Acetylator phenotype in spontaneous SLE and rheumatoid arthritis

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SUMMARY Acetylator phenotype was determined in 22 patients with spontaneous systemic lupus erythematosus and the proportion of 'slow' acetylators compared with that obtained in a group of patients with rheumatoid arthritis and a group of healthy controls. 73% of the SLE group were designated 'slow' compared with 72% of the rheumatoid group and 64% of the control group. These differences were not significant.

A number of primary amine drugs such as dapsone, isoniazid, hydralazine, procainamide, and many of the sulphonamides are acetylated by the N-acetyltransferase enzyme at rates which are bimodally distributed in man (Evans *et al.*, 1960; Evans and White, 1964; Gelbert *et al.*, 1971; Zacest and Koch-Weser, 1972; Karlsson *et al.*, 1975). Several of these drugs have been implicated in the development of systemic lupus erythematosus (SLE) (Alarcon-Segovia, 1976). This has been reported more frequently in slow acetylators of the suspected drug (Lunde *et al.*, 1977), a fact which could indicate either a genetic predisposition of such individuals or result from a direct effect of the parent drug which becomes inoperative once the acetylated derivative is formed. If the former is the explanation, it is possible that there would be an increased prevalence of slow acetylators among patients with spontaneously occurring SLE. There is already some evidence in support of this hypothesis, since Reidenberg and Martin (1974) reported that 11 of 14 patients with spontaneous SLE were slow acetylators as compared with an expected frequency of 50% in the local population.

The present report describes an investigation into the distribution of the acetylator phenotype in patients with spontaneous SLE, comparing them with rheumatoid arthritis and normal persons.

Patients and methods

In all instances acetylator phenotype was determined by the method of Schröder (1972). Patients were

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given 1g sulphadimidine orally, and their urine was collected for 1 hour between 5 and 6 hours after ingestion of the drug. Urine samples were analysed for free and acetylated sulphadimidine by the method described by Schröder. Results were expressed as a percentage of the acetylated drug in the urine. Slow acetylators were defined as having less than 70% acetylated sulphadimidine in the urine.

A total of 72 subjects were tested: 22 with spontaneous SLE as defined by the American Rheumatism Association criteria (Cohen *et al.*, 1971), 25 with either classical or definite rheumatoid arthritis (Ropes *et al.*, 1959), and 25 normal controls. All were attending hospital either as outpatients or as staff and were on normal diets. At the time of the study no patient was taking a drug which was metabolised by acetylation. All patients had normal renal function as shown by normal blood urea and serum creatinine concentrations at the time of the test. The mean ages, sex distribution, and blood urea concentrations in these subjects are shown in Table 1.

Results

The distribution of acetylator capacity in the 3 groups of subjects studied is shown in Fig. 1. Of the

Table 1 Characteristics of patients studied

	Spontaneous SLE	Rheumatoid arthritis	Normal subjects
Number	22	25	25
Number of males	6	9	10
Age ($\pm$ SD) years	36 $\pm$ 10	61 $\pm$ 14.2	25 $\pm$ 5.1
Blood urea mmol/l	5.2 $\pm$ 1.2	6.2 $\pm$ 2.1	4.4 $\pm$ 0.9

Fig. 1 Comparison of the proportion of acetylated sulphadimidine in patients with spontaneous SLE, rheumatoid arthritis, and healthy volunteers

22 patients with SLE 6 were fast acetylators (27%) as compared with 7 of the 25 rheumatoid arthritics (28%) and 9 of the 25 normal subjects (36%). These differences could readily have arisen by chance (X^2 (DF=2)=0.54, $P>0.1$). The mean proportion of acetylated sulphadimidine was 63.7% (SD=17.4) in those with SLE, 65.3% (SD=16.0) in those with RA, and 70.7% (SD=13.6) in normal volunteers.

Discussion

This study does not support the finding of Reidenberg and Martin (1974) that there is an excess of phenotypically slow acetylators among patients with spontaneous SLE. There were no significant differences in the prevalence of slow acetylators of sulphadimidine in a large group of patients with spontaneous SLE, a group with rheumatoid arthritis, and a group of normal volunteers. The test used was simple, reliable, and reproducible (Schröder, 1972), and easy to perform on large numbers of patients. The only 2 sources of error with this technique result from using it in patients with impaired renal function or in patients who are coincidentally receiving significant amounts of other acetylated drugs, for example, procainamide (Campbell *et al.*, 1976). Neither of these 2 situations pertained in the present study. Sulphadimidine was

used as the test drug, since its acetylation rates have been shown to correlate well with those of other polymorphically acetylated drugs (Lunde *et al.*, 1977).

More recently Larsson *et al.* (1977) studied acetylation capacity using isoniazid half-times in plasma in a group of 15 patients with SLE who were not taking concurrent drug therapy. Only 2 of these patients were rapid acetylators. However, 7 of them had chronic renal failure with glomerular filtration rates between 17 and 41 ml/min—a factor which could introduce difficulties in measuring acetylator capacity. A similar problem exists in the data presented by Reidenberg and Martin (1974). Moreover, Molin *et al.* (1977) showed that, although the distribution of slow and fast acetylators of sulphapyridine was 50:50 in Sweden when studying normal individuals, a distinct bias towards slow acetylators was apparent when patients admitted to hospital for cardiac or renal diseases were studied. Thus it is not clear from these observations whether the reported trend towards fewer than normal fast acetylators in patients with spontaneous SLE is a reflection of the disease itself or of extraneous factors associated with attendance at hospital. The present study compares the acetylator capacity of outpatients with spontaneous SLE with that of 2 other groups, one of which had rheumatoid arthritis and one of which was normal. It fails to confirm that acetylator phenotype is a useful marker for the spontaneous form of SLE.

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