MAOI		ImAA	MeImAA	MeHis	His	Rate of Absorption*	n
			(pmol/ml blood)			(nmol/min)	
[^{14}C]-Histamine (10μCi with 82 μmol/kg)							
———	PV	16,422	6,509	1,716	2,179	550	2
	CMA	8,783	4,901	616	559		
———	PV	5,173	6,982	9,611	55,763	6,100	2
	CMA	2,030	4,008	4,170	4,606		
Mebanazine	PV	1,396	2,319	6,941	11,198	685	4
(120 μmol/kg)	CMA	717	1,569	5,570	3,408		
Nialamide	PV	3,962	5,741	6,909	8,401	350	3
(80 μmol/kg)	CMA	2,995	2,916	9,882	4,460		
Tranylcypromine	PV	4,025	2,768	2,545	3,407	700	2
(14 μmol/kg)	CMA	1,050	1,254	1,650	810		
Deprenyl	PV	8,201	3,470	9,733	17,076	510	3
(4.5 μmol/kg)	CMA	6,251	3,309	5,504	4,514		
Clorgyline	PV	14,420	10,473	10,571	27,650	3,100	3
(24.5 μmol/kg)	CMA	8,439	8.038	6,154	4,769		
Tranylcypromine	PV	878	1,661	3,756	10,466	225	2
(80 μmol/kg)	CMA	874	1,561	3,948	789		

Values for histamine and metabolites are mean results of serial determinations (approx. 15 per experiment) from n experiments. n = No. of expts.

*The mean absorption rate of [^{14}C]-compounds at 35 min.

ImAA, Imidazoleacetic acid: MeImAA, *t*-Methylimidazoleacetic acid: MeHis, *t*-Methylhistamine: His, Histamine.

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Hepatic microsomal oxidative N-demethylation in rats with renal failure

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The incidence of adverse reactions to drugs is relatively high in patients with chronic renal failure (Smith, Seidl & Chuff, 1966). For some drugs it is possible that this may be related to a decrease in their metabolism (Reidenberg, 1975). In view of the importance of oxidative pathways for drug transformation in the liver, the hepatic microsomal N-demethylation of aminopyrine and ethyl morphine was examined in rats with renal failure.

The five-sixths nephrectomy described by McCance & Morrison (1956) was used to induce renal failure in male Wistar rats (180g). The animals were matched with pair-fed sham-operated control rats. At 7 and 14 days after nephrectomy, the activities of aminopyrine – (La Du, Gaudette, Trousof & Brodie, 1955) and ethyl morphine – (Holtzman, Gram, Gigon & Gilette, 1968) N-demethylases were determined in the 10,000g supernatant of livers from rats in each set. Hepatic microsomal cytochrome P_{450} was determined by the method of Omura & Sato (1964). Microsomal protein was determined on the 100,000g pellet of the liver-homogenates.

Plasma urea concentrations were significantly raised in the nephrectomized rats at both time intervals but there were no significant differences in body weight (Table 1) or in liver to body weight ratios (overall mean 0.033 ± .001) between test and control animals. The Km values for aminopyrine and ethyl morphine demethylation by the hepatic microsomes were unaltered by nephrectomy. However, for the nephrectomized rats at day 14, significant decreases were observed in the rates (V_{max}) of N-demethylation of the two substrates and in the amount of hepatic

cytochrome P_{450} when these values were expressed on the basis of liver weight (Table 1). When the parameters were expressed on the basis of microsomal protein, the differences in mean values between control and test animals were not significant ($P>0.05$). As there was a significant decrease in the concentration of microsomal protein in the liver of nephrectomized rats on day 14 (Table 1), it is likely that this was an important contributor to the decreased oxidative demethylation activity. Similar changes in oxidative metabolism pathways have been found in rats with severe acute renal failure (Leber & Schütterle, 1972).

It is suggested that altered drug metabolism may need to be considered when pharmacokinetic models are developed for application in cases of renal failure.

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Table 1 Effects of partial nephrectomy on hepatic† N-demethylation of aminopyrine and ethyl morphine in male rats

	Days after nephrectomy			
	7		*14*	
	C	*N*	*C*	*N*
Body weight (g)	189 ± 5	192 ± 5	215 ± 11	221 ± 8
Plasma urea (mg/100 ml)	40.5 ± 3.3	61.5 ± 3.1	49.0 ± 7.9	70.2 ± 3.1
Cytochrome P_{450}				
(µmol/g liver)	27.0 ± 3.3	18.8 ± 2.2	33.2 ± 1.9	22.2 ± 1.7*
(µmol/mg microsomal protein)	0.57 ± 0.04	0.48 ± 0.04	0.55 ± 0.04	0.51 ± 0.03
V_{max} of aminopyrine demethylation				
(µmol HCHO produced $h^{-1}g^{-1}$ liver)	4.00 ± 0.36	2.73 ± 0.46	3.18 ± 0.54	1.63 ± 0.28*
(µmol HCHO produced $h^{-1}mg^{-1}$ microsomal protein)	0.070 ± 0.010	0.060 ± 0.010	0.060 ± 0.014	0.036 ± 0.006
V_{max} of ethyl morphine demethylation				
(µmol HCHO produced $h^{-1}g^{-1}$ liver)	12.5 ± 4.3	9.9 ± 0.4	8.5 ± 1.1	3.0 ± 0.6*
(µmol HCHO produced $h^{-1}mg^{-1}$ microsomal protein)	0.23 ± 0.09	0.22 ± 0.01	0.15 ± 0.03	0.07 ± 0.02
Microsomal protein (mg/g liver)	59.7 ± 8.8	38.9 ± 4.2	57.6 ± 5.2	43.0 ± 3.0*

Values are means ± s.e. means of 5 experiments
C = control N = nephrectomized rats
†10,000 *g* supernatant of liver
*$p<0.05$