Clin. exp. Immunol. (1982) **48**, 155–162.

Deficient autologous mixed lymphocyte reactions correlate with disease activity in systemic lupus erythematosus and rheumatoid arthritis

J. B. SMITH & R. J. DEHORATIUS *Institute for Cancer Research, Fox Chase Cancer Center, Philadelphia, and Department of Medicine, Division of Rheumatology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pa, USA*

(Accepted for publication 16 October 1981)

SUMMARY

We have examined autologous mixed lymphocyte culture (AMLC) reactions in patients with systemic lupus erythematosus (SLE), classical rheumatoid arthritis (RA), and in normal age and sex matched healthy control individuals. AMLC responses were found to be lower than the median of all controls and patients in 30 of 31 individuals with SLE and RA and in only 2 of 15 healthy controls. In both SLE and RA there was a statistically significant correlation of decreased AMLC reaction with disease activity. On an individual basis, there was no direct correlation between decreased AMLC reactivity, concomitant steroid therapy, or the occurrence of clinical or laboratory parameters of autoimmunity.

INTRODUCTION

In the autologous mixed lymphocyte culture (AMLC) reaction, T cells from healthy individuals respond by proliferation when cultured with autologous non-T cells (Opelz *et al.*, 1975), most probably B cells (Smith, 1978) or B cells plus monocytes (Stobo & Loehnen, 1978). Recognition in this system occurs via Ia-like antigens (Gottleib *et al.*, 1979). The responding T cells are in the subpopulation not having receptors for the Fc portion of IgG (Wolos & Davey, 1979). Functionally, the responder cells fall within the subset of T cells which are stimulated by Concanavalin-A (Smith & Knowlton, 1981) and in our studies appear to be separate from cells responding to alloantigens although some controversy exists on this point (Stobo & Loehnen, 1978). T cells with helper (Weksler *et al.*, 1980; Hausman & Stobo, 1979) and suppressor (Smith & Knowlton, 1979) activity are recoverable from AMLC. Deficient or absent AMLC reactions have been found in patients with chronic lymphocytic leukaemia (CLL) (Smith, Knowlton & Koons, 1977; Kuntz, Innes & Weksler, 1976), Hodgkin's disease (Engleman *et al.*, 1980), non-Hodgkin's lymphoma (Smith, Knowlton & Harris, 1981), systemic lupus erythematosus (SLE) (Sakane, Steinberg & Green, 1978), and Sjogren's syndrome (Miyaska *et al.*, 1980). The experimental findings and disease distribution of AMLC reaction deficiency have led to the notion that AMLC may be an *in vitro* manifestation of an immunoregulatory pathway.

Correspondence: J. Bruce Smith, M.D., Jefferson Medical College, 1015 Walnut Street, Room 613, Philadelphia, Pa 19107, USA.

0009-9104/82/0400-0155$02.00 © 1982 Blackwell Scientific Publications

In an analogous system in mice, we (Pasternak, Bocchieri & Smith, 1980) and others (Lattime, Bolub & Stutman, 1980) have shown that the responding cells are LY $1^{+}23^{-}$ T cells and that stimulation occurs via recognition of cell surface determinants encoded by the I region of the major histocompatibility complex (Lattime *et al.*, 1980; Bocchieri & Smith, 1980). Suppressor cells can also be recovered from murine AMLC (Wolos, Smith & Pasternak, 1980) and recent studies show that the AMLC reaction can provide a helper effect in the generation of H-2 restricted cytotoxicity toward hapten-modified self antigens (Wolos & Smith, 1981). Murine AMLC reactions have been demonstrated in all 'normal' inbred strains but are absent or deficient in NZB (Smith & Pasternak, 1978) and other autoimmune strains (Glimcher *et al.*, 1980; Hom & Talal, 1980).

We report here studies in patients with SLE and rheumatoid arthritis (RA), designed to determine whether the distribution of AMLC reaction deficiency in these diseases correlated with disease activity, autoantibody formation, or other immunological abnormalities.

MATERIALS AND METHODS

Patient populations. Nineteen patients with SLE who met the preliminary American Rheumatism Association criteria for SLE (Cohen *et al.*, 1971) and 12 patients with classic RA (McEwen, 1976), were studied. Active SLE was determined by criteria previously published (DeHoratius, Tung & Pinkus, 1980). These patients were studied at least 24 hr after the last dose of corticosteroids and none was receiving other immunosuppressive drugs. Eight of 10 patients with active SLE and five of eight patients with inactive disease were receiving corticosteroids and the remaining patients were on non-steroid anti-inflammatory drugs. Patients with RA were judged to have active disease if their systemic activity index was greater than 30 (Lansbury, 1958). Corticosteroid therapy was being administered to two of seven patients with active disease and one of five patients with inactive disease.

Age and sex matched normal subjects were studied simultaneously with all SLE and RA patients. The studies of AMLC and MLC reactions were done without knowledge of the exact diagnosis, clinical status or laboratory values for the patients.

Cell cultures. The AMLC and MLC methodology has been described in detail in several publications (Smith, 1978; Smith & Knowlton, 1979; Smith *et al.*, 1977). Peripheral blood lymphocytes were separated by the Ficoll–hypaque method (Boyum, 1968) and triplicate cultures of 2×10^5 E-rosette purified T cells and an equal number of non-rosetting mitomycin-C treated stimulator cells were incubated at 37°C for 6 days in 96-well microtitre plates (IS-FB-96, Linbro). The medium used was RPMI-1640 (Microbiological Associates) containing 100 μg/ml penicillin, 100 μg/ml streptomycin, 5 mM Hepes buffer, and 20% normal human serum (NHS) or 20% fetal calf serum (FCS). All data presented are from cultures done in NHS unless otherwise noted. The NHS used was type O, Rh(−) and has been used extensively in this laboratory. This serum has never been shown to be enhancing or suppressive when compared to autologous serum. All cultures were pulsed with ^{125}Iudr (New England Nuclear) for 4–6 hr prior to harvesting onto glass fibre filter paper and results are given as net counts per min (c.p.m.) incorporated into cultured cells (c.p.m. in stimulated cultures minus c.p.m. in unstimulated cultures = Δ c.p.m.).

Laboratory parameters. The erythrocyte sedimentation rate (ESR) was measured by the standard Westergren method. Complement (C) levels were determined by radial-immunodiffusion. DNA binding was measured by radioimmunoassay (Pincus *et al.*, 1969) and was kindly performed by Dr David Koffler, Hahnemann Medical College, Philadelphia, Pa. Immune complexes (IC) were detected by C1q binding (DeHoratius *et al.*, 1980; Hay, Nineham & Roitt, 1975), and rheumatoid factor (RF) was determined by latex agglutination (Singer & Plotz, 1956).

Statistical analysis. Data were analysed by Dr S. Litwin and Mr L. Herring of the biostatistics group at ICR. Standard non-parametric tests were utilized. Comparison of specific results on normal control individuals with those of the patient populations was done using a one-tailed Mann-Whitney test. A two-tailed test was used to assess clinical laboratory test associations for comparing normal and SLE and RA populations, AMLCs were considered decreased if they were less than the median of all populations being tested.

Table 1. Analysis of AMLC reactions of patients with SLE and RA compared with those of healthy controls and relative to disease activity

Populations tested and AMLC reactions††	Healthy controls	Patients	Disease activity	
			Active	Inactive
All controls plus all patients				
AMLC normal	13	11	2	9
AMLC low	2	20*	16†	4
All controls plus SLE patients				
AMLC normal	12	6	1	5
AMLC low	3	13‡	10§	3
All controls plus RA patients				
AMLC normal	9	5	1	4
AMLC low	6	7	6**	1

†† AMLC reactions were considered normal if greater than the median AMLC of the groups being analysed.

Difference is significant: * $P<0.0005$; † $P<0.005$; ‡ $P<0.002$; § $P<0.03$; ** $P<0.05$.

RESULTS

AMLC reactions in normal control individuals and in SLE and RA patients

The normal healthy control individuals had AMLC responses ranging from 1,754 to 22,488 c.p.m. with a mean value of 10,051 ± 6,429 c.p.m. Counts in unstimulated cultures ranged from 100 to 575. Table 1 shows a summary of the data collected on AMLC reactions in normal controls and SLE and RA patients and Fig. 1 shows the data graphically. When all SLE and RA patients plus all normal controls were considered, only two of 15 controls had an AMLC reaction less than the median (4,019). Of the 31 SLE and RA patients, 20 were below the median. This difference is significant ($P<0.0005$). Of the 20 patients with low AMLC reactions, 16 had active disease compared with two of 11 patients having active disease and AMLC reactions greater than the median. This difference was also statistically significant ($P<0.0005$). As can be seen in Table 1, these patterns of low AMLC reactions associated with active disease also occur when SLE and RA patients are analysed separately.

Correlation of AMLC reactivity and other laboratory characteristics of autoimmunity or disease activity

Patients with decreased AMLC reactions had significantly increased levels of anti-ss DNA antibody ($P<0.01$), IC ($P<0.01$) and a significantly higher ESR ($P<0.01$) when compared to patients with normal AMLC reactions. There were no significant differences between these groups when measurements of serum complement and anti-native DNA were compared. Furthermore, significant differences were not found in measurements of haematocrit, white blood cell count or per cent and total lymphocytes. Individually, there were no correlations between the magnitude of the AMLC reactions and the presence or absence of IC, anti-DNA antibodies or C levels. RA patients with significantly decreased AMLC reactions also had significantly lower haematocrits ($P<0.01$) and significantly higher ($P<0.05$) levels of RF when these were compared to findings for the normal AMLC reaction group.

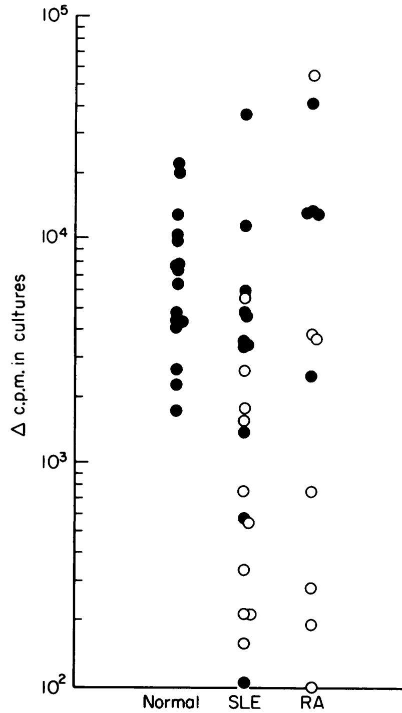

Fig. 1. AMLC reactions in 19 SLE, 12 RA and 15 healthy subjects. Tests were done in normal human serum and the net increase in c.p.m. is shown on the ordinate. Filled circles designate tests on healthy controls and patients with inactive disease. Empty circles designate patients with active disease. The median AMLC reaction for all normal controls plus all patients was 4,019 c.p.m., for all normals plus SLE patients it was 4,175 c.p.m., and for normal controls plus RA patients the median was 6,177 c.p.m.

AMLC reactions in medium supplemented with FCS compared to medium containing NHS

Another study (Sakane *et al.*, 1978) in which decreased AMLC reactions in patients with SLE was demonstrated, utilized FCS as a culture medium supplement but no comparison with results of cultures done in human sera was made. Date on 14 controls, 15 patients with SLE, and 11 patients with RA were available for analysis. As shown in Table 2, the frequency of significantly increased AMLC reactions in FCS in normal control individuals is greater than in patients with SLE

Table 2. Comparison of AMLC responses in cultures containing fetal calf serum with those containing normal human serum

	AMLC responses in FCS compared to NHS		
Diagnoses	Total tested	Significantly* increased	Significantly* decreased
Normal	14	8	2
SLE	14	1	2
RA	11	4	3

* Mann-Whitney test.

Table 3. AMLC and MLC responses of controls and SLE and RA patients selected for having decreased AMLC responses and active disease

Responder T cells	Unstimulated	Δc.p.m. in response to stimulation with	
		Autologous	Allogeneic
Normal	293±114	22,488±4172	66,236±4,576
SLE	182±123	223±141	29,457±4,250
Normal	272±111	4,508±596	25,442±1,827
SLE	153±42	344±534	14,790±3,417
Normal	180±83	7,101±556	13,542±1,432
SLE	208±66	153±218	14,810±1,637
Normal	575±159	7,577±1,955	29,968±6,637
SLE	134±5	743±294	14,852±2,995
Normal	166±36	6,177±434	5,407±837
SLE	110±48	271±210	10,820±2,146
Normal	148±25	10,089±1,131	23,215±732
SLE	274±170	192±189	42,437±891

($P < 0{\cdot}05$). This difference was not found when normal individuals and RA patients were compared. Differences in the frequency of decreased AMLC responses done in FCS compared to NHS were not found among the three groups.

Mixed lymphocyte culture reactivity

All patients tested, except one RA patient with active disease and a severely decreased AMLC reaction, responded vigorously to allogeneic normal lymphocytes. The mean net increase in c.p.m. incorporated in all MLC reactions of patients *vs* controls was 25,679±19,315 and of controls *vs* patients was 31,987±18,339. When MLC reactions were compared in all groups, no significant differences between patients with active or inactive disease or having normal or decreased AMLC reactions were found. Thus, all patients (with the one exception noted) had functional alloreactive T cells. Table 3 shows reciprocal MLC results of six healthy individuals and six patients selected for low AMLC. In each case, the MLC reactivity was vigorous despite severely depressed AMLC responses.

DISCUSSION

The data presented in this paper show a significant correlation between decreased AMLC responses and active disease in patients with SLE and RA. Decreased AMLC responses are therefore associated with some of the clinical and laboratory manifestations of disease activity. There is, however, no association in individual patients between decreased AMLC reactivity and other measurements of autoimmunity such as presence of circulating immune complexes, decreased complement levels, and antibodies to native or single-stranded DNA. Nor is there concordance among all of these traits in individual patients. This latter group of findings is similar to our recent findings in mice. Analysis of a number of autoimmune traits common to NZB mice in recombinant–inbred lines of C58 and NZB parentage (Riblet *et al.*, 1980) revealed separate genetic control for AMLC reactivity, Coomb's autoantibody, and antithymocyte antibody formation (Bocchieri, Riblet & Smith, 1981). More recent studies also indicate a lack of correlation between the presence of IgM hypersecretion, ecotropic and xenotropic virus expression (S. Datta *et al.*,

unpublished data), presence of antibodies to DNA (Raveche *et al.*, 1980), and the other autoimmune traits previously measured (Bocchieri *et al.*, 1981). It thus appears that the phenotypic expression of autoimmunity in both humans and in the NZB mouse model results from a disorder affecting many genes.

It has been previously reported that cortisone inhibits the AMLC reaction (Ilfeld, Krakauer & Blaese, 1977). The differences we report here, however, probably cannot be accounted for by the effects of corticosteroids since patients with both normal and decreased AMLC reactions were receiving such therapy. The problem of long-term steroid therapy affecting the AMLC reaction has not been examined. There are some studies, however, on the more immediate effects of these drugs. The immunosuppressive effects of a single oral dose of steroids on AMLR in humans are not evident after 24 hr (Hahn *et al.*, 1980) and our studies in mice show that the responder cells in AMLC are in the cortisone-resistant thymus (Pasternak *et al.*, 1980) and spleen (Wolos *et al.*, 1980) T-cell populations.

In one study demonstrating deficient AMLC reactions in SLE patients, cultures were done in fetal calf serum (Sakane *et al.*, 1978). Enhanced AMLC responses of healthy volunteers have been previously demonstrated (Gottlieb *et al.*, 1979) but remain unexplained. Failure, however, of SLE patients to exhibit FCS-induced enhancement could lead to difficulties in data interpretation. Our data show that patients with SLE do not exhibit enhanced AMLC responses in FCS as do normal controls and about half of the patients with RA (Table 4 and Fig. 2). The result does not appear to be due to a mitogenic response of T lymphocytes to elements in FCS as control (unstimulated) counts in cultures containing FCS did not differ significantly from those in NHS.

The mechanism of the AMLC defect in SLE and RA is not specifically addressed in this paper although the decreased AMLC reaction with preservation of vigorous alloreactivity argues against a generalized T-cell defect. Work from other laboratories on SLE suggests a defect at the stimulator cell level (Kuntz, Innes & Weksler, 1979) or in the responder population (Sakane *et al.*, 1978). Our findings (Bocchieri *et al.*, 1981; Wolos & Smith, 1981) and those of other (Glimcher *et al.*, 1980; Hom & Talal, 1980) in the murine system indicate that the defect in AMLC reactivity in autoimmune mice is the result of either decreased numbers or function of the responding T cells. In Hodgkin's disease, the decreased AMLC reactivity is due to failure of T cells to respond (Engleman *et al.*, 1980) and in Sjogren's disease decreased AMLC reactivity is also probably due to failure of the responding T cells (Miyasaka *et al.*, 1980). Experimental evidence so far does not suggest that decreased AMLC is due to suppressor cells or factors (Smith *et al.*, Kuntz *et al.*, 1976; Engleman *et al.*, 1980; Sakane *et al.*, 1978). The association between decreased AMLC responses and the presence of circulating immune complexes suggests the possibility that IC might bind to the responder T cells and adversely affect their function or to non-T cells and result in faulty stimulation. Alternatively, there may be a paucity of responder cells due to anti-lymphocyte antibodies known to occur in SLE (DeHoratius *et al.*, 1980) and in RA (Searles, Messner & Hermanson, 1981).

These results demonstrate again the complex nature of autoimmune diseases. The decreased AMLC reactions in SLE and RA provide additional evidence for faulty immunoregulation in these diseases.

This work supported by American Cancer Society Grant IM 251-A, USPHS Grant AI-15876, NIH Grants CA-06927 and RR-05539 and the Commonwealth of Pennsylvania. This work was also supported by the Lupus Foundation, and the PEW Foundation through a grant to the Eastern Pennsylvania Chapter of the Arthritis Foundation. R. J. DeHoratius is the recipient of NIH Young Investigator Award IR 23 A14574.

REFERENCES

Bocchieri, M.H., Riblet, R.J. & Smith, J.B. (1981) Autologous mixed lymphocyte reactions in NZB mice: Analysis in recombinant inbred lines show a T cell defect unrelated to autoantibody production. *Europ. J. Immunol.* **11**, 159.

Bocchieri, M.H. & Smith, J.B. (1980) Syngeneic mixed lymphocyte reactions (SMLR) in mice are mediated by Ia antigens. *IV Int. Congress Immunol.* 14.3.08 (abstract).

Boyum, A. (1968) Isolation of mononuclear cells and granulocytes from human blood. *Scand. J. clin Lab. Invest.* **97**, 77.

COHEN, A.S., RENOLDS, W.E., FRANKLIN, E.C., KULKA, J.B., ROPES, M.W., SHULMAN, L.E. & WALLACE, S.L. (1971) Preliminary criteria for the classification of systemic lupus erythematosus. *Bull. Rheum. Dis.* **21,** 643.

DEHORATIUS, R.J., TUNG, K.S.K. & PINCUS, T. (1980) Reduced T lymphocyte subsets in systemic lupus erythematosus: effects of immune complexes and lymphocytotoxic antibodies. *Clin. Immunol. Immunopathol.* **17,** 245.

ENGLEMAN, E.G., BENIKE, C.J., HOPPE, R.T., KAPLAN, H.S. & BERBERICH, F.R. (1980) Autologous mixed lymphocyte reaction in patients with Hodgkin's Disease. Evidence for a T cell defect. *J. clin. Invest.* **66,** 149.

GLIMCHER, L.H., STEINBERG, A.D., HOUSE, S.B. & GREEN, I. (1980) The autologous mixed lymphocyte reaction in strains of mice with autoimmune disease. *J. Immunol.* **125,** 1832.

GOTTLEIG, A.B., FU, S.M., YU, D.T.Y., WANG, C.Y., HALPER, J.P. & KUNKEL, H.G. (1979) The nature of the stimulatory cell in human allogeneic and autologous MLC reactions: Role of isolated IgM-bearing B cells. *J. Immunol.* **123,** 1497.

HAHN, B.H., MACDERMOTT, R.P., JACOBS, S.B., PLETSCHER, L.S. & BEALE, M.G. (1980) Immunosuppressive effects of low dose glucocorticoids: Effects on autologous and allogeneic mixed leukocyte reactions. *J. Immunol.* **124,** 2812.

HAUSMAN, P.B. & STOBO, J.D. (1979) Specificity and function of a human autologous reactive T cell. *J. exp. Med.* **149,** 1537.

HAY, F.C., NINEHAM, L.J. & ROITT, I.M. (1975) Routine assay for the detection of IgG and IgM antiglobulins in seronegative and seropositive rheumatoid arthritis. *Brit. med. J.* **iii,** 203.

HOM, J.T. & TALAL, N. (1980) Decreased syngeneic mixed lymphocyte response (SMLR) in genetically susceptible autoimmune mice. *Fed. Proc.* **39,** 1129 (Abstract no. 4539).

ILFELD, D.N., KRAKAUER, R.S. & BLAESE, R.M. (1977) Suppression of the human autologous mixed lymphocyte reaction by physiologic concentrations of hydrocortisone. *J. Immunol.* **119,** 428.

KUNTZ, M.M., INNES, J.B. & WEKSLER, M.E. (1976) Lymphocyte transformation induced by autologous cells. IV. Human T-lymphocyte proliferation induced by autologous or allogeneic non-T lymphocytes. *J. exp. Med.* **143,** 1042.

KUNTZ, M.M., INNES, J.B. & WEKSLER, M.E. (1979) The cellular basis of the impaired autologous mixed lymphocyte reaction in patients with systemic lupus erythematosus. *J. clin. Invest.* **63,**151.

LANSBURY, J. (1958) Report of a three-year study on the systemic and articular indexes in rheumatoid arthritis: theoretic and clinical considerations. *Arth. and Rheum.* **1,** 505.

LATTIME, E.C., GOLUB, S.H. & STUTMAN, O. (1980) Ly 1 cells respond to Ia-bearing macrophages in the murine syngeneic mixed lymphocyte reaction. *Europ. J. Immunol.* **10,** 723.

MCEWEN, C. (1976) The diagnosis and differential diagnosis of rheumatoid arthritis. *Arthritis and Allied Conditions* (ed. by J. L. Hollander) p. 403. Lea and Febiger, Philadelphia.

MIYASAKA, N., SAUVEZIE, B., PIERCE, D.A., DANIELS, T.E. & TALAL, N. (1980) Decreased autologous mixed lymphocyte reaction in Sjogrens Syndrome. *J. clin. Invest.* **66,** 928.

OPELZ, G., KIUCHI, M., TAKASUGI, M. & TERASAKI, P.I. (1975) Autologous stimulation of human lymphocyte subpopulations. *J. exp. Med.* **143,** 1327.

PASTERNAK, R.D., BOCCHIERI, M.H. & SMITH, J.B. (1980) Surface phenotype of responder cells in the syngeneic mixed lymphocyte reaction in mice. *Cell. Immunol.* **49,** 384.

PINCUS, T., SCHUR, P.H., ROSE, J.A., DECKER, J.L. & TALAL, N. (1969) Measurement of serum DNA activity in systemic lupus erythematosus. *N. Engl. J. Med.* **28,** 701.

RAVECHE, E.S., BORWN, L.J., NOVOTNY, E.A., TJIO, J.H., SHREFFLER, D.C. & STEINBERG, A.D. (1980) Evidence for separable genetic traits in NZB mice. *Fed. Proc.* **39,** 1129 (abstract).

RIBLET, R., CLAFFIN, L., GIBSON, D.M., MATHIESON, B.J. & WEIGERT, M. (1980) Antibody gene linkage studies in (NZB × C58) recombinant–inbred lines. *J. Immunol.* **124,** 787.

SAKANE, T., STEINBERG, A.D. & GREEN, I. (1978) Failure of autologous mixed lymphocyte reactions between T and non-T cells in patients with systemic lupus erythematosus. *Proc. Natl Acad. Sci. USA,* **75,** 3463.

SEARLES, R.P., MESSNER, R.P. & HERMANSON, S.M. (1981) Antilymphocyte antibodies in rheumatoid arthritis: Increased reactivity against activated lymphocytes. *Clin. Immunol. Immunopathol.* **20,** 246.

SINGER, J.M. & PLOTZ, C.M. (1956) The latex fixation test. I. Application to the serologic diagnosis of rheumatoid arthritis. *Amer. J. Med.* **21,** 188.

SMITH, J.B. (1978) Stimulation of autologous and allogeneic human T-cells by B-cells occurs through separate B-cell antigen systems. *Cell. Immunol.* **36,** 203.

SMITH, J.B. & KNOWLTON, R.P. (1979) Activation of suppressor T cells in human autologous mixed lymphocyte culture. *J. Immunol.* **123,** 419.

SMITH, J.B. & KNOWLTON, R.P. (1981) Autologous mixed lymphocyte culture responder T cells are in the Concanavalin-A reactive subpopulation and separate from alloreactive cells. *Clin. Immunol. Immunopathol.* **20,** 31.

SMITH, J.B., KNOWLTON, R.P. & HARRIS, D.T. (1981) Decreased autologous mixed lymphocyte reactions (AMLC) in patients with non-Hodgkin's lymphoma. *Proc. 7th Meeting Amer. Assoc. Cancer Res.* **22,** 317 (abstract 1261).

SMITH, J.B., KNOWLTON, R.P. & KOONS, L.S. (1977) Immunological studies in chronic lymphocytic leukemia: defective stimulation of T cell proliferation in autologous mixed lymphocyte culture. *J. Natl Cancer Inst.* **58,** 579.

SMITH, J.B. & PASTERNAK, R.D. (1978) Syngeneic mixed lymphocyte reaction in mice: strain distribution, kinetics, participating cells, and absence in NZB mice. *J. Immunol.* **121,** 1889.

STOBO, J.D. & LOEHNEN, C.P. (1978) Proliferative reactivity of T cells to autologous cell-animated antigens. *Arth. and Rheum.* **21,** supplement 210.

WEKSLER, M.E., MOODY, C., OSTRY, R.F. & CASAZZA, B.A. (1980) Lymphocyte transformation induced by autologous cells. X. Soluble factors that

generate cytotoxic T lymphocytes. *J. exp. Med.* **152,** 284.

Wolos, J.A. & Davey, F.R. (1979) T cells subpopulations in the autologous and allogeneic mixed lymphocyte reaction. *Cell. Immunol.* **48,** 415.

Wolos, J.A. & Smith, J.B. (1981) Helper cells in the autologous mixed lymphocyte reaction. I. Generation of cytotoxic T cells recognizing modified self H-2. *J. Immunol.* **127,** 711.

Wolos, J.A., Smith, J.B. & Pasternak, R.D. (1980) Effects of hydrocortisone on the activation of suppressor cells in the murine syngeneic mixed lymphocyte reaction (SMLR). *Fed. Proc.* **39,** 695 (abstract).