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Dynamics of mononuclear phagocyte system Fc receptor function in systemic lupus erythematosus. Relation to disease activity and circulating immune complexes

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SUMMARY

Seventeen pairs of longitudinal studies of mononuclear phagocyte system (MPS) Fc receptor function in 15 patients with sytemic lupus were performed to explore the dynamic range of Fc receptor dysfunction in lupus and to establish the relationships between MPS function, clinical disease activity and circulating immune complexes (CIC). Fc receptor function was measured by the clearance of IgG sensitized autologous erythrocytes. At the time of first study the degree of MPS dysfunction was correlated with both clinical activity ($P < 0{\cdot}05$) and CIC ($P < 0{\cdot}05$). At follow-up patients with a change in clinical status show significantly larger changes in clearance function compared to clinically stable patients (206 min *vs* 7 min; $P < 0{\cdot}001$). MPS function changed concordantly with a change in clinical status in all cases ($P = 0{\cdot}002$). Longitudinal assessments did not demonstrate concordance of changes in MPS function and CIC, measured by three different assays. The MPS Fc receptor defect in systemic lupus is dynamic and closely associated with disease activity. The lack of concordance of the defect with changes in CIC suggests that either CIC does not adequately reflect receptor site saturation or that other factors may also contribute to the magnitude of MPS dysfunction.

INTRODUCTION

The presence of defective splenic Fc receptor function, measured by mononuclear phagocyte system (MPS) clearance of IgG sensitized autologous erythrocytes, in patients with sytemic lupus erythematosus (SLE) (Frank *et al.*, 1979; Parris *et al.*, 1982; Williams, 1981) has stimulated interest in the pathogenetic role of circulating immune complexes (CIC). The degree of MPS dysfunction in SLE correlates well with clinical disease activity (Frank *et al.*, 1979; Parris *et al.*, 1982). The relationship of the MPS defect to levels of CIC is less clear since the correlation between these two variables in SLE is inconsistent (Frank *et al.*, 1979; Parris *et al.*, 1982) and since no correlation has been observed in Sjögren's syndrome and other disorders (Hamburger *et al.*, 1979; Lawley *et al.*, 1981). The presence of a correlation with disease activity, however, raises the possibility that MPS dysfunction might play an important role in the pathogenesis of lupus.

The status of the MPS, disease activity and CIC can be investigated by longitudinal study of individual patients as well as by cross-sectional comparison of different patients. A longitudinal

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approach minimizes the difficulties of assigning quantitative clinical activity scores in a disease such as lupus with variable clinical patterns since patients can be compared to themselves. Similarly, since current assays for CIC likely detect heterogeneous populations of complexes in different subjects, serial studies may minimize variability introduced by inter-patient comparisons and enhance the opportunity to demonstrate relationships between circulating complexes, clinical activity and MPS status.

Sequential observations of MPS function, available in 11 patients with SLE who manifested a decrease in disease activity, have shown improvement of IgG sensitized red cell clearance (Hamburger *et al.*, 1982). Concordance of directional changes in MPS function and in CIC was suggested. However, in this study clinically stable and worsened groups each contained only one patient. Analysis of all three clinical groups is important in order to demonstrate true directional associations. Accordingly we present data which analyse disease activity relationships for the three clinically improved, unchanged and worsened groups and show strong concordance between changes in both MPS function and clinical activity. Changes in CIC, measured by three different techniques, however, were not concordant with these directional relationships.

MATERIALS AND METHODS

Patient population. Fifteen patients (12 female, three male) with SLE followed by the Rheumatic Disease service at The Hospital for Special Surgery and The New York Hospital gave written informed consent for participation. The study protocol conformed to the principles of the Declaration of Helsinki and was approved by the committees on Human Rights in Research at The Hospital for Special Surgery and The New York–Cornell Medical Center.

All patients were Rh group positive, Coomb's test negative and greater than 18 years of age. Each patient satisfied at least four preliminary ARA criteria for the classification of SLE (Cohen *et al.*, 1971). Thirteen patients had two studies performed; two patients had three studies. A total of 17 pairs of studies were available for analysis. The mean interval between studies for all patients was $3{\cdot}7 \pm 2{\cdot}4$ months (median: 4 months). These 15 patients include all SLE patients with sequential studies from January 1980 through December 1981 and constitute a subset of 32 SLE patients in whom MPS status has been studied.

Assessment of clinical activity. All 15 patients were graded for clinical activity immediately prior to the time of study employing the ordinal scale of Frank *et al.* (1979) modified to exclude renal disease: grade 0—no clinical manifestations of SLE: grade 1—minimal clinical manifestations of SLE requiring no additional therapy; grade 2—active SLE requiring additional therapy for control of signs and symptoms: grade 3—severe flare requiring hospitalization for management of non-renal manifestations. This scale is comparable to the classification of Ropes (1976) with the addition of Grade 0. All 15 patients were also graded by the activity criteria of Rothfield & Pace (1962) and by the activity/severity score of Pearson & Lightfoot (1981) to examine inter-scale reproducibility of associations between clinical status and MPS function.

MPS Fc receptor-mediated clearance studies. Fc-mediated MPS studies were done with a slight modification of previously described techniques (Frank *et al.*, 1979). All subjects' erythrocytes were sedimented, washed three times in sterile physiological saline after removal of the buffy layer, and radiolabelled with ^{51}Cr (Amersham/Searle Corporation, Arlington Heights, Illinois, USA). The ^{51}Cr-labelled erythrocytes were then washed four times in physiological saline and an aliquot of the cells was then sensitized with an amount of anti-D IgG (kindly supplied by Ortho Pharmaceuticals, Raritan, New Jersey, USA) which results in a clearance half time ($t_{1/2}$) of approximately 30 min in normal controls. The anti-D preparation was sterile, pyrogen free, hepatitis B surface antigen negative, and free of IgM as determined by column chromatography, sucrose density gradient centrifugation and polyacrylamide gel electrophoresis. Following incubation at 37°C for 30 min and two washes in physiological saline, the cells were diluted to a total volume of 10 ml and injected into the subject. Survival was calculated by timed serial bleeding. Results are recorded as $t_{1/2}$, or the time in minutes necessary for 50% of the IgG sensitized ^{51}Cr-labelled cells to leave the circulation, based on a calculated zero point.

Serological studies. Antibodies to native double stranded DNA were assayed by the Farr technique (Pincus *et al.*, 1969). CH_{50} titration was performed by the method of Kent & Fife (1963). Immune complexes were measured by fluid phase C1q binding (Zubler *et al.*, 1976), Staphylococcal protein A binding (McDougal *et al.*, 1979) and Raji cell assay (Theophilopoulos, Wilson & Dixon, 1976). All sera were obtained at the beginning of each of the clearance studies and were stored at −70°C within 2·5 hr of venipuncture. For each serological parameter, all sera were assayed on a single test run. The mean ± s.d. values for each assay are given in Table 1.

Statistical analysis. Both parametric and non-parametric statistical techniques were used for analysis of MPS data (Daniel, 1978; Snedecor & Cochran, 1980). The Mann–Whitney *U*-test and Students' *t*-test were used to test whether two independent samples had been drawn from the same population; the Chi-square and Fisher exact tests for analysis of 2 × 2 and 2 × 3 tables; and the Spearman rank correlation coefficient, corrected for ties, for determination of correlation between two variables. The Kendall coefficient of concordance, *W*, was used to express the degree of association among the three different assays of circulating immune complexes. The mean, and standard deviation were used as descriptive statistics where applicable.

For data analysis, the $T_{1/2}$ value for each MPS assessment was classified as increased or decreased relative to the immediately previous study. Accordingly, a decrease in $T_{1/2}$ represents improvement. No quantitative definition of improvement was assigned *a priori.*

RESULTS

The clearance half times for IgG sensitized autologous erythrocytes were significantly longer for the 15 SLE patients than for 33 normal controls (SLE: median = 190 min; mean ± s.d. = 330 ± 332; normals: median = 25 min; mean ± s.d. = 29 ± 17; $P < 0{\cdot}0001$, Mann–Whitney *U*-test. See Figs 1 & 2, Study 1). The degree of MPS dysfunction was found to be significantly correlated with clinical activity assessed by the scales of Frank (1979) and Pearson & Lightfoot (1981) but not by the scale of Rothfield & Pace (1962) which places marked emphasis on the presence of fever ($\rho = 0{\cdot}44$, $P < 0{\cdot}05$; $\rho = 0{\cdot}51$, $P < 0{\cdot}05$; $\rho = 0{\cdot}35$, $P < 0{\cdot}10$, respectively).

Fourteen of the 15 patients had elevated levels of CIC by at least one assay and 12 of 15 had elevated levels by at least two assays (Table 1). The three different tests showed a high degree of inter-assay agreement with respect to relative ranks of initial values (Kendall's coefficient of concordance, $W = 0{\cdot}934$; $X^2 = 39{\cdot}22$, $P < 0{\cdot}001$). The degree of MPS dysfunction at first study was

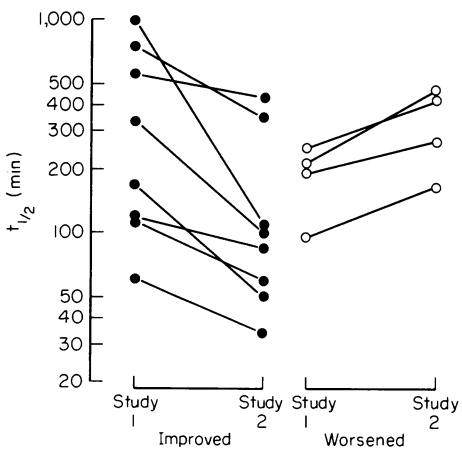

Fig. 1. MPS clearance ($t_{1/2}$) in clinically changed patients. $t_{1/2}$ values for the first (study 1) and second (study 2) studies of each study pair are given for the clinically improved (●) and clinically worsened (○) groups. Therapy in the two groups for study 1 and study 2 was not different. The mean intervals between studies were 3·7 months for the clinically improved group and 3·4 months for the clinically worsened group.

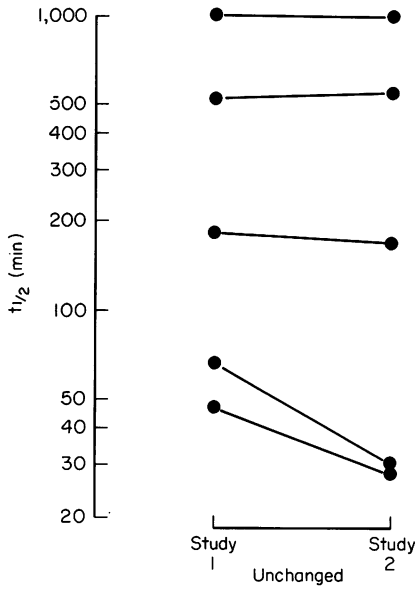

Fig. 2. MPS clearance ($t_{1/2}$) in clinically unchanged patients. $t_{1/2}$ values for the first (study 1) and second (study 2) studies are given. The mean difference (7 ± 27 min) between studies was significantly smaller in this group than in clinically changed groups. The mean interval between studies in this group was 3·8 months.

significantly correlated with CIC by each of the three assays (SBA: $\rho = 0{\cdot}51$, $P < 0{\cdot}05$; C1qBA: $\rho = 0{\cdot}56$, $P < 0{\cdot}05$; Raji: $\rho = 0{\cdot}70$, $P < 0{\cdot}01$).

Sequential studies

Prior to the follow-up clearance study, each patient was assessed for clinical activity and classified as either improved, unchanged or worsened in relation to the clinical status at the time of the previous clearance. Eight patients evidenced less clinical activity, four increased activity and five an unchanged level of activity. Medications were not significantly different for the paired studies in the three groups since patients with increased disease activity were studied prior to change in therapy.

All eight patients with clinical improvement had concomitant improvement in MPS function while all four patients with clinical deterioration showed more prolonged MPS clearance values (Fig. 1). The five clinically unchanged patients showed small differences in MPS function (Fig. 2). The concordance of directional change in clinical activity and MPS function was highly significant ($X^2 = 11{\cdot}75$, $P < 0{\cdot}01$). The magnitude of the difference between the first and second MPS clearance values was significantly larger in the clinically changed patients compared to the clinically unchanged (mean difference: 206 vs 7 min, $P < 0{\cdot}001$; Table 2). The clinically unchanged groups showed a mean difference of only 7 min suggesting a reproducible defect in MPS function when clinical status is unaltered.

To explore the hypothesis that MPS saturation by immune complexes might be the mechanism underlying MPS dysfunction, the relationship between sequential changes in MPS clearance and in CIC was investigated. Directional changes in circulating complexes were determined for all 17 study pairs for each of the three assays. Analysis of these changes in relation to changes in MPS function showed no statistical relationship (Table 3).

We investigated the possibility that this discordance was attributable to a large degree of disagreement among results of the three assays. Initial values of circulating complexes by the three tests showed a high degree of inter-assay agreement (*vide supra*). In nine patients the direction of change was concordant with all three assays. Analysis considering both direction and magnitude of change in CIC showed highly significant inter-assay agreement when either absolute or percentage

Table 1. Immunological profiles at the time of sequential MPS assessment

						CIC					
		Farr		CH_{50}		SBA		C1qBA		Raji	
Clinical category	*n*	1* % binding	2*	1 units	2	1 μg HAGG/ml	2	1 % binding	2	1 μg HAGG/ml	2
Improved (mean ± s.d.)	8	69 ±28	53† ±27	148 ±65	137 ±58	223 ±108	203 ±135	17·5 ±15·7	7·8 ±3·1	267 ±280	245 ±321
Unchanged	5	83 ±15	75 ±12	115 ±43	150 ±49	283 ±114	286 ±123	28·6 ±21·6	35·2 ±17·1	323 ±409	563 ±378
Worsened	4	52 ±27	60 ±35	134 ±69	112‡ ±67	217 ±113	230 ±126	17·0 ±19·5	11·5 ±9·3	311 ±337	436 ±499

* 1 refers to the first study of the pair; 2 refers to the second study.
† $t = 2{\cdot}307$, $P < 0{\cdot}05$; paired *t*-test, one tail
‡ $t = 3{\cdot}415$, $P < 0{\cdot}025$; paired *t*-test, one tail.

Table 2. Sequential changes in MPS function and changes in clinical disease status

		Mean change in $t_{1/2}$	
Clinical category	*n*	Absolute (min)	Percentage
Improved (mean ± s.d.)	8	−236 ± 293	−53 ± 22
Unchanged	5	−7 ± 27*	−20 ± 27*
Worsened	4	145 ± 89	77 ± 34

* Magnitude of the change in $t_{1/2}$ is significantly smaller in the clinically unchanged group compared to the clinically changed (improved and worsened) group: absolute change (minutes), $P < 0{\cdot}001$; percentage change, $P < 0{\cdot}025$ (Mann–Whitney *U*-test, one tail).

change was utilized (Kendall's coefficient of concordance; $W = 0{\cdot}630$, $X^2 = 30{\cdot}22$, $P < 0{\cdot}02$ and $W = 0{\cdot}688$, $X^2 = 33{\cdot}01$, $P < 0{\cdot}01$, respectively). No statistical relationship was seen between changes in MPS function and changes in any of the three assays taken individually (Table 3). The change in MPS $t_{1/2}$ was not correlated with the change in circulating complexes (C1qBA) whether assessed by absolute or percentage differences ($\rho = 0{\cdot}08$ and $\rho = 0{\cdot}01$ respectively).

DISCUSSION

We have investigated mononuclear phagocyte system Fc receptor function in patients with SLE. The majority demonstrated a defect in MPS function which was correlated with both clinical activity and the level of CIC at the time of initial evaluation. Follow-up assessment showed large and concordant changes in MPS status associated with changes in clinical activity; that is, clinically

Table 3. Directional changes: concordance of CIC and MPS function

$t_{1/2}$	CIC assay	Levels of CIC: Increased	Unchanged	Decreased
Decreased	SBA	5	3*	3
	C1qBA	3	3	5
	Raji	5	1	5
Increased	SBA	2	1	3
	C1qBA	1	3	2
	Raji	3	1	2

$X^2 = 0{\cdot}3286$, $P > 0{\cdot}10$ for the 2×3 analysis summing changes for all three CIC assays. This conclusion is unchanged by consideration of each assay individually and by exclusion of clinically unchanged patients with small changes in $t_{1/2}$.

* Unchanged levels in the SBA represent an indeterminate value in one pair member due to floating of the PEG precipitate.

improved patients had improved clearance function while clinically worsened patients showed even greater MPS dysfunction. Changes in MPS status, however, did not correlate with changes in CIC measured by three different assays.

Several studies have investigated Fc receptor-mediated MPS function in autoimmune diseases and have suggested that the degree of dysfunction is correlated with disease activity and clinical manifestations (Frank *et al.*, 1979; Parris *et al.*, 1982) but may not be correlated with levels of CIC (Parris *et al.*, 1982; Hamburger *et al.*, 1979; Lawley *et al.*, 1981). The nature and reproducibility of these relationships are of great interest since defective FC receptor function may contribute to disease pathogenesis. According to the CIC deposition model of immune complex disease, circulating complexes deposit in tissue sites thereby leading to tissue injury (Haakenstad & Mannik, 1976; Haakenstad, Case & Mannik, 1975). Saturation of the system in experimental models leads to delayed removal of CIC from the circulation and to enhanced deposition (Haakenstad & Mannik, 1974) while acceleration of clearance, induced by infection with *Corynebacterium parvum* (Barcelli *et al.*, 1981) or by zymosan treatment (Raij, Sibley & Keane, 1981), leads to decreased deposition.

In vitro evidence suggests that interaction of immune complexes with macrophage Fc receptors impairs their ability to bind IgG sensitized erythrocytes (Rabinovitch, Manejias & Nussenzweig, 1975; Griffin, 1980; Kurlander, 1980; Ragsdale & Arend, 1980). The *in vivo* clearance of IgG sensitized erythrocytes which is Fc receptor-dependent (Engelfriet *et al.*, 1980) is also presumably modified by immune complexes. Correlations between MPS dysfunction and both disease activity and levels of CIC would support a mass action balance between disposal and deposition with saturation of MPS as a central event leading to increased disease. Lack of such correlations might suggest more complex relationships.

Both cross-sectional and longitudinal study designs allow investigation of these associations. In cross-sectional analysis, we observed a significant correlation between disease activity and MPS dysfunction as found by Frank *et al.* (1979). This correlation was confirmed with another independently derived scale of activity (Pearson & Lightfoot, 1981), but was less strong with the Rothfield and Pace scale which places strong emphasis on the presense of fever (Rothfield & Pace, 1962). A correlation between CIC levels and MPS dysfunction was also seen in our sample of 15 patients, although this relationship was lost when the sample analysis was extended to a much larger group studied at a single point in time (Parris *et al.*, 1982). The reason for this loss is not clear at the present time.

Longitudinal analysis supported a strong association between disease activity and MPS dysfunction since MPS function changed concordantly in all cases with a change in clinical status. Clinically unchanged patients had significantly smaller differences in MPS clearance values. Longitudinal analysis of CIC, however, showed no relationship between changes in the MPS and changes in levels of CIC. This dissociation was unaffected by considering direction of change alone as opposed to both direction and magnitude. The lack of relationship is consistent with some findings in SLE (Parris *et al.*, 1982) and Sjögren's syndrome (Hamburger *et al.*, 1979) but would appear at variance with the correlation between MPS function and CIC suggested in smaller populations (Hamburger *et al.*, 1982).

The lack of direct correlation between changes in MPS clearance and in CIC suggests that this relationship may involve several factors. Although interaction of CIC with mononuclear phagocyte Fc receptors is likely to be at least partly responsible for Fc receptor dysfunction, a linear relationship between MPS status and CIC assumes constant production of CIC and constant Fc receptor association constants for binding of CIC. The measured level of circulating complexes reflects the net of both production and disposal; and therefore, the free circulating pool of CIC does not tell us directly about the receptor bound pool. Other serum factors (Svenson, 1975), anti-monocyte reactive antibodies (Arend *et al.*, 1977), other antibody coated cells (Butler *et al.*, 1972) or qualitative differences in CIC themselves as measured (Anderson & Stillman, 1980; Horsfall *et al.*, 1981) may also be important factors modulating Fc receptor function. The capacity or saturability of the MPS may also vary between patients (Lawley *et al.*, 1981).

Whatever the basis for defective Fc receptor-mediated MPS function, the relationship to disease activity is clear. Whether by delayed clearance of CIC allowing for greater deposition of CIC or by delayed clearance of an offending antigen allowing for its direct deposition followed by *in situ* formation of immune complexes (Couser *et al.*, 1978; Ford & Kosatka, 1979; Fleuren, Grono & Hoedemaeker, 1981), MPS dysfunction may play an important role in disease pathogenesis. Further study will provide insight into the basis for and modulation of this dysfunction.

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REFERENCES

ANDERSON, C.L. & STILLMAN, W.S. (1980) Raji cell assay for immune complexes. Evidence for detection of Raji-directed immunoglobulin G in sera from patients with systemic lupus erythematosus. *J. clin. Invest.* **66,** 353.

AREND, W.P., EMMERICH, T.E., STURGE, J.C. & STARKEBAUM, G.A. (1977) Monocyte-reactive antibodies in patients with SLE. *Arthrit. Rheum.* **20,** 1049.

BARCELLI, U., RADEMACHER, R., OOI, Y.M. & OOI, B.S. (1981) Modification of glomerular immune complex deposition in mice by activation of the reticuloendothelial system. *J. clin. Invest.* **67,** 20.

BUTLER, W.T., SHARP, J.T., ROSSEN, T., LIDSKY, M.D., MITTAL, K.K. & GARD, D.A. (1972) Relationship of clinical course of sytemic lupus erythematosus to the presence of circulating lymphocytotoxic antibodies. *Arthrit. Rheum.* **15,** 231.

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

COUSER, W.C., STEINMULLER, D.R., STILMANT, M.M., SALANT, D.J. & LOWENSTEIN, L.M. (1978) Experimental glomerulonephritis in the isolated perfused rat kidney. *J. clin. Invest.* **62,** 1275.

DANIEL, W.W. (1978) *Applied Nonparametric Statistics.* Houghton-Mifflin, New York.

ENGELFRIET, C.P., VON DEM BORNE, A.E.G., FLEER, F.W., VAN DER MEULEN, F.W. & ROOS, D. (1980) *In vivo* RES function of erythrocytes to complement binding and non-complement binding antibodies. In *Immunobiology of the Erythrocyte* (ed. by S. G. Sandler, J. Nusbacher & M. S. Schanfield) pp. 213. A. R. Liss Inc., New York.

FLEUREN, G., GRONO, J. & HOEDEMAEKER, P.J. (1981) *In situ* formation of subepithelial glomerular immune complexes in passive serum sickness. *Kidney Int.* **17,** 631.

FORD, P.M. & KOSATKA, I. (1979) *In situ* formation of antigen–antibody complexes in the mouse glomerulus. *Immunology*, **38,** 473.

FRANK, M.M., HAMBURGER, M.I., LAWLEY, T.J., KIMBERLY, R.P. & PLOTZ, P.H. (1979) Defective reticuloendothelial system Fc-receptor function in systemic lupus erythematosus. *N. Engl. J. Med.* **300,** 518.

GRIFFIN, F.M. (1980) Effects of soluble immune complexes on Fc-receptor- and C3b receptor-

mediated phagocytosis by macrophages. *J. exp. Med.* **152,** 905.

HAAKENSTAD, A.O., CASE, J.B. & MANNIK, M. (1975) Effect of cortisone on the disappearance kinetics and tissue localization of soluble immune complexes. *J. Immunol.* **114,** 1153.

HAAKENSTAD, A.O. & MANNIK, M. (1974) Saturation of the reticuloendothelial system with soluble immune complexes. *J. Immunol.* **112,** 1939.

HAAKENSTAD, A.O. & MANNIK, M. (1976) The disappearance kinetics of soluble immune complexes prepared with reduced and alkylated antibodies and with intact antibodies in mice. *Lab. Invest.* **35,** 293.

HAMBURGER, M.I., LAWLEY, T.J., KIMBERLY, R.P., PLOTZ, P.H. & FRANK, M.M. (1982) A serial study of splenic reticuloendothelial system Fc receptor functional activity in sytemic lupus erythematosus. *Arthrit. Rheum.* **25,** 48.

HAMBURGER, M.I., MOUTSOPOULOS, H.M., LAWLEY, T.J. & FRANK, M.M. (1979) Sjögren's syndrome: a defect in reticuloendothelial system Fc-receptor specific clearance. *Ann. Intern. Med.* **91,** 534.

HORSFALL, A.C., VENABLES, P.J.W., MUMFORD, P.A. & MAINI, R.N. (1981) Interpretation of the Raji cell assay in sera containing anti-nuclear antibodies and immune complexes. *Clin. exp. Immunol.* **44,** 405.

KENT, J.F. & FIFE, E.H. (1963) Precise standardization of reagents for complement fixation. *Am. J. trop. med. Hyg.* **12,** 103.

KURLANDER, R.J. (1980) Reversible and irreversible loss of Fc receptor function of human monocytes as a consequence of interaction with immunoglobulin G. *J. clin. Invest.* **66,** 773.

LAWLEY, T.J., HALL, R.P., FAUCI, A.S., KATZ, S.I., HAMBURGER, M.I. & FRANK, M.M. (1981) Defective Fc-receptor functions associated with the HLA-B8/DRw3 haplotype. Studies in patients with dermatitis herpetiformis and normal subjects. *N. Engl. J. Med.* **304,** 185.

MCDOUGAL, J.S., REDECHA, P.B., INMAN, R.D. & CHRISTIAN, C.L. (1979) Binding of immunoglobulin G aggregates and immune complexes in human sera to Staphylococci containing protein A. *J. clin. Invest.* **63,** 627.

PARRIS, T.M., KIMBERLY, R.P., INMAN, R.D., MCDOUGAL, J.S., GIBOFSKY, A. & CHRISTIAN, C.L. (1982) Defective Fc receptor mediated function of the mononuclear phagocyte system in lupus nephritis. *Ann. Intern. Med.* **97,** 526.

PEARSON, L. & LIGHTFOOT, R.W. (1981) Correlation of DNA–anti-DNA association rates with clinical activity in sytemic lupus erythematosus (SLE). *J. Immunol.* **126,** 16.

PINCUS, T., SCHUR, P.H., ROSE, J.A., DECKER, J.L. & TALAL, N. (1969) Measurement of serum DNA-binding activity in systemic lupus erythematosus. *N. Engl. J. Med.* **281,** 701.

RABINOVITCH, M., MANEJIAS, R.E. & NUSSENZWEIG, V. (1975) Selective phagocytic paralysis induced by immobilized immune complexes. *J. exp. Med.* **142,** 827.

RAGSDALE, C.G. & AREND, W.P. (1980) Loss of Fc receptor activity after culture of human monocytes on surface-bound immune complexes. *J. exp. Med.* **151,** 32.

RAIJ, L., SIBLEY, R.K. & KEANE, W.F. (1981) Mononuclear phagocyte system stimulation. Protective role from glomerular immune complex deposition. *J. lab. clin. Med.* **98,** 558.

ROPES, M.W. (1976) *Systemic lupus erythematosus.* pp. 6. Harvard University Press, Cambridge.

ROTHFIELD, N.F. & PACE, N. (1962) Relation of positive L.E.-cell preparations to activity of lupus erythematosus and corticosteroid therapy. *N. Engl. J. Med.* **266,** 535.

SNEDECOR, G.W. & COCHRAN, W.G. (1980) *Statistical Methods* 7th edn. Iowa State University Press, Ames.

SVENSON, B.O. (1975) Serum factor causing impaired macrophage function in SLE. *Scand. J. Immunol.* **4,** 145.

THEOPHILOPOULOS, A.N., WILSON, C.B. & DIXON, F.J. (1976) The Raji cell radioimmune assay for detecting immune complexes in sera. *J. clin. Invest.* **57,** 169.

WILLIAMS, R.C. (1981) Immune complexes: A clinical perspective. *Am. J. Med.* **71,** 743.

ZUBLER, R.H., LANGE, G., LAMBERT, P.H. & MIESCHER, P.A. (1976) Detection of immune complexes in unheated sera by a modified ^{125}I-C1q binding test. *J. Immunol.* **116,** 232.