and 10 days. P_{450} levels were found to increase in the 4 day period which included the higher doses. The blood and brain cholinesterase levels were found to fall consistently with increased dose of Abate.

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Metabolites of intraduodenally instilled histamine after pretreatment with monoamine oxidase inhibitors (MAOI)

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Ingested histamine was reported to be metabolized in cats by N-methylation followed by oxidation by monoamine oxidase to *t*-methyl-imidazoleacetic acid (Schayer, 1956). The absorption therefore of large amounts of histamine following its intraduodenal instillation in cats pretreated with a hydrazine MAOI was unexpected (Blackwell & Marley, 1966). Subsequently, instilled- and by implication ingested histamine was found (Imrie, Marley & Thomas, 1978) to be metabolized predominately and equally to *t*-methylimidazoleacetic acid and to imidazoleacetic acid, indicating diamine oxidase (DAO) to be as important as N-methylation for metabolizing ingested histamine. Since hydrazine MAOI inhibit DAO (Burkard, Gey & Pletscher, 1962), an action possibly accounting for Blackwell & Marley's (1966) findings, the effect of non-selective and selective MAOI including MAOA and MAOB inhibitors was examined with both a small and a large dose of histamine. [^{14}C]-Histamine and its metabolites were assayed by scintillation spectrometry following paper chromatography (Thomas & Marley, 1978).

After pretreatment with mebanazine or nialamide (Table 1), the concentrations of histamine and *t*-methylhistamine compared to controls were elevated in portal venous blood with both doses of histamine, slow rates of absorption of ^{14}C-compounds occurring with the large dose (rate of absorption also appears to determine type of metabolite; slow rates giving rise to acid metabolites and a negligible proportion of histamine). In contrast, the consequences of tranylcypromine, deprenyl (MAOB-inhibitor) or clorgyline (MAOA-inhibitor) pretreatment depended on the amount of histamine instilled, the blood concentrations of histamine and *t*-methylhistamine decreasing with the small dose but increasing with the large dose. Unlike the other MAOI, clorgyline enhanced the rate of absorption of ^{14}C compounds. Intestinal 5HT and β-phenethylamine oxidation (Robinson, Lovenberg, Keiser & Sjoerdsma, 1968) at the end of experiments were reduced by deprenyl ($n = 6$) to 68 ± 11.9 and 66 ± 12.6% of control values while the corresponding values with clorgyline ($n = 4$) were 33.6 ± 7.3 and 65.6 ± 11.3%.

In conclusion, the non-selective MAOI led to increased circulating histamine and *t*-methylhistamine with both doses of histamine while the selective MAOI enhanced circulating histamine only with the large dose of histamine.

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Table 1 [^{14}C]-Histamine and its metabolites in portal venous (PV) and cranial mesenteric arterial (CMA) blood for control cats and those pretreated with MAOI

MAOI		*ImAA*	*MeImAA*	*MeHis*	*His*	*Rate of Absorption* (nmol/min)*	*n*
			(pmol/ml blood)				
[^{14}C]-Histamine (5μCi with 1.7 μmol/kg)							
———	PV	398	344	99	98	16	6
	CMA	255	189	66	53		
Mebanazine	PV	183	241	223	231	27.5	3
(120 μmol/kg)	CMA	94	151	138	25		
Nialamide	PV	392	531	1,327	377	49.5	2
(80 μmol/kg)	CMA	234	309	987	67		
Tranylcypromine	PV	247	229	14	17	40.5	2
(14 μmol/kg)	CMA	78	81	7	8		
Deprenyl	PV	211	149	59	22	10.5	2
(4.5 μmol/kg)	CMA	177	112	40	7		
Clorgyline	PV	605	326	45	11	20.5	2
(24.5 μmol/kg)	CMA	379	191	37	9		

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