JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY, 1993, 44, 3, 187—197

Review Article

M. SCHNEIDER

PATHOPHYSIOLOGY AND PHARMACOLOGY OF SYSTEMIC LUPUS ERYTHEMATOSUS

Medical Clinic and Policlinic B, Westphalian Wilhelms-University Münster, Germany.

Systemic lupus erythematosus (SLE) is the classical example of an immune complex (IC) associated systemic autoimmune disease. Although an important part of SLE etiopathogenesis has yet to be discovered, it is generally accepted that genetic factors, sex hormones, alternations in T- and B-lymphocyte activity and defects in RES-function contribute to the development of SLE. In an SLE patient, symptoms and severity of the disease are linked to the pattern of autoantibodies expressed, referring to some pathophysiological importance of antibodies found in SLE. In addition, the interindividually variable expression of antibodies to ds-DNA, Ro or anticardiolipin, for example, permit a subtyping of SLE and indicate SLE as collective concept of heterogenous systemic connective tissue diseases with overlapping, e. g. to dermatomyositis, progressive systemic sclerosis or Sjögren's syndrome. In view of the variable, heterogeneous disease manifestations, it is obvious that the strategy in SLE therapy is to treat manifestations and not just SLE per se. Using this concept together with pathophysiologically related control parameters and standard clinical investigations, 90 to 95% of SLE patients are adequately treated with NSAID, steroids, antimalarials and immunosuppressiva. Only 5—10% need experimental therapy, and this kind of treatment should be strictly limited to this group.

Key words: *systemic lupus erythematosus, etiopathogenesis, pathophysiology, autoantibody profiles, subtypes, therapy.*

Since the first description of systemic lupus erythematosus (SLE) in the last century, almost everything has changed in lupus except the classical clinical picture. Today SLE has became the No. 1 systemic connective tissue disease; widespread clinical manifestations include SLE in virtually every differential diagnosis and an increasing sensitivity in detecting SLE is improving general prognosis.

ETIOPATHOGENESIS

Autoimmune disease SLE is accepted as the prototype of an immune complex (IC) associated disease. The etiology of SLE is largely unknown, though genetic factors influence susceptibility to the disease in part, as do sex and race. SLE in males is rare: 9 out of every 10 patients are females; first symptoms are manifested in childbearing years. The highest prevalence is reported in black women with 1 : 300, with the frequency among Caucasians 1 : 2,000 (1). During the past 3 decades, the prevalence of SLE may have undergone a 3—6-fold increase. This may be due in part to milder forms being detected by the introduction of more sensitive immunological tests.

Differences in rates of concordance for SLE between monozygotic (rate 57%) and dizygotic twins (5%) underline the role of genetic phenomena as does the association with some special HLA haplotypes (e.g. A1, B8, DR3, C4AQ0) and with the inherited absence of classical pathway complement components (2, 3).

Deficiencies in these components prevent the deposition of C4b and C3b on IC; these are important for maintaining IC in soluble forms and for enhancing their clearance by mononuclear phagocyting cells (4). Like defects in complement receptors, complement deficit supports IC deposition e.g. in glomeruli. Dysfunction of the reticuloendothelial system may additionally augment IC maintenance.

Another mechanism of pathophysiological significance in SLE is the proven B-cell hyperactivity accompanied by hypergammaglobulinemia including the building of classical autoantibodies typically found in SLE. B-Cells may be activated by a decreased T-suppressor function, stimulated T-helper cells, altered NK cell activity or direct polyclonal stimulation (5). Changes in idiotype network may also contribute to development of SLE (6).

In general, circulation of IC and local production of IC lead to immunohistochemically detectable deposition of IC in basement membranes of involved organs, e.g. kidney and skin. Interactions with basement membrane structures stimulate cellular and humoral mediators; complement activation is followed by synthesis of proteins and prostanoids leading to increased permeability of vessel walls and leukocyte infiltration. Secretion and activation of PMN-proteases support tissue destruction; morphological studies demonstrate also monocyte participation in this inflammatory process.

PATHOPHYSIOLOGICAL ASPECTS OF CLINICAL FEATURES

SLE may be associated with complaints involving multiple or single organ systems and with certain laboratory abnormalities. Because no symptom or laboratory parameter is SLE-specific and because presentation is so hetero-

geneous that only two out of 100 patients exhibit identical signs, SLE is diagnosed by bringing some pictures together into one painting, like constructing a jigsaw puzzle. When SLE is manifested by only one or few complaints or by some exceptionally non-specific systemic complaints such as fever and fatigue, diagnosis is usually more troublesome.

The commonest symptoms of SLE are articular und muscular. In these cases, arthritis often presents symmetrically in smaller joints as in rheumatoid arthritis, but the underlying pathophysiological process supports deformations such as swan necks without erosions. Hypermobile digits with classical reducible deformities seem to be secondary to involvement of joint capsule, ligaments and tendons, whereas, in contrast to alterations in rheumatoid arthritis synovial membrane exhibits only some mild inflammation and articular cartilage is almost normal.

At specific anatomical sites, e. g. femur head, small-vessel vasculitis may lead to disruption of vascular supply, causing another joint manifestation: aseptic necrosis. This pathophysiological basis of most SLE symptoms may be seen and probably palpated in skin. Cutaneous manifestations are found in about 80% of patients, with photosensitivity and malar rash being most prevalent. Immunohistochemical studies confirm deposition of complements and immunoglobulins at the dermal-epidermal junction in the upper collagen fibers and along the lamina densa of the epidermal basement membrane zone. Because immunoglobulin deposits are also found in normal skin of SLE patients, cell-mediated immune injury may at least additionally cause skin alterations.

Both CNS involvement and lupus nephritis manifested with the need for therapy are accompanied by a generally poorer prognosis than other forms of the disease (7). The pathophysiological basis of CNS lupus is still not completely clear; true vasculitis is surprisingly uncommon. Microinfarcts and a noninflammatory vasculopathy are the main microscopical findings. An antibody-mediated pathogenesis, e. g. by antibodies to neural membranes, may explain the diffuse and reversible manifestations of the major neuropsychiatric features of SLE. In pathophysiology of lupus nephritis, the association with circulating antibodies to dsDNA has been established by demonstration in glomeruli. Their deposition leads to an apparent fall in dsDNA antibody titer in serum.

Leukopenia is a classical finding in SLE, and especially helpful in differential diagnosis occurring together with fever, for example. Other hematological disorders with diagnostic importance in SLE are hemolytic anemia, lymphopenia and thrombocytopenia (8). Most of these hemocytopenias are caused by cell-specific or cross-reacting antibodies; a factor-mediated suppression of hematopoiesis is also discussed. Thrombocytopenia is a typical sign in patients with anti-phospholipid syndrome (9).

AUTOANTIBODIES

The selected ARA criteria for SLE (8) — a vast quantity of other symptoms may occur — combined with some immunological phenomena may be helpful in defining a complex of complaints as SLE . In 1948, LE cell was the first autoimmune phenomenon to be described in SLE (10). Although 70—80% of SLE patients exhibit LE cells which are related to the presence of IgG antibodies to DNA-histone complexes, the test has become redundant for technical reasons and because of more precise characterisation of antinuclear antibodies (ANA). ANA typed on HEp-2 cells are found in nearly every SLE patient. Positive reactions in mitotic cells indicate ds-DNA antibodies, a relatively specific finding of SLE. The importance and specificity of ds-DNA antibodies depend essentially on the test used, e.g. ELISA or Farr assay. In SLE, additional antibodies are found against various nuclear antigens, against a wide variety of non-specific antigens and against organ-specific antigens (11).

In contrast to the numerous clinical presentations which may occur in almost any constellation and to the almost monthly increase in the spectrum of autoantibodies, a number of disease patterns tend to recur in the patient. In addition, it is generally accepted that the antibody figure is constant in one patient after the disease has established itself (12). Whether these antibodies are related to the cause or merely to the effect of a disordered immune system is still under discussion, as is the possible link between specific clinical features and the presence of certain autoantibodies (13). Such an association is supported by the disease related antibody pattern found when comparing different forms of systemic connective tissue diseases (CTD).

ANA are the classical immunological sign of connective tissue diseases (CTD). About 50% of ANA positive patients are suffering from a CTD, with half diagnosed as SLE (14). Beside ds-DNA antibodies, U1-RNP, Sm, Ro, La, SCL 70 and Jo-1 antibodies are characterized by immunodiffusion, counter--immunoelectrophoresis or ELISA. Immunoblotting shows that these antibodies may be directed against one or more antigens (*Fig. 1*).

Fig. 2 demonstrates the presentation of these antibodies in various forms of CTD; less sensitive antibodies e.g. against PCNA and Ku are not indicated. The height of a column is an indicator of antibody sensitivity (frequencies of less than 5% are not shown). The disease specificity of an antibody can be calculated in a left-to-right row. In general, all information may be drawn directly from the picture: e.g. in SLE, U1 RNP, Ro, La, Sm and ds-DNA antibodies may be found, with the last two being relatively disease specific. The sensitivity of ds-DNA antibodies (about 60%) is higher than that of Sm (30%), especially in Europe (Sm: 10—15%). In contrast, U1-RNP antibodies may be found in nearly every CTD and are therefore not specific to any CTD. The sensitivity of 100% in MCTD/Sharp syndrome is given by definition, with high

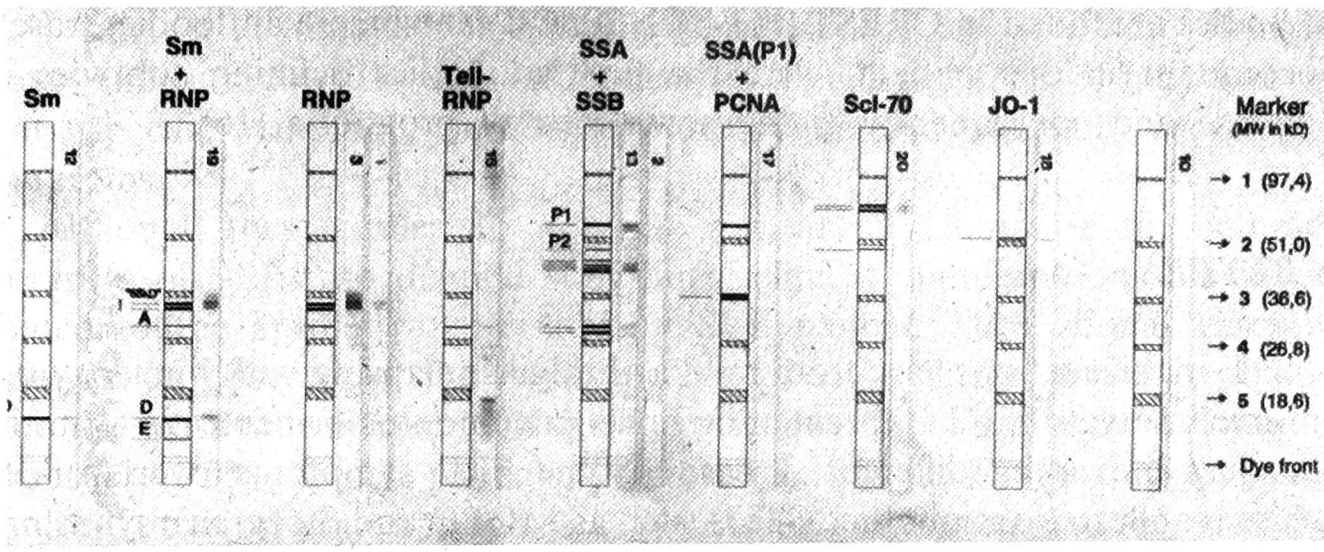

Fig. 1. Differentiating nuclear antibodies by immunoblotting (Biolab, Belgium): (from left to right) Sm; RNP/SM; RNP; part RNP; Ro (P1, P2)/LA; Ro (P1)/PCNA; SCL70; Jo-1

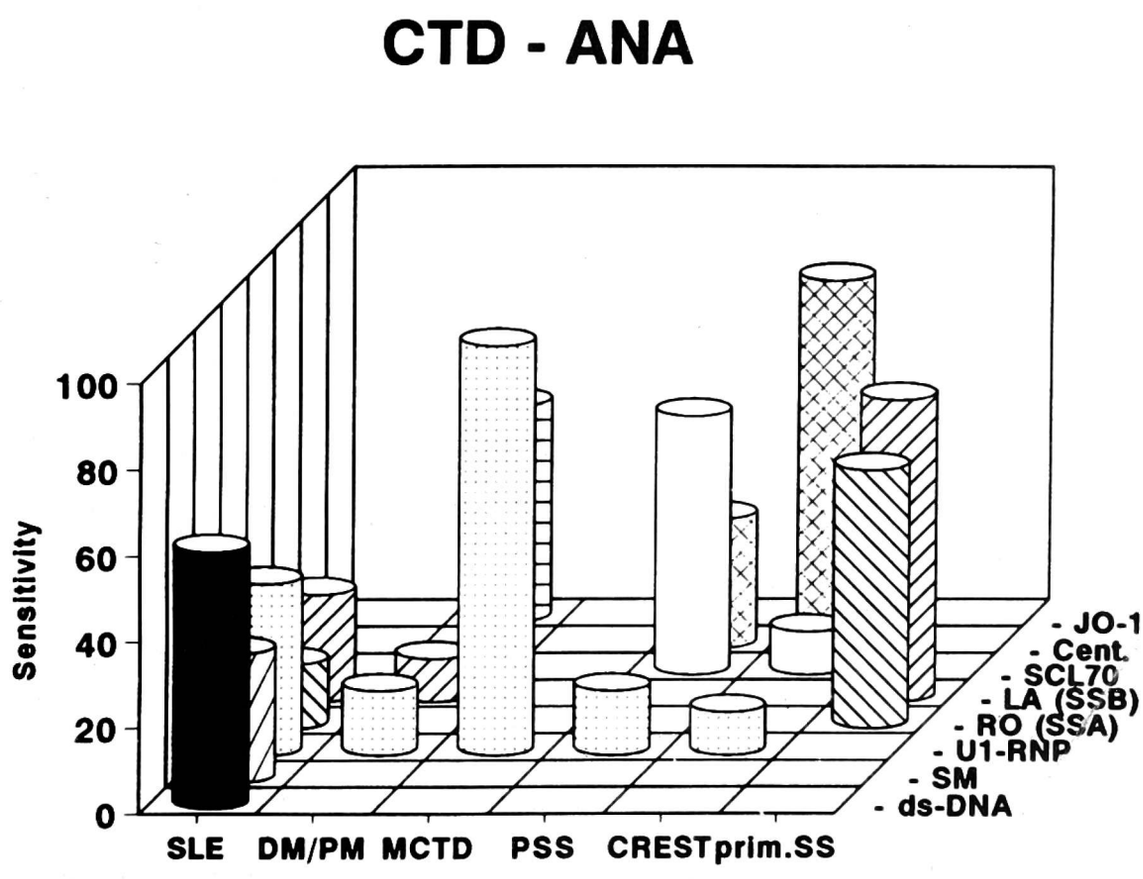

Fig. 2. Specificity (frequency in right-to-left row) and sensitivity of various nuclear antibodies in systemic connective tissue diseases. PSS: diffuse form of systemic sclerosis, CREST: acral form; DM: dermatomyositis, PM: polymyositis; prim. SS: primary Sjoegrens's syndrome, Cent: centromere antibodies

titers being highly specific (15). Other disease specific antibodies are Jo-1 in poly-/dermatomyositis and SCL 70 or centromere in systemic sclerosis (11). In *Fig. 2,* systemic sclerosis is differentiated into the diffuse form PSS and the acral form CREST, showing that SCL 70 is linked to PSS and centromere

antibodies are found in CREST (16). SCL 70 and centromere antibodies, rarely concomitant in one patient, were the first antibodies defining subtypes of a disease and consequently giving some idea of prognosis (16).

SUBTYPES

SLE manifestations vary from mild arthralgias relapsing with longer symptom-free intervals to a life-threatening lupus pneumonitis or nephritis as initial signs just indicating different diseases. Some SLE symptoms overlap with disease manifestations in other CTDs such as MCTD and Sjoegren's syndrome and in primary anti-phospholipid syndrome (*Fig. 3*). As seen in

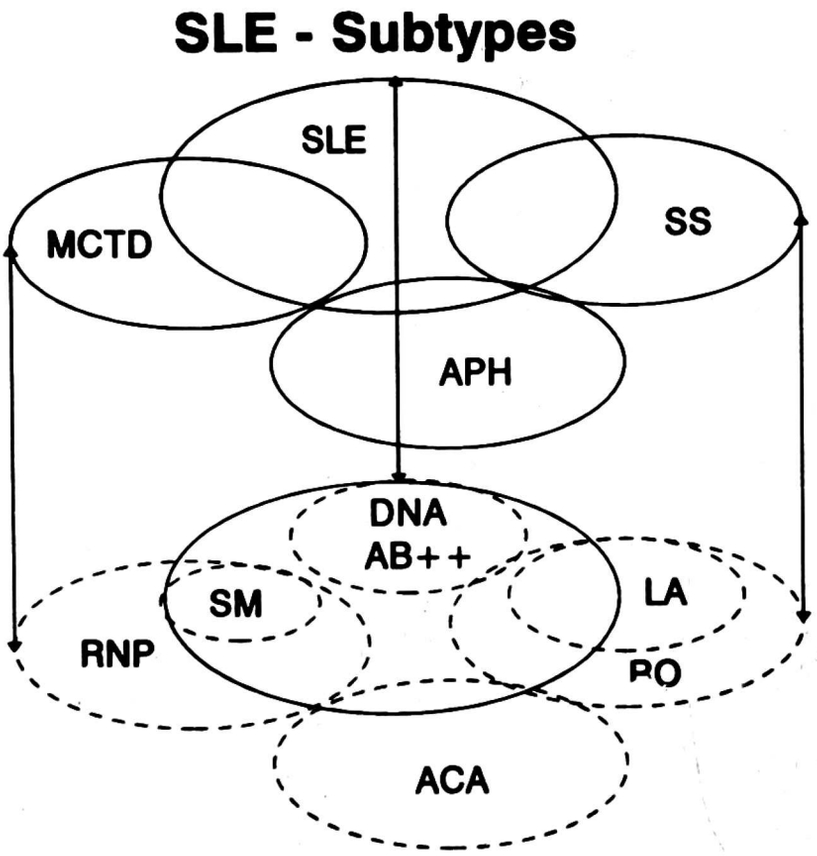

Fig. 3. above: Circles indicating overlap between SLE, MCTD, Sjoegren's syndrome (SS) and primary antiphospholipid syndrome (APH); below: Circles indicating SLE and various autoantibodies in comparison with the above clinical entities.

Fig. 2, there is also some overlap in antibodies between SLE and other CTDs: U1-RNP or Ro and La antibodies are not helpful in differentiating MCTD or scleroderma and Sjoegren's syndrome respectively from SLE. In *Fig. 3,* therefore, circles related to these antibodies intersect the SLE ring, whereas circles of highly disease-specific antibodies, ds-DNA and Sm, are within the

SLE ring, with diameter indicating sensitivity of an antibody. Bringing circles indicating CTDs and antibodies to concidence (*Fig. 3*) may indicate that specific common antibodies are concealed behind overlapping symptoms.

Although these circles do not give a clear-cut picture of the complete spectrum of SLE into definite subgroups, clinical manifestations are indeed related to the antibody pattern of an SLE patient. Thus, digital vasculitis reminds the observer of the syndrome described by Sharp, and it is obvious that this patient will carry U1-RNP antibodies. This antibody is found in about 20—25% of SLE patients; in most of them U1-RNP is accompanied by low titers of Sm antibodies (17). Another symptom of the U1-RNP subtype of SLE may be Raynaud's syndrome and the physican must be aware of pulmonary hypertension developing. Therefore regular control of pulmonary pressure and right heart function by echography is mandatory if secondary right heart decompensation is to be prevented. On the other hand there is only a low risk of U1-RNP patients having renal involvement, another parallel to MCTD.

Although there is an overlap with U1-RNP as indicated in *Fig. 3*, patients with Sm antibodies exhibit a very different clinical feature: a high percentage of patients carrying this highly disease-specific antibody will develop lupus nephritis and/or CNS involvement. As organ manifestations will be of mild expression, lupus nephritis is in general not a diffuse proliferative glomerulonephritis. The clinical feature of Sm positive patients will be characterized by symmetrical small joint arthritis, often misinterpreted as rheumatoid arthritis. Differential diagnosis is frequently facilitated by severe photosensitivity, with concomitant sign of acute cutaneous lupus in some patients.

A second area of overlap is found between SLE and Sjoegren's syndrome (*Fig. 3*). SLE patients with Ro and La antibodies, also related to Sjoegren's, syndrome, suffer from dry eyes and a dry mouth, meaning a secondary sicca syndrome. Patients with both antibodies are one type of ANA negative SLE, because antigens may be found exclusively in cytoplasma and ds-DNA antibodies are missing in many Ro and La positive patients. But these patients show classical signs of SLE with one important exception: lupus nephritis will never develop. Mothers carrying Ro antibodies have an increased risk of giving birth to a baby with neonatal lupus or with a congenital heart block (18).

SLE patients positive only for Ro share ANA negativity and sicca syndrome with patients positive for Ro and La, but it is prognostically important to differentiate the two types. Nearly every Ro positive, La negative patient will develop lupus nephritis necessitating therapy. Most of these patients are also positive for rheumatoid factor. Others exhibiting classical subacute cutaneous lupus with superficial, non-scarring small erythematous papules or peripheral

annular lesions will develop only mild nephritis. This clinical feature is often associated with C2 complement deficiency and HLA DR2 or DR3.

The center of the SLE circle in *Fig. 3*, designated „DNA AB ++" is the classical SLE as detailed in almost any short description of the disease. Patients with high ds-DNA antibody titers are highly susceptible to severe lupus nephritis. An additional complement consumption is a prognostic sign for end-stage renal failure. These classical SLE patients must be carefully monitored with changes in antibody titers and complement as control parameters and need strong immunosuppressive therapy.

A well described subtype of SLE is presented by clinical symptoms related to antiphospholipid antibodies and/or lupus anticoagulant. Especially with high titers of IgG antibodies, these patients may offer the complete feature of arterial and venous thrombotic events, recurrent miscarriage and thrombocytopenia (9). Cutaneous manifestations such as livedo reticularis and leg ulcers offer immediate evidence of this subtype, which has to be borne in mind when seeing young patients suffering from strokes or, less often, other CNS symptoms. There is an endless list of other clinical phenomena relating to this symptom complex, e.g. Libman-Sacks endocarditis, but for clinical purposes it is important to know that 100 mg acetylsalicylic acid pd are more than enough for most patients. There is no need to treat thrombocytopenia associated with antiphospholipid antibodies, because it will not be manifested as bleeding or purpura, for example.

Complement deficiency is one of the predisposing inherited marks of SLE, as argued above, and a defect of first classical pathway components causes another SLE subtype. The clinical sign in most cases is urticarial vasculitis with a poor response to steroids. To differentiate this type from a more severe complement consuming type, e.g. high ds-DNA type, it is necessary to pheno- or genotype the complement. This discrimination is important in the proper care of these patients because of a wide difference in prognosis between these types and a possible treatment of complement defect type by complement substitution.

There are some additional subtypes of SLE, e.g. related to age at onset, such as late-onset or neonatal lupus, or drug-induced lupus; all have their special symptoms and share some common signs with other types (19). This may be a factor in the failure of retrospective and some prospective studies to define SLE subtypes clearly. Nor is the accepted differentiation between SLE and chronic discoid LE absolute; 5% of discoid LE patients will develop systemic manifestations. But generally speaking, subtyping is helpful in clinical management of SLE patients with special observation of high-risk patients and attention to highly frequent symptoms. Therapy in SLE is not the treatment of a disease but the treatment of its clinical manifestations, and early detection will offer advance medication with improved prospects.

THERAPY

NSAID, steroids, antimalarias and immunosuppressive drugs are generally used as medications in SLE. Therapy is based mainly on empiric data; only in the management of lupus nephritis do results of controlled investigations exist (20). In arthritis and arthralgia, NSAID are very helpful and may be the only medication, because arthritis is in general not erosive and destructive. Other indications for NSAID are the often very painful pleurisy and pericarditis; one third of all patients with serositis can be optimally treated with NSAID, the remainder need short-term treatment with steroids. When using NSAID in SLE, the well-known side-effects of these prostaglandin inhibitors have to be borne in mind; in SLE because of lupus nephritis, the reducation of glomerular filtration rate in particular lowers the extent of indications. Long-acting NSAIDs of the oxicame type carry the additional risk of aggravating existing photosensitivity.

Antimalarias, e. g. (hydroxy-) chloroquine, are most effective in skin and joint symptoms. Because of the low risk of side-effects, the risk/benefit ratio is excellent and antimalarials are drugs of first choice in SLE patients with no major organ involvement. Results published by the Canadian SLE study group may indicate that the use of antimalarials lowers the frequency of flares (21). Therefore antimalarials may offer some preventive effect and an improved prognosis. Problems in using antimalarias are the delayed onset in efficacy and some CNS side-effects hard to differentiate from CNS involvement. In combination with immunosuppressive drugs, antimalarias allow dosages of immunosuppressiva and steroids to be reduced, preventing some dose-related side-effects of those drugs.

This effect is very important, bearing in mind the regular steroid intake of up to 2/3 of SLE patients, a factor contributing to so-called late morbidity (22). Short-term use of steroids is helpful, necessary and possibly life-saving in acute flares and in vasculitis by preventing necrosis. In major organ discorders, steroids are only indicated to bridge the time until the immunosuppressive drugs take effect. Myocarditis, lupus nephritis and central nervous vasculitis are absolute indications for immunosuppressive drugs such as azathioprine and cyclophosphamide, with the latter being used more often as pulse therapy. Cyclophosphamide administered i. v. or in combination with azathioprine seems to be superior in preventing end-stage organ failure in lupus nephritis (20). But results of long term studies on possible cancerogenic side effects of these treatment strategies are still lacking.

90 to 95% of SLE patients are adequately treated with NSAID, steroids, antimalarials and immunosuppressiva. Only 5—10% of patients need other, experimental strategies, e. g. ciclosporin or CD4 antibodies. An apparently harmless new therapy consists in high doses of intact immunoglobulins. The

effect may be due to anti-idiotypes against pathogenic autoantibodies in immunoglobulin preparations or to normalisation of idiotypic network by controlling regulatory autoantibodies (23). Preliminary results indicate some help especially in hemocytopenia, but acute renal failure has been observed as an important side-effect.

Although in use for more than 10 years in SLE, the benefit of plasmapheresis is still under discussion (24). A major international study by the LPSG will hopefully answer all questions (25); until now controlled data are missing or indications were insufficient to elaborate the effect of plasmapheresis documented in so many cases. Our own results show that plasmaperfusion provides similar results to plasmapheresis when phenylalanine is used as ligand (26); new, more selective adsorbers are in the proline and have still to be tested.

In conclusion, it is possible to separate the proverbial wolves and butterflies in SLE management. In general, the outcome has improved and most patients have a good prognosis concerning life expectation. But patients need better information to allay their fears and to intensify their sensitivity to real changes in their disease.

REFERENCES

1. Hochberg Mc. Racial differences in the descriptive and clinical epidemiology of systemic lupus erythematosus in the United States. in: Proceedings of the second International Conference on Systemic Lupus Erythematosus, PPS United States 1989; 32—34.
2. Agnello V. Lupus diseases associated with hereditary and acquired deficiencies of complement. *Springer Semin Immunopathol* 1986; 9: 161—178.
3. Winchester RJ, Lahita RG. Genetic susceptibility of systemic lupus erythematosus. In: Systemic Lupus Erythematosus (ed. RG Lahita), Wiley Medical, New York 1987; 81—118.
4. Gatenby PA. The role of complement in the aetiopathogenesis of systemic lupus erythematosus. *Autoimmunity* 1991; 11: 61—66.
5. Kalden JR. Chronisch-entzündliche Immunopathien. *Therapiewoche* 1986; 36: 707—714.
6. Rodey GE. Anti-idiotypic antibodies and regulation of immune response. *Transfusion* 1991; 32: 361—376.
7. Lee P, Urowitz MB, Bookman AAM et al. Systemic lupus erythematosus: a review of 110 cases with respect to nephritis, the nervous system, infection, aseptic necrosis and prognosis. *Q J Med* 1977; 46: 1—32.
8. Tan EM, Cohen AS, Fries JF et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271—1277.
9. Hughes GRV. The syndrome of thrombosis, abortions and neurological disease. In: Connective tissue diseases, Blackwell Scientific Publications, Oxford 1987: 72—79.
10. Hargraves MM, Richmond H, Morton R. Presentation of two bone marrow elements: The tart cell and the LE cell. *Proc Staff Meet Mayo Clinic* 1948; 23: 25—28.
11. Tan EM. Antinuclear antibodies: diagnostic markers for auotimmune diseases and probes for cell biology. *Adv Immunol* 1989; 44: 93—125.

12. Shapiro PE, McAllister G, Lerner EA, Lerner MR. Healthy individuals and patients with SLE have unique, person-specific spectra of autoantibodies detectable on immunoblots. *Clin Immunol Immunopathol* 1991; 59: 129—138.
13. Harley JB, Scofield RH. Systemic lupus erythematosus: RNA-protein autoantigens, models of disease heterogeneity, and theories of etiology. *J Clin Immunol* 1991; 11: 297—316.
14. Shiel WC, Jason M. The diagnostic associations of patients with antinuclear antibodies referred to a community rheumatologist. *J Rheumatol* 1989; 16: 782—785.
15. Sharp GC, Irvin WS, Tan EM, Gould RG, Holman HR. Mixed connective tissue disease — an apparently distinct rheumatic disease syndrome associated with specific antibody to an extractable nuclear antigen (ENA). *Am J Med* 1972; 52: 148—159.
16. Steen VD, Powell DL, Medsger TA. Clinical correlations and prognosis based on serum autoantibodies in patients with systemic sclerosis. *Arthritis Rheum* 1988; 31: 196—203.
17. Venrooij WJ van, Sillekens PTG. Small nuclear RNA associated proteins: autoantigens in connective tissue diseases. *Clin Exp Rheumatol* 1989; 7: 635—645.
18. Lockshin MD, Bonfa E, Elkon K, Druzin ML. Neonatal lupus — risk to newborns of mothers with systemic lupus erythematosus. *Arthritis Rheum* 1988; 31: 691—701.
19. Stevens MB: Systemic lupus erythematosus — clinical issues. *Springer Semin Immunopathol* 1986; 9: 251—270.
20. Austin HA, Klippel JH, Balow JE et al. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 1986; 314: 614—619.
21. The Canadian Hydroxychloroquine Study Group. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. *N Engl J Med* 1991; 324: 150—154.
22. Urowitz MB. Late mortality and morbidity. Proceedings of the second International Conference on Systemic Lupus Erythematosus, PPS United States 1989; 190—193.
23. Dwyer JM. Manipulating the immune system with immune globulin. *N Engl J Med* 1992; 326: 107—116.
24. Campion EW. Desperate diseases and plasmapheresis. *N Engl J Med* 1992; 326: 1425—1427.
25. Lupus Plasmapheresis Study Group: Clark WF, Dau PC, Euler HH et al. Plasmapheresis and subsequent pulse cyclophosphamide versus subsequent pulse cyclophosphamide alone in severe lupus. Design of the LPSG trial. *J Clin Apheres* 1991; 6: 40—46.
26. Schneider M, Berning T, Waldendorf M, Glaser J, Gerlach U. Immunoadsorbent plasma perfusion in patients with systemic lupus erythematosus. *J Rheumatol* 1990; 17: 900—907.

Received: March 10, 1993
Accepted: April 15, 1993

Author's address: M. Schneider, Medical Clinic and Policlinic B, Westphalian Wilhelms-University, Albert-Schweitzer-Str. 33, D-48129 Münster, Germany.