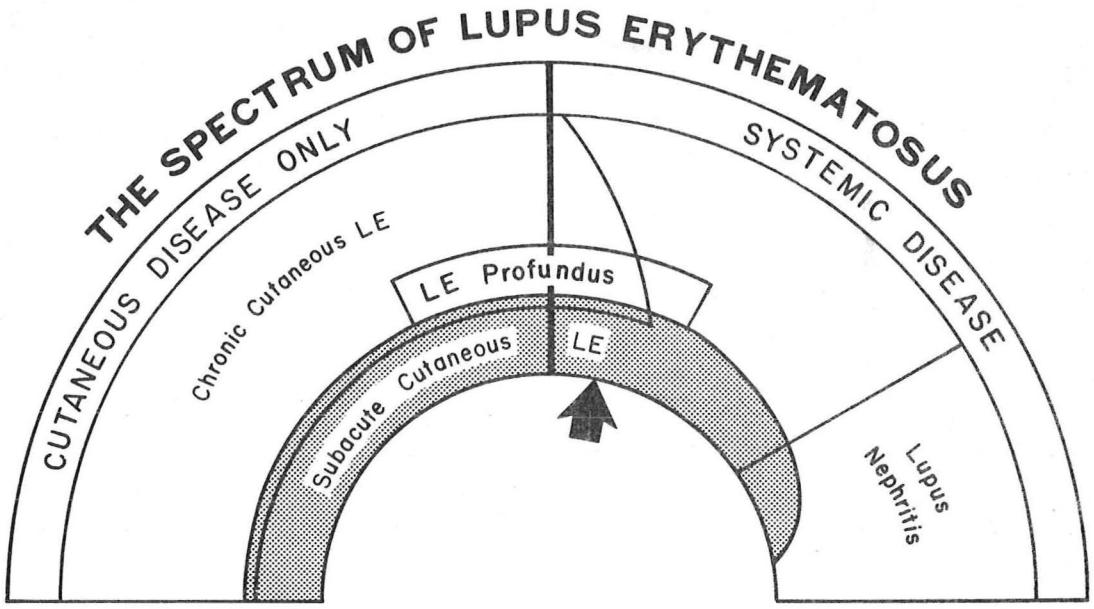
Most workers have reported subepidermal immunoglobulin deposits in over 90% of the skin biopsies taken from chronic or acute LE skin lesions [124]. The presence of subepidermal immunoglobulin is often used therefore to confirm the diagnosis of cutaneous LE. The table below gives the immunofluorescence findings in biopsies from SCLE lesions.

DIRECT IMMUNOFLUORESCENCE IN LESIONAL AND NON-LESIONAL SKIN OF SCLE PATIENTS

Biopsy Site	Number Tested	No. With DEJ Ig
Lesional	15	9 (60%)
Non-Lesional		
Deltoid	13	6 (46%)
Flexor Forearm	23	6 (26%)

Since 40% of our SCLE patients had negative findings by direct immunofluorescence staining of skin lesions this finding cannot be used to exclude the diagnosis of cutaneous LE.

In summary, SCLE patients have a clinically distinct form of cutaneous LE. These patients frequently have a mild systemic illness marked by a low incidence of severe nephritis and CNS disease. The predominant clinical feature is recurring episodes of widespread non-scarring cutaneous LE. These findings suggest that SCLE identifies a distinct subset of LE patients that generally have an illness intermediate in severity between that of scarring DLE and SLE with nephritis as illustrated below.

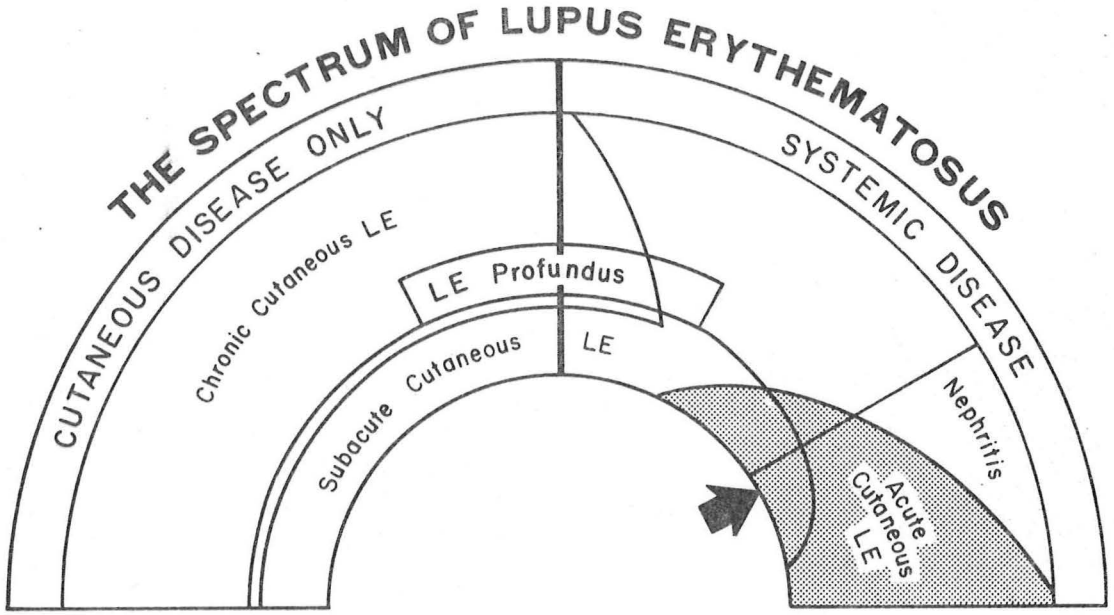


E. Acute Cutaneous LE (ACLE)

Case V, PMH # 23-05-87: L. B., an albino black female, was seen in Galveston in 1958 at the age of 44 years with fever, polyarthritis, a malar rash and pleuritic chest pain. Laboratory evaluation revealed proteinuria (exact amount unknown), a positive LE preparation and hyperglobulinemia. A diagnosis of SLE was made and she was given corticosteroids with improvement of her symptoms. Four years later, in January, 1962, she was hospitalized at Parkland with recurrent chest pain, a right pleural effusion and ascites. A renal biopsy showed membranous glomerulonephritis. Following discharge she was followed in the Arthritis Clinic and on steroid therapy underwent a remission with disappearance of her proteinuria and nephrotic syndrome. In October, 1963, she again developed a "butterfly rash", fever and right pleuritic chest pain. Her symptoms abated with an increase in the steroid dose and she was discharged. She remained more or less asymptomatic until 1969. At that time she experienced another episode of activity with fever, facial rash and a right sided pleural effusion. Resolution of her symptoms and the effusion followed an increase in steroid therapy.

This case demonstrates several important important features of acute cutaneous LE. On several occasions her malar ("butterfly") rash signaled an acute flare-up of her disease. This type of facial rash is invariably associated with multisystem disease. As in the above case, the lesions often appear transiently during times of active disease. In a matter of hours or a few days the lesions resolve without residual changes. The clinical course of her disease was punctuated by several acute episodes separated by long symptom free intervals. These characteristic patterns of recurrent activity for individual patients has long been recognized as a feature of SLE [134]. It is this consistent nature of LE that makes it possible to recognize similarities in disease patterns and to define subsets of patients.

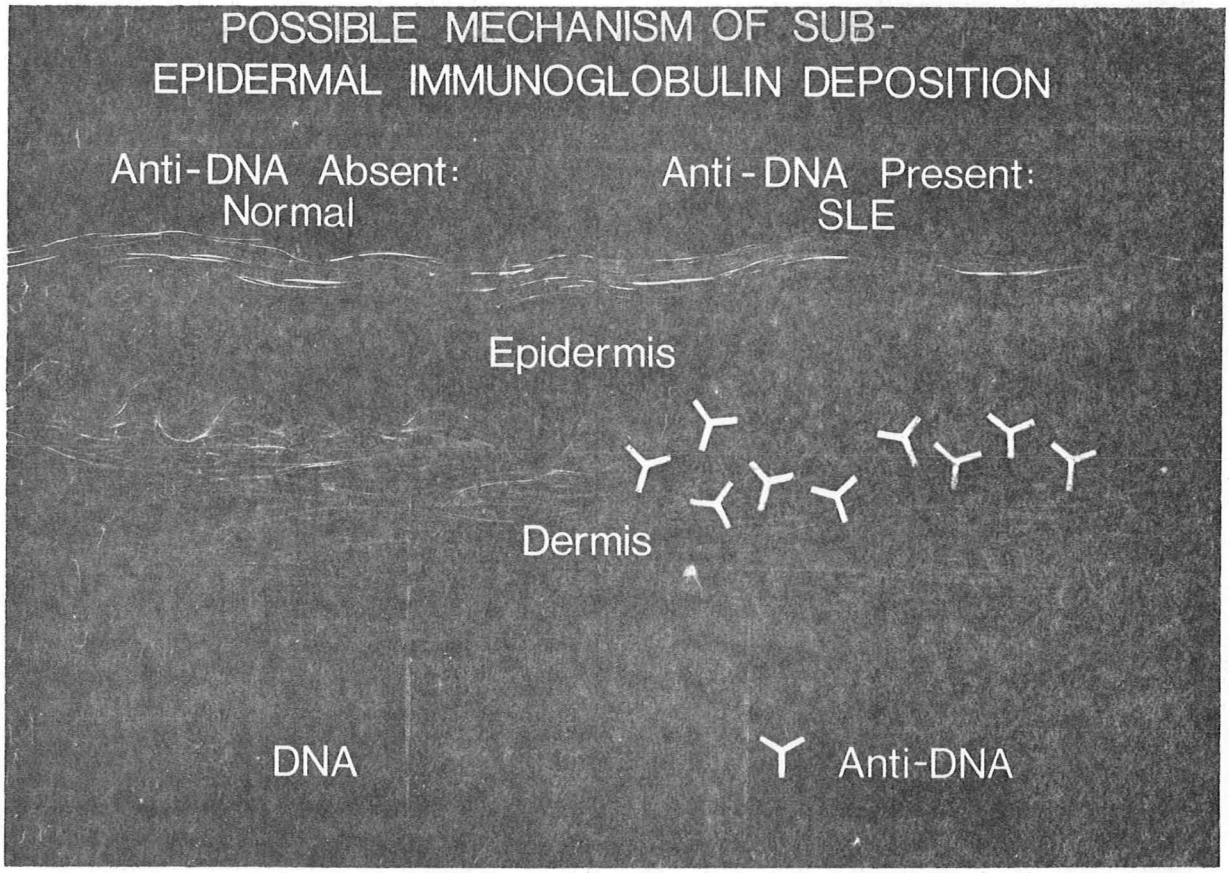
Acute cutaneous LE occurred in 32.5% of the series by Rothfield [95] and in 36.7% of the large series by Tuffanelli and Dubois [123]. It is sometimes the presenting symptom and it occurs frequently after sun exposure. At the onset the patient may mistake this butterfly blush for a sunburn and seek medical advice only after the lesion has persisted for several days or after new areas of erythema have appeared elsewhere. More widespread erythema or a "maculopapular rash" which may resemble a drug eruption can also be seen. The histologic picture in acute cutaneous LE may be quite unimpressive and non-diagnostic in the early phases. However, a careful examination will usually reveal a number of the distinct basal layer changes characteristic of cutaneous LE. This skin manifestation of LE is usually seen in young women with active and often severe forms of SLE. These patients usually have immune deposits at the dermal epidermal junction of normal skin, high levels of anti-DNA antibodies, low complement levels and severe progressive lupus nephritis. The figure below illustrates the position these patients occupy on the LE spectrum.



VI. IMMUNOLOGIC BASIS FOR VARIATION IN EXPRESSION OF CUTANEOUS LE

SLE is the prototype of autoimmune disease, and the current concept is that it is a disease of B cell hyperactivity, resulting in antibodies directed toward a variety of cellular antigens including native DNA. Indiscriminate B cell activity of this type has recently been attributed to a deficiency in suppression of B lymphocytes by suppressor T lymphocytes [129]. Patients with SLE and discoid skin lesions (SLE/DLE) or those with subacute cutaneous LE (SCLE) may possess comparatively normal T cell regulation of B cell function. Therefore they are not disposed to autoantibody or to immune complex mediated injury. On the other hand, these same patients may be subject to persistent cell mediated or T cell autoimmune injury which causes damage in areas of DNA release, such as the skin [37].

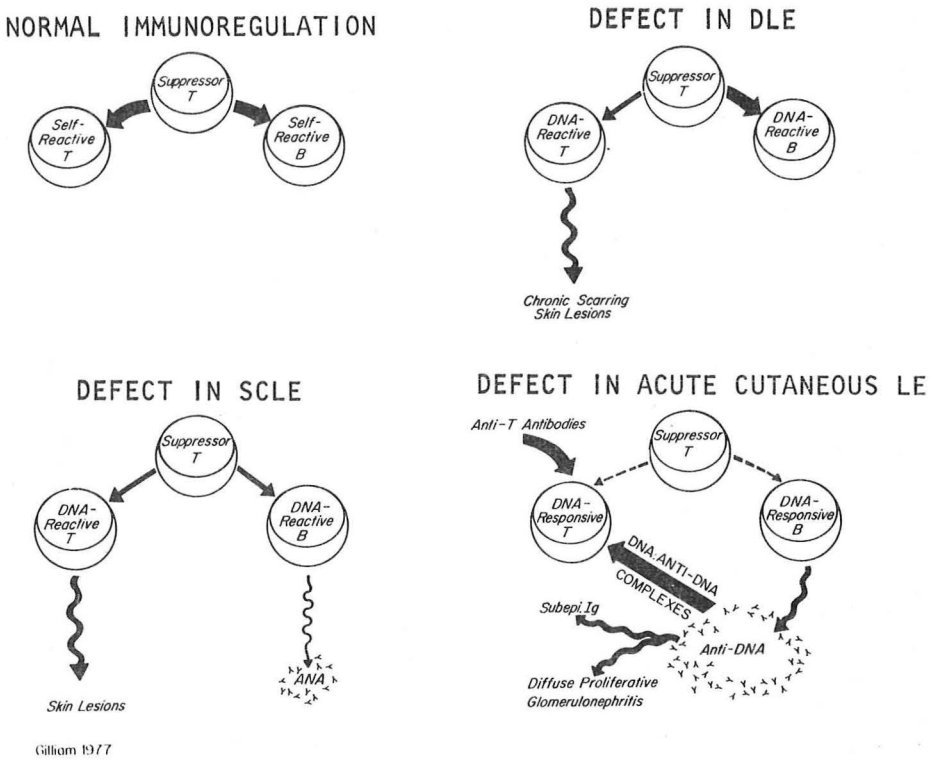
Epithelial cell nuclei are broken down during the final stages of follicular and epidermal keratinization. The DNA released by these cells is not found in the mature keratin [34] and supposedly some of this nuclear material, presumably containing short strands or fragments of DNA may diffuse back toward the dermis.



DNA responsive T cells may encounter this DNA in the dermis and be stimulated to secrete lymphokines leading to the observed skin lesions. In both chronic and subacute cutaneous LE, autoantibody production, particularly anti-DNA production is minimal. This may reflect some measure of T cell control over autoantibody-producing B cells. In some patients with SLE, the DNA antibody response may be more profound and lupus nephritis more common. In such patients a more severe suppressor T cell defect may exist. This would allow DNA responsive B lymphocytes to produce DNA antibody and T lymphocytes to react with DNA released in the skin. Large quantities of anti-DNA antibodies might then lead to the formation of nephrotoxic DNA:anti-DNA complexes. The anti-DNA antibodies would also be available to form complexes beneath the epidermis with DNA release from keratinizing epidermal cells. On the other hand, the DNA responsive effector T cells may be blocked by these immune complexes or by DNA antibodies. Effector T cell function could be reduced further in patients with active SLE by lymphocytotoxic antibodies which are commonly present in such patients [2,12,113,114]. For any or all of these reasons the LE skin disease in these SLE patients may be either prevented or reduced to a transient hypocellular lesion of the type commonly present in acute systemic lupus erythematosus. The following figures illustrate this proposed mechanism.

PROPOSED

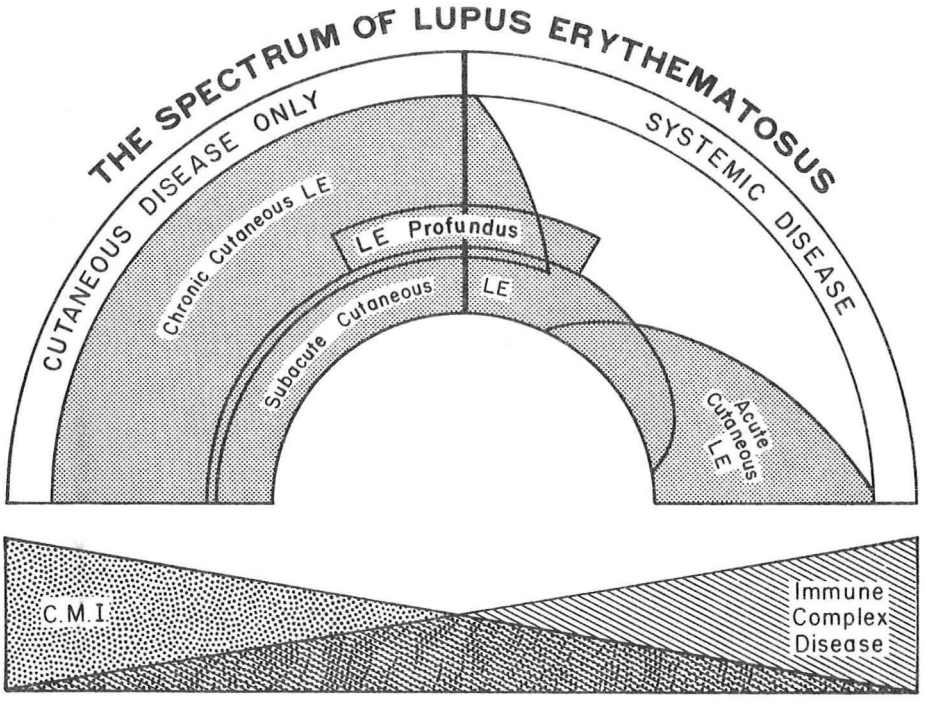
PATHOGENESIS OF CUTANEOUS LE



Gilliam 1977

VII. CONCLUSION

Lupus erythematosus is an extremely variable disease which expresses a borad spectrum of clinical manifestations and pathologic changes. The related or underlying immunologic features of this disease spectrum are illustrated in the figure below. As shown here patients with chronic cutaneous LE may express predominately cell mediated autoimmunity with little autoantibody production. In contrast patients with LE nephritis or vasculitis have major manifestations of immune complex mediated injury with little evidence of cell mediated cutaneous injury. These patients usually show some impairment of T cell function and tend to form large quantities of nephrotoxic DNA:anti-DNA complexes. SLE patients with chronic cutaneous LE or patients with subacute cutaneous LE occupy an intermediate position on this spectrum. In this way the cutaneous expression of LE may reflect the nature of the underlying immunologic defect and serve as a useful marker for the identification of LE subsets.



REFERENCES

1. Alger, M., D. Alarcon-Seqovia, S. J. Rivero: Hemolytic anemia and thrombocytopenia purpura: Two related subsets of systemic lupus erythematosus. J. Rheum. 4:351-357, 1977.

2. Allen, J. I., R. P. Searles, R. P. Messner, A. D. Bankhurst: Antilymphocyte antibodies in systemic lupus erythematosus patients and their relatives: Reactivity with non-human lymphocytes. Clin. Immunol. Immunopathol. 9:301-317, 1978.

3. Allison, A. C., A. M. Denman, R. D. Barnes: Cooperating and controlling functions of thymus-derived lymphocytes in relation to autoimmunity. Lancet 2:135-140, 1971.

4. Bach, J. F., M. A. Bach, F. Tron: New conceptions of autoimmunity and of systemic lupus erythematosus. Adv. Nephrol. 6:5-35, 1976.

5. Beaucher, W. N., R. H. Garman, J. J. Condemi: Familial lupus erythematosus: Antibodies to DNA in household dogs. N. Engl. J. Med. 296:982-984, 1977.

6. Beck, S. W., N. R. Rowell: Discoid lupus erythematosus: A study of the clinical features in 120 patients with observations of the relationship of this disease to systemic lupus erythematosus. Quarterly J. Med. 35: 119-136, 1966.

7. Bille, B. S. V.: Lupus erythematosus disseminatus with and without skin eruption. Acta Med. Scand. 140:280-289, 1951.

8. Billingham, R. E. and J. W. Streilein: Toxic epidermal necrolysis and homologous disease in hamster. Arch. Derm. 98:528-538, 1968.

9. Block, S. R., M. D. Lockshin, J. B. Winfield, et al.: Immunologic observations on nine sets of twins either concordant or discordant for SLE. Arth. Rheum. 19:545-554, 1976.

10. Bresnihan, B., H. E. Jasin: Suppressor function of peripheral blood mononuclear cells in normal individuals and in patients with systemic lupus erythematosus. J. Clin. Invest. 59:106-116, 1977.

11. Burnham, T. K., G. Fine: The immunofluorescent "band" test for lupus erythematosus. Arch. Derm. 103:24-32, 1971.

12. Butler, W. T., J. T. Sharp, R. D. Rossen, M. D. Lidsky, K. K. Mittal, D. A. Sard: Relationship of the clinical course of systemic lupus erythematosus to the presence of circulating lymphocytotoxic antibodies. Arth. Rheum. 15:231-238, 1972.

13. Cazenave, P. L. A.: Lupus erythemateux (Erythème Centrifuge) Ann. Malad. Peau. Syph. 3:297-299, 1851.

14. Chubick, A., R. D. Sontheimer, J. N. Gilliam, M. Ziff: An appraisal of test for native DNA antibodies in connective tissue diseases. Ann. Int. Med. 89:186-192, 1978.

15. Clark, W. H., R. J. Reed, M. C. Mihn: Lupus erythematosus. Histopathology of cutaneous lesions. Hum. Path. 4:157-163, 1973.

16. Cohen, A. S., W. E. Reynolds, E. C. Franklin, J. P. Kerika, M. W. Ropes, L. E. Shulman, S. L. Wallace: Preliminary criteria for the classification of systemic lupus erythematosus. Bull. Rheum. Dis. 21:643, 1971.

17. Cripps, D. J., J. Rankin: Action spectra of lupus erythematosus and experimental immunofluorescence. Arch. Derm. 107:563-567, 1973.

18. Davis, P., J. S. Percy: Role of ultraviolet light and UV-DNA in the induction of skin lesion in experimental animals. Brit. J. Derm. 99:201-205, 1978.

19. De Dobbeleer, G. D., M. H. Ledoux-Corbusier, G. A. Achten: Graft versus host reaction: An ultrastructural study. Arch. Derm. 111:1597-1602, 1975.

20. De Horatius, R. J., R. Pillarisetty, R. P. Messner, N. Talal: Anti-nucleic acid antibodies in systemic lupus erythematosus patients and their families. Incidence and correlation with lymphocytotoxic antibodies. J. Clin. Invest. 56:1149-1154, 1975.

21. Díaz-Jouanan, E., R. J. De Horatius, D. Alarcón-Segovia, R. P. Messner: Systemic lupus erythematosus presenting as panniculitis (lupus profundus). Ann. Int. Med. 82:376-379, 1975.

22. Dostál, C., D. Iványi, H. Macurová, J. Hána, J. Strejcek: HLA antigens and systemic lupus erythematosus. Ann. Rheum. Dis. 36:83-85, 1977.

23. Dubois, E. L., S. Martel: Discoid lupus erythematosus: An analysis of its systemic manifestations. Ann. Int. Med. 44:482-496, 1956.

24. Dubois, E. L., D. L. Tuffanelli: Clinical manifestations of systemic lupus erythematosus. JAMA 170:104-111, 1964.

25. Ellis, F. A., W. R. Bundick: Histology of lupus erythematosus. Arch. Derm. 70:311-324, 1954.

26. Estes, D., C. L. Christian: The natural history of systemic lupus erythematosus by prospective analysis. Medicine 50:85-95, 1971.

27. Fauci, A. S., A. D. Steinberg, B. F. Haynes, G. Whalen: Immunoregulatory aberrations in systemic lupus erythematosus. J. Immunol. 121:1473-1479, 1978.

28. Feely, R. H.: Skin manifestations in systemic lupus erythematosus. Irish J. Med. Sci. 145:253-259, 1976.

29. Fenyk Jr., J. R., P. I. Warkentin, R. W. Goltz, et al.: Sclerodermatous graft-versus-host disease limited to an area of measles exanthem. Lancet i:472-473, 1978.

30. Fessel, W. J.: ANA-negative systemic lupus erythematosus. Am. J. Med. 64:80-86, 1978.

31. Folomeeva, O., V. A. Nassowova, A. S. Alekberova, N. Talal, R. C. Williams, Jr.: Comparative studies of antilymphocyte, antinucleotide, and antiviral antibodies among families of patients with systemic lupus erythematosus. Arth. Rheum. 21:23-27, 1978.

32. Fountain, R. B.: Lupus erythematosus profundus. Br. J. Derm. 80: 571-579, 1968.

33. Fries, J. F.: The clinical aspects of systemic lupus erythematosus. Medical Cl. No. Am. 61:229-240, 1977.

34. Fukuyama, K., I. A. Bernstein: Autoradiographic studies of the incorporation of thymiding -H^3 into deoxyribonucleic acid in the skin of young rats. J. Invest. Derm. 36:321-326, 1961.

35. Ganor, S., F. Sagher: Systemic lupus erythematosus changing to the chronic discoid type. Dermatologica 125:81-92, 1962.

36. Gershon, R. K., K. Kondo: Cell interactions in the induction of tolerance: The role of thymic lymphocytes. Immunology 18:723-725, 1970.

37. Gilliam, J.N.: The significance of cutaneous immunoglobulin deposits in lupus erythematosus and NZB/NZW F_1 hybrid mice. J. Invest. Derm. 65: 154-161, 1975.

38. Gilliam, J. N., D. E. Cheatum, E. R. Hurd, P. Stastny, M. Ziff: Immunoglobulin in clinically uninvolved skin in systemic lupus erythematosus. J. Clin. Invest. 53:1434-1438, 1974.

39. Gilliam, J. N., A. J. Cox: Epidermal changes in B_{12} deficiency. Arch. Derm. 107:23-1236, 1973.

40. Gilliam, J.N., S. D. Prystowsky: Mixed connective tissue disease syndrome. Arch. Derm. 113:583-587, 1977.

41. Gilliam, J. N., S. D. Prystowsky: Conversion of discoid lupus erythematosus to mixed connective tissue disease. J. Rheum. 4:165-169, 1977.

42. Gilliam, J. N.: DNA binding to normal skin connective tissue as localizing factor for DNA:anti-DNA complexes. Arth. Rheum. 20:117, 1977 (abstract).

43. Gladman, D. D., A. Chalmers, M. B. Urowitz: Systemic lupus erythematosus with negative LE cells and antinuclear factor. J. Rheum. 5:142-147, 1978.

44. Goeckerman, W. H.: Lupus erythematosus as a systemic disease. JAMA 80:542-547, 1923.

45. Goldberg, M. A., F. C. Arnett, W. B. Bias, L. E. Shulman: Histocompatibility antigens in systemic lupus erythematosus. Arth. Rheum. 19:129-132, 1976.

46. Gratwhol, A. A., H. M. Moutsopolous, T. M. Chused, et al.: Sjögren-type syndrome after allogeneic bone marrow transplantation. Ann. Int. Med. 87:703-706, 1977.

47. Grogan, T. M., R. B. Odom, J. H. Burgess: Graft-vs-host reaction. Arch. Derm. 113:806-812, 1977.

48. Grossman, J., M. L. Callerme, J. J. Condemi: Skin immunofluorescence studies on lupus erythematosus and other anti-nuclear antibody positive diseases. Ann. Int. Med. 80:496-500, 1974.

49. Harris, R. B., R. K. Winkelmann: Lupus mastitis. Arch. Derm. 114: 410-412, 1978.

50. Hood, A. F., N. A. Soter, J. Rappeport, I., Gigli: Graft-versus-host reaction -- cutaneous manifestations following bone marrow transplantation. Arch. Derm. 113:1087-1091, 1977.

51. Howitz, J., S. Ullman: Lupus erythematosus hypertrophicus: A case report. Acta Derm. Venereol. 58:90-91, 1978.

52. Irgang, S.: Lupus erythematosus profundus report of an example with clinical resemblance to Darrier-Roussy sarcoid. Arch. Derm. 42:97-108, 1940.

53. Iványi, D., C. Dostál, L. Maklas: HLA-B8 in systemic lupus erythematosus. Tissue Antigens 8:91-93, 1976.

54. Jablonska, S., T. Chorzelski, E. Maciejowska: The scope and limitations of the immunofluorescence method in the diagnosis of lupus erythematosus. Brit. J. Derm. 83:242-247, 1970.

55. Janis, J. F., R. K. Winkelmann: Histopathology of the skin in dermatomyositis. Arch. Derm. 97:640-650, 1968.

56. Keil, H.: Conception of lupus erythematosus and its morphologic variants. Arch. Derm. 36:729-757, 1937.

57. Kennedy, B. J., R. Smith, R. W. Goltz: Skin changes secondary to hydroxyurea therapy. Arch. Dermatol. 111:183-187, 1975.

58. Kierland, R. R.: Classification and cutaneous manifestations of lupus erythematosus. Proc. Mayo Clin. 15:675-677, 1940.

59. Klein, S. A., A. J. Tomaro: Lupus erythematosus profundus: Review of the literature and report of case. J. Oral Surg. 33:454-457, 1975.

60. Krakauer, R. S., T. A. Waldmann, W. Strober: Loss of suppressor T cells in adult NZB/NZW mice. J. Exp. Med. 144:662-673, 1976.

61. Kushniruk, W.: Systemic involvement in chronic lupus erythematosus. Canad. M. A. J. 76:184-193, 1957.

62. Kyle, R. A., R. S. Schwartz, H. L. Oliner, W. Damishek: A syndrome resembling adrenal vortical insufficiency associated with long term busulfan (Myleran) therapy. Blood 18:497-510, 1961.

63. Lai A Fat, R. F. M., R. H. Cormane, R. Van: An immunohistopathological study on the synthesis of immunoglobulin and complement in normal and pathological skin and the adjacent mucous membrane. Brit. J. Derm. 90: 123-126, 1974.

64. Lawley, T. J., G. L. Peck, H. M. Moutsopoulos, A. A. Gratwhol, A. B. Deisseroth: Scleroderma, Sjögren-like syndrome and chronic graft-versus-host disease. Ann. Int. Med. 87:707-709, 1977.

65. Lerner, K. G., G. F. Kao, R. Storb, C. D. Buckner, R. A. Cliff, E. D. Thomas: Histopathology of graft-versus-host reaction (GVHR) in human recipients of marrow from HL-A matched sibling donors. Transpl. Proc. 6:367-371, 1974.

66. Lever, W. F.: Histopathology of the Skin, Philadelphia, J. B. Lippincott Company, 1967.

67. Lowenstein, M. B., N. F. Rothfield: Family study of systemic lupus erythematosus: Analysis of the clinical history, skin immunofluorescence, and serologic parameters. Arth. Rheum. 20:1293-1303, 1977.

68. McCreight, W. G., H. Montgomery: Cutaneous changes in lupus erythematosus. Arch. Derm. 61:1-11, 1950.

69. Martin, R. H., E. K. Blackburn: Lupus erythematosus: Clinical and hamatological studies in seventy-seven cases. Arch. Derm 73:1-14, 1956.

70. Mellors, R. C., J. W. Mellors: Antigen related to mammalian type-C RNA viral p30 proteins is located in renal glomeruli in human systemic lupus erythematosus. Proc. Natl. Acad. Sci. (USA) 73:233-237, 1976.

71. Merritt, C., D. Mann, G. Rogentine: Cytotoxic antibody for epithelial cells in human graft versus host disease. Nature 232:638-639, 1971.

72. Messner, R. P., R. J. De Horatius: Epidemeology of antilymphocyte antibodies in systemic lupus erythematosus. Arth. Rheum. 21:S146-152, 1978.

73. Millard, L. G., N. R. Rowell, S. M. Rajah: Histocompatibility antigens in discoid and systemic lupus erythematosus. Brit. J. Derm. 96:139-144, 1977.

74. Milner, A. N. P.: Systemic lupus erythematosus with nodular lesions. Brit. J. Derm. 65:204-211, 1953.

75. Mirimoto, C.: Loss of suppressor T-lymphocyte function in patients with systemic lupus erythematosus (SLE). Clin. Exp. Immunol. 32:125-133, 1978.

76. Natali, P. G., E. M. Tan: Experimental skin lesions in mice resembling systemic lupus erythematosus. Arth. Rheum. 16:579-589, 1973.

77. Nesbitt, L. T., O. B. Gum: Direct cutaneous immunofluorescent test in lupus erythematosus. South Med. J. 66:991-997, 1973.

78. O'Leary, P. A.: Disseminated lupus erythematosus. Minnesota Med. 17:637-644, 1934.

79. O'Laughlin, S., A. L.Schroeter, R. E. Jordan: A study of lupus erythematosus with particular reference to generalized discoid lupus. Brit. J. Derm. 99:1-11, 1978.

80. Panem, S., N. G. Ordoñez, H. Dalton, K. Soltani: Viral immune complexes in systemic lupus erythematosus: C-type viral complex deposition in skin. J. Invest. Derm. 71:260-262, 1978.

81. Pascher, F: Lupus erythematosus. Med. Clin. No. Am. 43:917-928, 1959.

82. Peck, G. L., G. P. Herzig, P. M. Elias: Toxic epidermal necrolysis in a patient with graft-vs-host reaction. Arch. Derm. 105:561-569, 1972.

83. Percy, J. S., C. J. Smith: The immunofluorescent skin test in systemic lupus erythematosus. JAMA 203:485-488, 1969.

84. Pennebaker, J. B., J. N. Gilliam, M. Ziff: Immunoglobulin classes of DNA binding activity in serum and skin in systemic lupus erythematosus. J. Clin. Invest. 60:1331-1338, 1977.

85. Persselin, J. E., R. P. Messner, R. J. De Horatius, G. M. Troup: Antilymphocyte antibodies in systemic lupus erythematosus: Familial clustering of lymphocyte antigens. J. Rheum. 4:11-14, 1977.

86. Phillips, P. E.: Recent attempts at implicating viruses in systemic lupus erythematosus. pp. 265-267, In. Dumonde, D.C., ed. Infection and Immunology in the Rheumatic Diseases. Oxford, Blackwell Scientific, 1976.

87. Phillips, P. E.: Viruses and systemic lupus erythematosus. Bul. Rheum. Dis. 28(7):954-959, 1977-78.

88. Pinkus, H.: Lichenoid tissue reactions. Arch. Derm. 107:840-846, 1973.

89. Provost, T. T., A. Razzaque, P. J. Madison, M. Reichlin: Antibodies to cytoplasmic antigens in lupus erythematosus. Serologic marker for systemic disease. Arth. Rheum. 20:1457-1463, 1977.

90. Prystowsky, S. D., J. N. Gilliam: Discoid lupus erythematosus as part of a larger disease spectrum. Correlation of clinical features with laboratory findings in lupus erythematosus. Arch. Derm. 111:1448-1452, 1975.

91. Prystowsky, S. D., J. N. Gilliam: Antinuclear antibody studies in chronic cutaneous discoid lupus erythematosus. Arch. Derm. 113:183-186, 1977.

92. Prystowsky, S. D., J. H. Herndon, J. N. Gilliam: Chronic cutaneous lupus erythematosus (DLE) -- a clinical and laboratory investigation of 80 patients. Medicine 55:183-191, 1975.

93. Reinertson, J. L., J. H. Klippel, A. H. Johnson, et al.: B-lymphocyte alloantigens associated with systemic lupus erythematosus. N. Engl. J. Med. 299:515-517, 1978.

94. Rigby, R. J., R. L. Dawkins, J. D. Wetheroll, B. R. Hawkins: HLA in systemic lupus erythematosus: Influence on severity. Tissue Antigens 12:25-31, 1978.

95. Rothfield, N. F., C. H. March: Lupus erythematosus. Dermatology in General Medicine. First edition. T. B. Fitzpatrick, New York, McGraw-Hill Company, pp. 1513-1514, 1971.

96. Rothfield, N., C. H. March, P. Meischer, C. McEwen: Chronic discoid lupus erythematosus: A study of 65 patients and 65 controls. New Engl. J. Med. 269:1155-1161, 1963.

97. Roubinian, J. R., N. Talal, J. S. Greenspan, J. R. Goodman, R. K. Siiteri: Effect of castration and sex hormone treatment of survival, anti-nucleic acid antibodies and glomerulonephritis in NZB/NZW F_1 mice. J. Exp. Med. 147:1568-1583, 1978.

98. Sale, G. E., K. G. Lerner, E. A. Barker, H. M. Shulman, E. D. Thomas: The skin biopsy in the diagnosis of acute graft-versus-host disease in man. Amer. J. Pathol. 89:621-633, 1977.

99. Saurat, J. H., L. Didier-Jean, E. Gluckman, et al.: Graft-versus-host reaction and lichen planus-like eruption in man. Brit. J. Derm. 92: 591-592, 1975.

100. Scott, A., E. G. Rees: The relationship of systemic lupus erythematosus and discoid lupus erythematosus. Arch. Derm. 79:422-435, 1959.

101. Scherak, O., G. Kolarz, W. R. Mayr: HLA-B8 in caucasian patients with systemic lupus erythematosus. Scand. J. Rheum. 7:3-6, 1978.

102. Sharp, G. C., W. S. Irvin, E. M. Tan, et al.: Mixed connective tissue disease -- an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). Amer. J. Med. 52:148-159, 1972.

103. Shrank, A. B., D. Doniach: Discoid lupus erythematosus. Correlation of clinical features with serum auto-antibody pattern. Arch. Derm. 87: 677-685, 1963.

104. Shulman, H. M., G. E. Sale, K. G. Lerner, et al.: Chronic cutaneous graft-versus-host disease in man. Amer. J. Path. 91:545-564, 1978.

105. Sidky, Y. A., R. Averbach: Lymphocyte induced angiogenesis: A quantitative and sensitive assay of the graft-versus-host reaction. J. Exp. Med. 141:1084-1100, 1975.

106. Slavin, R. E., G. W. Santos: The graft-versus-host reaction in man after bone marrow transplantation: Pathology, pathogenesis, clinical features and implication. Clin. Immunol. Immunopathol. 1:472-498, 1973.

107. Sontheimer, R. D., Gilliam, J. N.: DNA antibody class, subclass and complement fixation in systemic lupus erythematosus with and without nephritis. Clin. Immunol. Immunopathol. 10:459-467, 1978.

108. Sontheimer, R. D., J. N. Gilliam: An immunofluorescence assay for double-stranded DNA antibodies using the Crithidia luciliae kinetoplast as a double-stranded DNA substrate. J. Lab. Clin. Med. 91:550-558, 1978.

109. Sontheimer, R. D., J. R. Thomas, J. N. Gilliam: The clinical and immunological features of patients with subacute cutaneous lupus erythematosus -- a distinct LE subset. J. Invest. Derm. 71:278, 1978 (abstract).

110. Sontheimer, R. D., J. N. Gilliam: A reappraisal of the relationship between subepidermal immunoglobulin deposits and DNA antibodies in systemic lupus erythematosus: A study using the Crithidia luciliae immunofluorescence anti-DNA assay. J. Invest. Dermatol. 72:29-32, 1979.

111. Spielvogel, R. L., R. W. Goltz, J. H. Kersey: Scleroderma-like changes in chronic graft-versus-host diseases. Arch. Derm. 113:1424-1428, 1977.

112. Stastny, P., V. A. Stembridge, M. Ziff: Homologous disease in the adult rat, a model for autoimmune disease. J. Exp. Med. 118:635-648, 1963.

113. Stastny, P., M. Ziff: Antibodies against cell membrane constituents in systemic lupus erythematosus and related diseases. I. Cytotoxic effect of serum from patients with systemic lupus erythematosus (SLE) for allogeneic and for autologous lymphocytes. Clin. Exp. Immunol. 8:543-550, 1971.

114. Stastny, P., M. Ziff: Direct lysis of lymphocytes by complement in patients with systemic lupus erythematosus. Arth. Rheum. 14:733-736, 1971.

115. Stastny, P: HLA-D and Ia antigens in Rheumatoid Arthritis and Systemic Lupus Erythematosus 21:S139-143 (supplement), 1978.

116. Sulzberger, M. B.: Discussion of chronic discoid lupus erythematosus cases presented at Minnesota Dermatologic Society. Arch. Derm 85: 152-153, 1962.

117. Talal, N., J. R. Roubinian, R. J. Pillarisetty, S. Sawada: Biological significance of IgM and IgG antibodies to DNA and RNA in autoimmune disease. Am. J. Clin. Path. 68:543-646, 1977 (supplement).

118. Talal, N.: Natural history of murine lupus. Modulation by sex hormones. Arth. Rheum. 21:858-863, 1978.

119. Tay, C. H.: Cutaneous manifestations of systemic lupus erythematosus. Aust. J. Derm. 11:30-41, 1970.

120. Touraine, R., J. Revuz, B. Dreyfus, et al.: Graft-versus-host reaction and lichen planus. Brit. J. Derm. 92:589, 1975.

121. Tsoi, M., R. Storb, E. Jones, et al.: Deposition of IgM and complement at the dermo-epidermal junction in acute and chronic cutaneous graft-versus-host disease in man. J. Immunol. 120:1485-1491, 1978.

122. Tuffanelli, D. L.: Lupus erythematosus panniculitis (profundus). Arch. Derm. 103:231-242, 1971.

123. Tuffanelli, D. L., E. L. Dubois: Cutaneous manifestations of systemic lupus erythematosus. Arch. Derm. 90:377-386, 1964.

124. Tuffanelli, D. L.: Lupus erythematosus. Arch. Derm. 106:553-566, 1972.

125. Twomey, J. J., A. H. Laughter, A. D. Steinberg: A serum inhibitor of immune regulation in patients with systemic lupus erythematosus. J. Clin. Invest. 62:713-715, 1978.

126. Uitto, J., D. J. Santa-Cruz, A. Z. Eisen, P. Leone: Verrucous lesion in patients with discoid lupus erythematosus. Clinical, histopathological and immunofluorescence studies. Brit. J. Derm. 98:497-506, 1978.

127. Urowitz, M. B.: SLE subsets -- divide and conquer. J. Rheum. 4:332-333, 1977.

128. Van Vloten, W. A., E. Scheffer, L. J. Dooren: Localized scleroderma-like lesions after bone marrow transplantation in man. Brit. J. Derm. 96: 337-341, 1977.

129. Waldman, T. A., R. M. Blaese, S. Broder, R. S. Krakauer: Disorders of suppressor immunoregulatory cells in the pathogenesis of immunodeficiency and autoimmunity. Ann. Int. Med. 88:226-238, 1978.

130. Wilson, A. P., J. W. Jordan: Relationship of chronic discoid and disseminated lupus erythematosus. N. Y. State J. Med. 50:2449-2452, 1950.

131. Winkelmann, R. K.: Panniculitis and systemic lupus erythematosus. JAMA 211:472-475, 1970.

132. Wong, K. O.: Systemic lupus erythematosus. A report of forty-five cases with unusual clinical and immunological features. Brit. J. Derm. 81: 186-190, 1969.

133. Woodruff, J. M., J. A. Hansen, R. A. Good, G. W. Santos, R. E. Slavin: The pathology of the graft-versus-host reaction (GVHR) in adults receiving bone marrow transplants. Transplantation Proc. 8:675-684, 1976.

134. Ziff, M., P. Esserman, C. McEwen: Observations on the course and treatment of systemic lupus erythematosus. Arth. Rheum. 1:332-350, 1958.

135. Zwieman, B., R. H. Tomar, P. R. Gross: Lupus erythematosus profundus following thrombocytopenic purpura. Arch. Derm. 111:347-351, 1975.