Table 1. Rate of Ethyleneimine Production by Di(aziridin-1-yl)-Sulphoxide (1 mg/ml.) when Incubated (37° C) in Phosphate Buffer (0·067 M: *p*H 5·3–8·0)

Time incubated (min)	Percentage of available ethyleneimine liberated			
	*p*H 5·3	*p*H 6·3	*p*H 7	*p*H 8
10	24	20	12	3
20	42	36	23	6
30	54	49	32	9
40	62	57	41	11
50	67	62	47	14
60	69	65	54	16

respectively of ethyleneimine by 2 h. *NNN'N'*-diethyleneurea, which is structurally related to DESO (carbon replacing sulphur), only yielded ethyleneimine in alkaline solution and then only in small amounts (6 per cent in 3 h, *p*H 8).

While it is generally agreed that the chemical reactivity of ethyleneimine derivatives forms the basis of their tumour-inhibitory activity, little is known about the *in vivo* circumstances which may contribute to or inhibit the biological effect. It is possible that the present data explain why DESO fails to inhibit the growth of experimental tumours, since ethyleneimine lacks tumour-inhibitory activity[2].

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Serum Concentration of Phenylbutazone in Tests for Antiphlogistic Activity and under Clinical Treatment

Owing to marked individual variations in the rate of metabolic transformation in man, the daily doses of phenylbutazone used in therapy show a relatively wide range. Burns *et al.*[1] found a biological half-life for phenylbutazone ranging from 1·5 to 6 days, and correspondingly found plateau plasma concentrations ranging from 60 to 150 mg/l. in different individuals. After an initial dose of 800 mg orally followed by 200 mg four times daily, Wilson *et al.*[2] found plasma concentrations from 50 to 100 mg/l. and consider these concentrations necessary for therapeutic effect. Currie[3] found 80–110 mg/l. at the beginning of the therapy and later under maintenance dose-levels of 46–80 mg/l. Bruck *et al.*[4] are of the opinion that, in order to avoid side-effects, plasma concentrations should not exceed 100 mg/l., and during treatment they maintained concentrations of between 50 and 90 mg/l. They propose that treatment should begin with 200 mg per day orally, and that the dose should increase by 100 mg daily until the response is satisfactory.

On an mg/kg base these doses lie considerably below those necessary for the demonstration of antiphlogistic effects in animal experimentation. In experiments in this laboratory, these doses amounted to 25–50 mg/kg when a maximal reduction of several forms of experimental oedema in rats was to be achieved[5,6].

Since it seemed possible that the difference in the dose might be compensated for by the much shorter half-life of phenylbutazone in the rat, we decided to compare the serum concentrations reached after oral application of doses effective in the different tests for antiphlogistic activity in the rat with those determined in patients under treatment with phenylbutazone.

Phenylbutazone was determined spectrophotometrically using the method of Burns *et al.*[1]. Fig. 1 shows the serum concentrations after oral application of 10, 25, and 50 mg/kg in male and female rats. The concentrations present during 5½ h (the duration of the test for antiphlogistic activity) agree closely with those obtained under clinical treatment for the two higher doses. The lower serum concentrations after a dose of 10 mg/kg correspond to the submaximal effect in the test for antiphlogistic activity[5,6]. We are inclined, therefore, to regard the effect of phenylbutazone on the different models of inflammation used in our laboratory (kaolin, aerosil and carrageenin) as a true correlate of clinical antiphlogistic activity, the more so as a similar sensitivity of peripheral processes to drugs should exist even in different species.

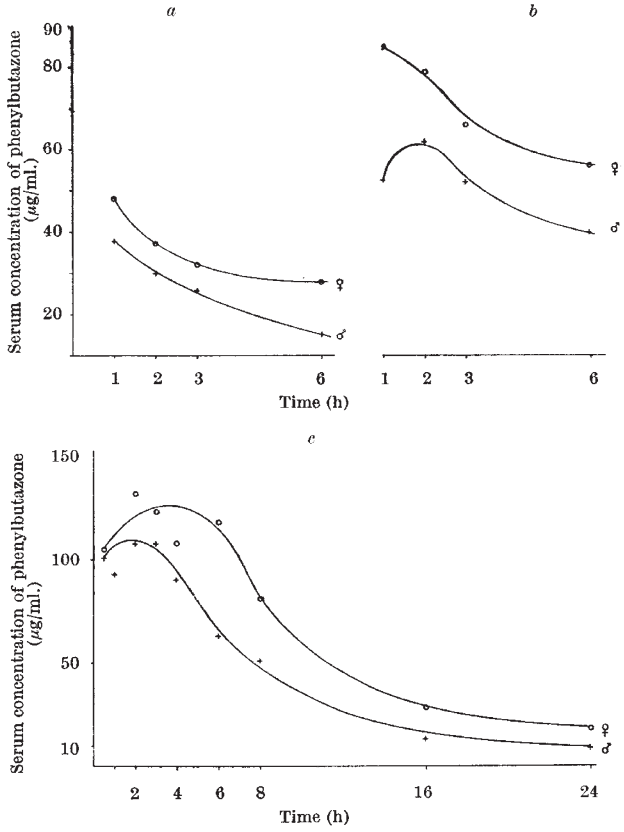

Fig. 1. Serum concentrations of phenylbutazone after oral application to male and female rats (Leo strain). Dosage: *a*, 10 mg phenylbutazone/kg; *b*, 25 mg phenylbutazone/kg; *c*, 50 mg phenylbutazone/kg

It can be seen from Fig. 1 that the concentrations obtained in female rats were always higher than those in the male ones. This sex difference cannot be explained by a different metabolic rate alone, since the half-lives determined for both sexes lie rather close together (5·2 h for the males, 6 h for the females), and since the difference could not be abolished by pretreatment with *SKF 525-A*. Besides the difference in half-life, a lower volume of distribution and a higher haematocrit were found in our female rats, all three factors contributing to the higher phenylbutazone serum concentrations in this sex.

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