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Value of serum C-reactive protein measurement in the investigation of fever in systemic lupus erythematosus

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SUMMARY The concentration of C-reactive protein (CRP) in the sera of patients with systemic lupus erythematosus (SLE) was higher when the disease was active than when it was inactive, but was only markedly raised in patients suffering from identifiable microbial infection. CRP levels greater than 60 mg/l suggest the presence of intercurrent infection and may therefore be a valuable aid to the differential diagnosis of pyrexia in SLE.

Pyrexia in systemic lupus erythematosus SLE is a common and important clinical problem (Hughes, 1977), particularly in patients who are being treated with anti-inflammatory or immunosuppressive drugs. The differential diagnosis, which usually lies between intercurrent infection and simple exacerbation of the underlying disease, may often be difficult to resolve rapidly. The erythrocyte sedimentation rate (ESR) is not a good index of disease activity in SLE (Hughes, 1977). Although the ESR does tend to rise with intercurrent infection, this does not differentiate it from active SLE alone with high ESR. Furthermore plasma viscosity and to an even greater extent ESR are determined by many variables and respond rather slowly and very variably to alterations in disease activity and other stimuli (Pepys, 1979a).

Patients and methods

Forty-one patients fulfilling the American Rheumatology Association criteria for the classification of SLE were studied longitudinally with a total of 214 sera collected over the 24-month period prior to June 1978. Their disease was regarded as active if vasculitis, serositis, arthritis, cerebral lupus, or severe glomerulonephritis was present. Infection was diagnosed only when clinical evidence was supported by microbiological studies. Patients with mild polyarthralgia or rash as well as those with no symptoms were included in the 'inactive' group.

Serum samples were stored at −20° until tested. CRP levels were measured by a monospecific sheep antiserum in electroimmuno assay (Kindmark, 1969) in the presence of EDTA, with the isolated pure protein (Pepys *et al.*, 1977a) as the standard. The lower limit of sensitivity was 1 mg/l, and the coefficient of variation in replicate assays was less than 10%. Results can be obtained within 8 hours of venepuncture. The highest CRP level found in each patient during phases of infection, activity, or inactivity were compared. Significance of differences between the groups was assessed by Wilcoxon's rank sum test.

Results

During the 2-year period 9 of the 41 patients suffered from proved infections (Table 1); 25 patients

Table 1 *Nature of infective episodes*

Infection	*Number of patients*
Staphylococcus aureus cellulitis	3
Streptococcus pneumoniae septicaemia	2
Streptococcus pneumoniae pneumonia	1
Streptococcus group D septicaemia	1
Candida albicans infection of mouth and vagina	1
Escherichia coli urinary tract infection	
Cytomegalovirus pulmonary infection	
Proteus mirabilis urinary tract infection	1

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had periods of disease activity and 28 patients had periods with inactive disease. The maximum CRP levels reached during these different phases are shown in Fig. 1 and Table 2. The CRP levels in infected patients with SLE were significantly higher than in patients with active SLE alone ($P<0.01$). The CRP levels in patients with active SLE were higher that in the inactive group ($P<0.01$).

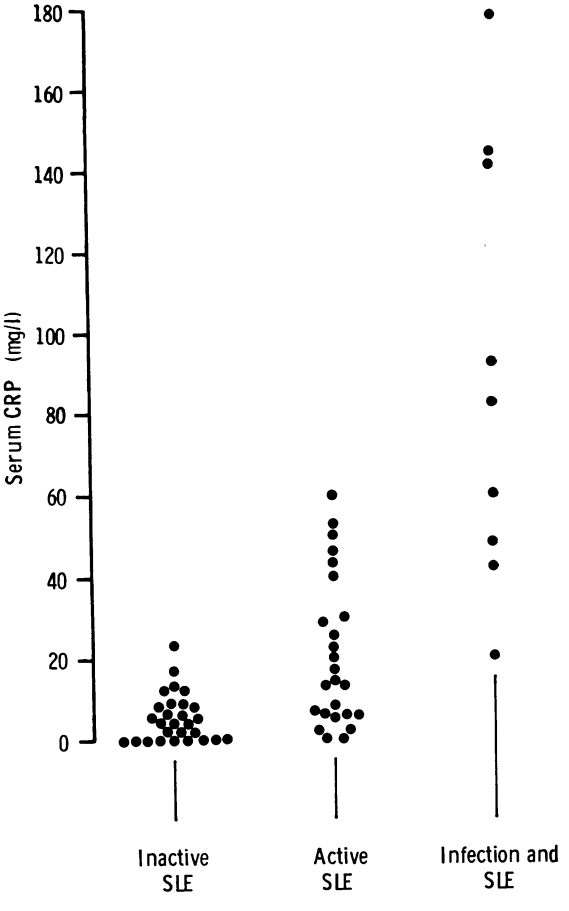

Fig. 1 *Maximum serum CRP levels in patients with SLE*

Table 2 *Maximum serum CRP levels*

Clinical category	*No. of patients*	*Serum CRP level (mg/l)*		
		Median	*Interquartile range*	*Range*
Inactive SLE	28	4	0–8	0–23
Active SLE	25	14	6–30	0–60
Infection and SLE	9	82	48–141	20–177

Discussion

CRP is a major acute phase reactant, the serum level rising from normal values of less than 1 mg/l to as much as 400 mg/l within 1 or 2 days following many forms of actue tissue damage or inflammation (Kindmark, 1976; Pepys *et al.*, 1978a). In some chronic inflammatory conditions and with malignant neoplasia CRP levels remain raised and may reflect disease activity (Claus *et al.*, 1976; Pepys *et al.*, 1978a). Thus, although elevation of CRP is a non-specific response, its assay is clinically useful in monitoring the activity of rheumatoid arthritis (Amos *et al.*, 1977), rheumatic fever (Stollerman *et al.*, 1953) and Crohn's disease (Pepys *et al.*, 1977b). In contrast we have observed that in ulcerative colitis (Pepys *et al.*, 1977b) and SLE (Pepys *et al.*, 1978a) CRP is only moderately raised even in severe exacerbations and may correlate poorly with disease activity. Honig *et al.* (1977), using a semiquantitative precipitation assay to study CRP levels in SLE, found raised levels in the sera of patients who were suffering from microbial infection.

With a more sensitive and precise technique we here confirm that in SLE marked elevation of CRP is largely confined to patients with identifiable microbial infections. We also show that CRP levels tend to be higher in active than in inactive lupus, although in the absence of infection the value did not exceed 60 mg/l even in patients with florid disease activity. Estimation of serum CRP may therefore be valuable in management of patients with SLE, up to 80% of whom are febrile at some time in their illness (Estes and Christian, 1971; Hughes, 1977). The modest increase of CRP even in patients with very active lupus is surprising in view of the extensive tissue damage and the frequent presence of circulating immune complexes. Such complexes are known to stimulate CRP production in the rabbit (Hokama *et al.*, 1960; Kushner and Kaplan, 1964). Mechanisms for the lack of high CRP levels in SLE which we are currently studying include reduced production, enhanced consumption, and complexing of CRP in the serum.

One intriguing possibility is that there might be individual genetic differences in the capacity to respond to some stimuli with CRP production. This has recently been observed in inbred strains of mice both for CRP (Siboo and Kulisek, 1978), which is only a trace protein in this species (Siboo and Kulisek, 1978; Pepys 1979b), and for SAP (serum amyloid P-component) (Skinner and Cohen, 1976; Pepys *et al.*, 1979), which is closely related to CRP (Osmand *et al.*, 1977; Pepys *et al.*, 1977c, 1978b), and is a major murine acute phase plasma protein (Pepys *et al.*, 1979). Human CRP interacts with

complement (Kaplan and Volanakis, 1974; Siegal *et al.*, 1975) and phagocytic cells (Kindmark, 1971; Mortensen *et al.*, 1976). Hereditary effects on production of these proteins might therefore be of pathogenetic significance in inflammatory disease and possibly play a part in determining the pattern of diseases evoked in different individuals by the same agent.

Our present observations might, however, be secondary to the well recognised immunological abnormalities which characterise SLE. Elucidation of this issue must wait for further information on the control mechanisms for CRP production and the role of CRP in inflammation in vivo. In any event at the purely clinical level the measurement of serum CRP is a valuable aid to the detection of intercurrent microbial infection in patients with SLE.

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