LITERATURE REVIEW

A. Interleukin 2 and interleukin 2 receptor

1. Properties of interleukin 2

Culture supernatants from Con A-stimulated rat spleen cells contained at least one of the biological activities, namely T cell growth factor (IL-2) (Gillis et al., 1978a). It has also been demonstrated that successful long-term cultures and maintaining proliferation of normal (Morgan et al., 1976) and cytotoxic (Gillis et al., 1978b) human T lymphocytes can be established using IL-2 found in culture supernatants of mitogen-stimulated human peripheral blood T lymphocytes. The homologies between murine, rat, and human IL-2 have been examined (Gillis et al., 1980). Although the biological activities of rat and human IL-2 were identical to mouse IL-2, their molecular characteristic were considerably different (Table 1 ; Watson and Mochizuki, 1980). It is possible that IL-2 from each of these species may interact with common cellular receptors on or in murine cells, implying that murine, rat, and human IL-2 share structural homologies (Smith et al., 1980).

Table 1 Properties of Murine, Rat, and Human Interleukin 2

Chemical and Biological Properties	Interleukin 2 from Murine	Rat	Human
1. Size (gel filtration)	30,000	15,000	15,000
2. Elution from DEAE ion exchange resin pH 7.6	0.15 MNaCl	0.05 MNaCl	0.05 MNaCl
3. Isoelectric points	4.3-4.9	5.4-5.5	6.0-6.5
4. Stable in pH range	2.0-9.0	2.0-9.0	2.0-9.0
5. Absorbed on activated murine T cell	Yes	Yes	Yes
6. Stimulate growth of murine T cells lines	Yes	Yes	Yes
7. Stimulated proliferation of murine thymocytes in presence of Con A or PHA under culture conditions where these mitogens alone are limiting	Yes	Yes	Yes
8. Generate CTL in murine thymocyte cultures and nude spleen cultures	Yes	Yes	Yes
9. Stimulate antibody responses to heterologous erythrocyte antigens in nude spleen cultures	Yes	Yes	Yes

Source : Data from Watson and Mochizuki, 1980.

2. Bioassay of IL-2

The assay is simply a lymphocyte proliferation assay. However, the target cell utilized is the one important difference between the IL-2 assay and other lymphocyte proliferation assay. Because long-term T cell lines are completely dependent upon IL-2 for their growth, such cells will proliferate in a dose dependent manner only in response to IL-2 supplied exogenously. Detailed studies showed that IL-2 was the sole proliferative stimulant, and IL-2 dependent T cell lines did not respond to lectin or antigen in the absence of IL-2 (Gillis et al., 1978a). Moreover, T cells harvested from IL-2 dependent culture, washed and placed back in culture medium in the absence of IL-2, invariable die within 24 hours (Gillis et al., 1982). IL-2 purified by molecular gel chromatography, ion-exchange chromatography, and isoelectric focusing, which migrated as a single band on SDS-PAGE, was found to mediate the proliferation of IL-2 dependent T cells. The addition of lectin to such material did not enhance or suppress its proliferative effect (Smith et al., 1980). Therefore, when IL-2 containing medium were assayed on IL-2 dependent T cells, we could be confident that any proliferative effect which occured was actually due to the presence of IL-2.

3. IL-2 production

The production of IL-2 appeared to be T cell specific. Only T-cell lectins (PHA, Con A) or antigen (alloantigens, tumor antigens) elicited IL-2 production from mononuclear cell populations (Gillis et al, 1978a). Previous study revealed that mature T cells were the producing cells (Smith et al., 1979). Thymocytes released only 1-2 % of IL-2 as compared to splenocytes, and lymphoid cells from athymic (nu/nu) mice did not release detectable IL-2 activity upon lectin or antigen stimulation (Gillis et al., 1979a). Furthermore, adherent cells were required for IL-2 production (Smith et al., 1979). The removal of adherent cells (by passage through nylon wool column) markedly reduced IL-2 production and the response was completely restored by the addition of 1-2 % adherent cells.

Human T cells have been separated into two major subsets. One subset bears the differentiation antigen CD4 whereas the other have the surface antigens CD8 (Reinherz et al., 1979). The capacity of $CD4^+$ and $CD8^+$ cells to secrete IL-2 were studied. The majority of IL-2 activity after stimulated with alloantigens or PHA was restricted to the $CD4^+$ subset (Meuer et al., 1982 ; Moretta, 1985). However, combination of PHA and phorbol myristate acetate (PMA) or Con A and PMA triggered equivalent amounts of IL-2 activity from $CD4^+$ and $CD8^+$ cells (Luger et al., 1982 ; Meuer et al., 1982).

The $CD4^+$ population in man has been subdivided by monoclonal antibodies such as anti-2H4 which recognizes an epitope on the gp 220/205 CD45-restricted antigen, and anti-4B4, which identifies the 135,000 MW CD_w29 structure (Morimoto et al., 1985a ; 1985b). $CD4^+$ $2H4^+$ $4B4^-$ cells are suppressor - inducers, whilst $CD4^+$ $2H4^-$ $4B4^+$ cells are true helper cells (Morimoto et al., 1986; Takeuchi et al.,1987). The capacity of this $CD4^+$ subset to secrete IL-2 was examined. Only the $CD4^+$ $2H4^+$ $4B4^-$ suppressor-inducer cells are capable to producing IL-2 in response to PHA or Con A stimuli. The $CD4^+$ $2H4^-$ $4B4^+$ helper cells produced no detectable IL-2 activity (Salmon et al., 1988).

4. IL-2 receptor expression

There are at least two classes of IL-2 receptors that differ in their affinities for IL-2 (Robb et al., 1984). One has a very high affinity [10 pM dissociation constant (Kd)], whereas the other has a much lower affinity (10 nM Kd). High-affinity IL-2 receptor that functions to signal T cell cycle progression is composed of at least two distinct polypeptide chain, each of which contains an IL-2 binding site (Teshigawara et al., 1987). The larger IL-2 binding protein (Mr = 75,000) is designated as p75 peptide (non-Tac IL-2 binding peptide),whereas the smaller protein (Mr = 55,000) is termed a p55 Tac peptide (Smith, 1987). The association between p55 and p75 peptide is noncovalent link and necessary to form high-affinity IL-2 receptors (Wang and Smith, 1988). Low-affinity IL-2 receptors is expressed singly by either p55 Tac or p75 peptide

(Greene et al., 1985 ; Tsudo et al., 1987a). Anti-Tac monoclonal antibody inhibited all high - affinity and almost all low-affinity IL-2 binding (Leonard et al., 1982 ; Robb et al., 1984). The IL-2 receptor p75 peptide binds to amino acid residues on IL-2 that are distinct from those bound by p55 peptide (Robb et al ; 1987). Since the p75 peptide does not contain the Tac epitope, and there are no mRNA transcripts hybridizable with Tac cDNA, it is an inescapable conclusion that the p75 peptide is encoded by an entirely separate gene from p55 peptide (Smith, 1988).

Until recently, it was thought that only the high-affinity IL-2 receptor was internalized and capable of transducing the IL-2 signal (Kuo et al., 1986 ; Robb et al., 1987 ; Teshigawara et al., 1987 ; Smith, 1988). However, several laboratories, using either cultured cell lines or peripheral blood mononuclear cells, have demonstrated that IL-2 binds to the p75 peptide and can be internalized with kinetics similar to that of the high-affinity IL-2 receptor (Tsudo et al., 1986 ; Robb and Greene, 1987 ; Siegel et al., 1987). These experiments, along with the observation that IL-2 bound only to the p55 subunit is not internalized, strongly suggest that p75 peptide is the essential component for the internalization of the IL-2 - IL-2R ligand. The binding of IL-2 to the p75 peptide on large granular lymphocytes is responsible for the initial augmentation of NK and early lymphokine-activated killer (LAK) cells activity (Siegel et al., 1987 ; Tsudo et al., 1987b).

5. Soluble IL-2 receptor

Shortly after activation, resting T lymphocytes express receptors for interleukin 2 (IL-2R) on their cell surfaces. High - affinity membrane-bound IL-2R enable the cells to proliferate in response to this lymphokine (Robb et al., 1981 ; Smith, 1988). Membrane-bound IL-2R expression reaches maximum levels within 48-72 hours and then declines (Depper et al., 1984). Corresponding to the decline in surface expression of membrane-bound IL-2R is the expression of serum IL-2R, which can be detected in culture supernatants (Rubin et al., 1985). The release of soluble IL-2R was reaching optimal levels within 72 hours and gradually declining to back ground levels (Nelson et al., 1986 ; Reske - Kunz et al., 1987). The receptors that are shed or secreted into the surrounding medium are glycoproteins with a molecular weight of approximately 45,000 daltons, which is 8,000 - 10,000 daltons less than their parent cell surface membrane receptor (Rubin et al., 1986). Competitive binding studies indicated that soluble IL-2R retained an ability to bind IL-2 with a low-affinity (Kd of 11.1 nM) (Robb and Kutny, 1987).

6. Immunoregulatory effect of IL-2

6.1 Effect on B cells function

It has been reported that antigen-nonspecific soluble factors secreted by T cells play an important role in the process of proliferation and differentiation of B lymphocytes (Howard and Paul,

1983 ; Kehrl et al., 1984). Dutton et al (1971) were the first to report the concept that T cell helper function was replaceable with mixed lymphocyte reaction (MLR) - supernatant. They demonstrated that the anti-SRBC responses in T cell depleted - murine spleen lymphocyte cultures were reconstituted with MLR-supernatant. Schimple and Wecker (1972) confirmed their data by reporting that Con A stimulated murine T cell supernatant had the same effect as MLR-supernatant.

In human system, it was shown that PHA-stumulated peripheral blood lymphocyte - supernatant (PHA - supernatant) had interferon activity (Wheelock, 1965). The others group reported that this PHA-supernatant had an activity that stimulated T cells to proliferation (Morgan et al., 1976). Therefore, the PHA-supernatant was called helper T cell factor. This discovery encouraged investigators to study how this helper T cell factor affected proliferation and differentiation of B cells. Many investigators have endeavored to separate and purify each factor contained in helper T cell factor. Recent progress in recombinant DNA technology has made highly purified IL-2 (Taniguchi et al., 1983) and IFN-γ (Gray and Goeddel, 1982) available. The effects of IL-2 and IFN-γ on the activation of human B cells was studied with recombinant IL-2 and IFN-γ. The results demonstrated that activated human B cells expressed Tac peptide and that IL-2 induced proliferation of activated B cells (Nakagawa et al., 1985). This result confirmed

the experiment done with murine B cells (Robb et al., 1981). However, IL-2 could not induce immunoglobulin secretion in activated human B cells, and IFN-γ together with IL-2 was required for the final maturation of B cells into immunoglobulin - secreting cells (Nakagawa et al., 1985). From all of these results, it can be concluded that IL-2 is one of the growth factors for B cells and IFN-γ is one of the differentiation factors for B cells.

6.2 Effect on T cell proliferation

In vitro studies have provided much information about IL-2 function as a T cell proliferative signal (Robb et al., 1981 ; Smith and Ruscetti, 1981). The specific binding of antigen/mitogen to T cell bearing clonally distributed antigen/mitogen receptors provides the first signal for IL-2 receptor expression (Cantrell et al., 1984 ; Smith and Cantrell, 1985). Furthermore, such activation also lead to endogenous IL-2 production, secretion, and subsequent binding to IL-2 receptor. Once a critical number of IL-2 receptor have bound IL-2, DNA synthesis and cell mitosis occur (Meuer et al., 1984). Therefore, any defect in the production or secretion of IL-2, or in the expression of membrane IL-2R can contribute to a low proliferative response. Moreover, IL-2 can support the growth of T cells in vitro, which makes it possible to maintain T cell lines in long term culture (Fathman and Fitch, 1984).

6.3 Effect on cytotoxic T cells

Cytotoxic T cells (CTL), capable of specifically lysing target cells in vitro, have long been implicated as the principle effector cells in allograft rejection (Cerottini and Brunner, 1974), tumor immunity (Schrader and Edelman, 1976), and lysis of virally infected cells (Glaser and Law, 1978). CTL recognize lysable targets by binding to specific target cell surface antigens and class I proteins of the major histocompatibility complex (MHC) (H-2k,D in mice and HLA-A,B in humans).

CTL responses to alloantigens occur as a result of interactions between the antigen-bearing cells (accessory cells), helper T cells and the CTL-precursors (CTL-P) (Cantor and Simpson, 1975 ; Bach et al., 1977). An important consequence of the interaction between antigen-bearing cells (accessory cells) and helper T cells is the production of soluble factors that can acitvate CTL-P. The most extensively studied of these soluble factors is the T-cell growth factor or IL-2 (Smith and Ruscetti, 1981 ; Wagner et al., 1982). It was found that after interaction with specific antigen, CTL-P express receptor for IL-2. The binding of IL-2 to these receptors derived the activated CTL-P to proliferate and differentiation into effector cells (Wagner and Rollinghoff, 1978 ; Symington and Teh, 1980). Recently, several groups have provided evidence to indicate that following antigen or mitogen stimulation of CTL-P IL-2 is the only lymphokine that is

required for the proliferation and differentiation of the CTL-P into effector CTL (Erad et al., 1985 ; Vohr and Hunig, 1985). By contrast, other workers have shown that, in addition to IL-2, other lymphokines are required for the induction of cytotoxic responses. These non-IL-2 factors were initially found in supernatants of Con A stimulated spleen cells (Raulet and Bevan, 1982), MLR supernatants (Garman and Fan, 1983), and supernatants from T cell hybridomas (Falk et al., 1983). These factors appear to be necessary for the maturation of CTL (Wagner et al., 1982 ; Finke et al., 1983) and for the induction of IL-2 receptor expression on antigen or Con A activated CTL-P (Falk et al., 1985 ; Hardt et al., 1985). It is unclear at this time whether the difference in activation requirements reflects unique requirements for activating different subsets of CTL-P, or whether these are alternative mechanisms for the activation of CTL-P.

6.4 Effect on natural killer cells

Natural killer (NK) cells are large granular lymphocyte (LGL) that able to spontaneously kill target cells in short term chromium release assay without evidence of prior antigenic sensitization (Timonen et al., 1981). NK cells are particulary cytotoxic against tumor cell lines and virus infected cells (Roder and Haliotis, 1980 ; Djeu et al., 1982).

IL-2 that was devoid of antiviral activity was also shown to be capable of enhancing NK cell cytotoxic activity (Henney et al., 1981 ; Timonen et al., 1982). On the other hand, a major factor for activation of NK cells both in vivo and in vitro is known to be IFN (Djeu et al., 1979). Recently, it was found that highly purified IL-2, free of IFN activity, enhanced NK cell activity against tumor cells in mouse spleen cell cultures and in human peripheal lymphocyte cultures in manner similar to that IFN-γ (Handa et al., 1983 ; Weigent et al., 1983). Specific antibodies either to natural IFN-γ or to a synthetic peptide corresponding to the human IFN-γ N-terminal amino acid, when added to cultures treated with IL-2, completely block IL-2 enhancement of NK cell activity for both mouse and human systems (Weigent et al., 1983 ; Ortaldo et al., 1984) Thus, this finding clearly indicate that the enhancement of NK cell activity by IL-2 is completely mediated by IL-2 induced IFN-γ production.

6.5 Effect on IFN-γ production

It is well known that IFN-γ is produced by mitogen-stimulated lymphocytes and by antigen-stimulation of sensitized lymphocyte (Epstein et al., 1971 ; Langford et al., 1978). The IFN species produced by IL-2 stimulated human T lymphocytes appeared to belong to γ-type, because its biologic activity was largely destroyed by exposure to pH 2.0 and antisera prepared against IFN-α and IFN-β did not neutralize IFN activity (Yip et al., 1981). IL-2

alone does not induce appreciable amounts of IFN-γ in any system. Thus, there seems to be a requirement for a simultaneous antigenic signal. The IL-2 dependent antigen-specific spleen cell clones will produce IFN-γ under appropriate stimulatory condition (Marcucci et al., 1981). Recently it was found that IL-2 acted in synergy with a suboptimal dose of Con A to enhance IFN-γ production (Kasahara et al., 1983). When T cell were separated further into $CD4^+$ and $CD8^+$ subsets by negative selection with monoclonal antibody and complement. Both $CD4^+$ and $CD8^+$ enriched cells produced significant levels of IFN-γ in response to IL-2 in the presence of suboptimal dose of Con A.

The requirement for monocytes and macrophages in IFN-γ production is also of particular interest. The requirement of accessory monocytes for elaboration of IFN-γ has also been reported with PHA or staphylococcal enterotoxin A used as stimulants of peripheral blood lymphocytes (Arbeit et al., 1982 ; O'Malley et al., 1982). However, murine and human T cell lines or IL-2 dependent T cell clones could elaborate IFN-γ production without any addition of exogenous macrophages or macrophage mediators (Nathan et al., 1981 ; Klein et al., 1982).

B. Autorosetting T cells

Human peripheral blood lymphocytes (PBMC) are capable of binding autologous erythrocyte to form rosettes (Sandilands et al.,

1974 ; Kaplan, 1975). However, rosette levels never exceed 3% of PBMC. When this cells were stimulated with low dose of Con A, in the presence of autologous plasma, the autorosette - forming cells (A-RFC) levels were strongly enhanced (Fournier and Charreire, 1978). A-RFC were shown to belong to a T cell subset (Gluckman and Montambault, 1975).

Con A - activated T cells can under appropriate circumstances perform helper, suppressor, and killer function (Dutton, 1975). It is found that Con A induced suppressor T cells can be identified and separated from Con A induced heper T cells by the autologous erythrocyte rosette technique, suppressor and helper T cells are confined to the autorosetting and non-rosetting T cells population respectively (Sakane et al., 1981). The autorosetting T cells can exert potent suppressor activity regardless of their phenotypes of $CD4^+$ and $CD8^+$ antigens : $CD4^+$ non-rosetting cells serve adequately as radioresistant helper cells, but are devoid of suppressor cells : and $CD8^+$ non-rosetting cells are found to lack either suppressor or helper activity (Takada et al., 1983).

C. Effect of glucocorticoid on immunosuppression

1. Effect on leukocyte number

Administration of glucocorticoids causes a lymphopenia, which reaches a nadir at 4-6 hours and which resolves within 24-48 hours (Bishop et al., 1968 ; Dale et al., 1975). The duration of

the lymphopenia and the nature of the lymphocyte subpopulations affected depend on the dose of steroid given (Cooper et al., 1977). The mechanism of the lymphopenia involves a redistribution of circulating lymphocytes such that recirculating lymphocytes leave the intravascular space (Fauci and Dale, 1975 ; Parrillo and Fauci, 1979). The process of redistribution, however, emphasizes the possibility that changes in peripheral lymphocyte function after in vivo administration of steroid may reflect changes in both cell populations and cell function. The T-inducer/helper subset, bearing the CD4 surface marker, shows a greater absolute and percentage decrease than the T-cytotoxic/suppressor subset, which usually bears the CD8 surface marker (Bast et al., 1983). As a consequence, the CD4/CD8 ratio decreases with steroid therapy and shows larger changes as the dose of steroid increases (Ten Berg et al., 1984). B lymphocytes show an absolute decrease in number but usually no change in percentage ; non-T/non-B lymphocytes show an increase in percentage, especially with doses of prednisone greather than 30 mg (Slade and Hepburn, 1983). The circulating traffic of monocytes can be suppressed ; therefore, access of monocytes to sites of antigen localization can be diminished (Bast et al., 1983 ; Ten Berg et al., 1984).

2. Effect on CMI function

Various aspects of cell-mediated immunity (CMI) are suppressed by glucocorticoids. Steroids decrease proliferation in the mixed leukocyte reaction and in response to mitogen (Mendelsohn et al., 1977 ; Webel and Aritts, 1977). They also can alter T-lymphocyte-mediated cytotoxicity (Katz et al., 1984). Glucocorticoids inhibit IL-2 production by lymphocytes, which is important in the maintenance of T cell proliferation (Gillis et al., 1979a,b). Some effects of steroids on cell-mediated immunity may also reflect effects on macrophages whether by altering circulation monocyte populations, by decreasing the production of monokines such as IL-1, or by inhibiting the response of macrophages to various lymphokines (Balow and Rosenthal, 1973). Suppression of cutaneous delayed hypersensitivity is an example of an effect on monocytes leading to delayed recruitment to the local site rather than an effect on the sensitize lymphocyte (Weston et al., 1973).

D. Systemic lupus erythematosus (SLE)

SLE is a disease of relapsing acute and chronic inflammation of unknown etiology. The frequency of SLE is substantially increased in females, particularly during the reproductive years. The female to male sex ratio is about 9 : 1 (Lahita et al., 1983). The hallmark of the disease is an immunologic state resembling autoimmunity and characterized by the

development of antibodies to multi nuclear, cytoplasmic, and cell membrane antigen (Schwartz and Datta, 1989).

SLE is also classified as immune complex disease. Many reports found high circulating immune complex in serum of SLE (Tan et al., 1966 ; Abrass et al., 1980 ; Elkon et al., 1983). The formation of circulating immune complexes can result in direct tissue deposition with consequent inflammation and tissue injury (Theofilopoulos and Dixon, 1979 ; Inman and Day, 1981). Circulating antigen - antibody complexes appears to deposit in the vascular basement membranes of target organs and mediate inflammation (Cochrane and Koffler, 1973 ; Gilliam et al., 1974 ; Inman and Day, 1981). Multiple organs may be affected, including the skin, joints, serosal surfaces, heart, lungs, kidneys, and central nervous system (Cochrane and Koffler, 1973). Once deposited, the immune complexes seem to initiate a localized in flammatory response involving activation of complement, immigration of neutrophils, the release of kinin and postaglandins, and antibody - dependent cell - mediated tissue injury (Cruickshank, 1987).

The serum of SLE patients usually contains many autoantibodies ; among them are the antibodies to double - stranded (native), single - stranded (denatured) deoxyribonucleic acid (DNA), deoxyribonucleoprotein, histones, nuclear ribonucleoprotein, the so - called Sm antigen, and other nuclear constituents. These antibodies are termed antibodies to nuclear antigen (ANA).

Antibodies may be to cytoplasmic antigen (RNA, ribosome), to clotting factors, to antigens on circulating cells (red cells, neutrophils, platelets, T lymphocytes, B lymphocytes), and to cardiolipin to produce a false - positive serological test for syphilis (Schwartz and Datta, 1989).

The regulation of antibody production of B lymphocytes seem to be defective in SLE (Blaese et al., 1980). Although, spontaneous B lymphocyte activity is increased, B lymphocytes from SLE patients secreted abnormally low levels of immunoglobulin in response to mitogen (Bobrove and Miller, 1977 ; Ginsberg et al., 1979 ; Tan et al., 1981) or to specific antigen (Gottlief et al., 1979 ; Delfraissy et al., 1980 ; Nies et al., 1980). The decreased immunoglobulin secretion can be restored by adding of normal T lymphocytes (Bobrove and Miller, 1977 ; Nies et al., 1980). This suggested that B lymphocyte hyporesponsiveness to mitogen or specific antigen was caused by a T helper cell defect in SLE. In addition, T cells of SLE decrease proliferative response to mitogen (Rosenthal and Franklin, 1975 ; Utsinger and Yount, 1977 ; Hamilton et al., 1982). These T cell defects can be corrected by the addition of helper T cells of normal subjects (Nies et al., 1980) or by the addition of IL-2 (Bidulo et al., 1985). Moreover, cytotoxic T cells (Charpentier et al., 1979 ; Tsokos et al., 1983) and NK cells activity is decreased in SLE patients (Hoffman, 1980). IL-2 can restore these defect (Tsokos et al., 1985). These observation

suggested that decreased IL-2 activity may contribute to a lupus diathesis such as viral and fungal infection (Drutz and Graybill, 1987).

The clinical manifestation of this disease is remarkably diverse, including fever, erythematosus rash, polyarthralgia and arthritis ; polyserositis (especially pleuritis and pericarditis), anemia, thrombocytopenia as well as renal, neurologic and cardiac abnormalities (Hughes, 1982). Because of multisystem involvement in SLE, the diagnosis of SLE requires criteria for diagnosis. The most popular criteria for diagnosis of SLE was an American Rheumatism Association (ARA ; 1979). In 1982' ARA revised the old criteria to a new one (Tan et al., 1982). The latter criteria for diagnosis of SLE are shown in Table 2. Scoring of severity of clinical disease on a 0 or 3 scale was base on the following definitions (Barada et al., 1981) : 0 = no activity ; 1 = mild clinical disease (e.g.; fatique, arthralgias, mild skin rash) or significant improvement from 2 ; 2 = moderately severe disease, but without manifestation of renal or CNS involvement with the disease flare (e.g.; polyarthritis, serositis, rash) or significant improvement from 3 ; 3 = significant multisystem disease with renal and/or CNS involvement.

Table 2 Revised criteria for diagnosis of systemic lupus erythematosus*

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a) Pleuritis-convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion OR

Table 2 (Continued)

Criterion	Definition
	b) Pericarditis-documented by ECG or rub or evidence of pericardial effusion
7. Renal disorder	a) Persistent proteinuria greater than 0.5 g per day or greater than 3 + if quantitation not performed OR b) Cellular casts-may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	a) Seizures-in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance OR b) Psychosis-in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic disorder	a) Hemolytic anemia-with reticulocytosis OR

Table 2 (Continued)

Criterion	Definition
	b) Leukopenia-less than 4,000/mm³ total on 2 or more occasions OR c) Lymphopenia-less than 1,500/mm³ on 2 or more occasions OR d) Thrombocytopenia-less than 100,000/mm³ in the absence of offending drugs
10. Immunologic disorder	a) Positive LE cell preparation OR b) Anti-DNA : antibody to native DNA in abnormal titer OR c) Anti-Sm : presence of antibody to Sm nuclear antigen d) False-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test

Table 2 (Continued)

Criterion	Definition
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrom

* The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.

E. Interleukin 2 and interleukin 2 receptor in SLE patients

1. IL-2 production in SLE patients

In human with SLE, study of IL-2 production has recently been reported. Deficiency of IL-2 appears to exist in certain SLE patients. Some investigators have suggested that decreased production of IL-2 by the peripheral blood lymphocytes when stimulated with PHA in patients with SLE may, at least in part, account for the immune disregulation (Alcocer - Varela and Alarcon - Segoria, 1982 ; Linker - Israeli et al., 1983 ; Miyasaka et al., 1984 ; Murakawa et al., 1985 ; Huang et al., 1986).However, others have reported normal production of IL-2 by the peripheral blood mononuclear cells when costimulated Con A and PMA (Sibbitt et al., 1984 ; Draeger et al., 1986). This discrepancy may be due to differences in the patients studied or the agents (mitogen) used for cellular activation (Murakawa and Sakane, 1988 ; Chopra et al., 1989).

2. IL-2 receptor expression in SLE patients

Some investigators have reported that PHA-activated or autologous mixed lymphocyte reaction - activated peripheral blood lymphocytes from patients with SLE have a significantly diminished proliferative response to exogenous IL-2 (Alcocer - Varela and Alarcon - Segovia, 1982 ; Murakawa et al., 1985). In contrast, others have reported normal responsiveness of Con A - activated peripheral blood lymphocytes to IL-2 in patients with SLE (Miyasaka et al., 1984 ; Draeger et al., 1986). This discrepancy may be due

to different stages of immunological activity of the autoimmune process or the methods used (Volk et al., 1986). Recently, it was found that the defect in recombinant IL-2 (r IL-2) responsiveness may be due to an impairment in induction of high affinity IL-2 receptors expression (Ishida et al., 1987 ; Lakhanpal and Handwerger, 1987).

3. Soluble IL-2 receptor in SLE patients

Levels of serum IL-2R can be detected with a double-antibody "sandwich" enzyme-linked immunosorbent assay (ELISA), (Rubin et al., 1985). Elevated levels of serum IL-2R were significantly increased in SLE patients compared with controls (Wolf and Brelsford, 1988). The level was correlated strongly with clinical and laboratory indicators of disease activity (Campen et al., 1988).