by Jonsson & Sachs (1970), Furness (1971), Wadsworth (1973), Gillespie & McGrath (1975) or Aprigliano & Hermsmeyer (1976). Thus there may be a minimum time of 1–2 h required for destruction of adrenergic nerves with 6-hydroxydopamine.

Norephedrine is a sympathomimetic drug (Goodman & Gilman 1970). Since the response to norephedrine was abolished by 6-hydroxydopamine, we conclude that it is predominantly an indirectly-acting sympathomimetic amine, according to the classification of Fleckenstein & Burn (1953).

It is concluded that this treatment schedule is an effective method for selective destruction of adrenergic nerves in the human vas deferens in vitro. It is particularly suitable for human tissues where in vivo treatment would be impossible.

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Genetic evidence for the involvement of different oxidative mechanisms in drug oxidation

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In general, the metabolic oxidation of drugs is considered to be mediated by the cytochrome P450 monooxygenase system found in the liver and other tissues. However, it is by no means clear whether or not the oxidation of a given substrate in man is achieved by one or more similar forms of this enzyme, or indeed by a different enzyme not involving cytochrome P450. Recently, metabolic pharmacogenetic studies have demonstrated that the carbon oxidation of three structurally dissimilar drugs is under the control of a single gene locus and exhibits polymorphism (Sloan et al 1978b). It was shown in these investigations that a clearly identifiable proportion of the population (some 5% of British whites), who were phenotypically poor hydroxylators of debrisoquine (Mahgoub et al 1977), were also defective hydroxylators of guanoxan and deficient O-de-ethylators of phenacetin.

In this communication, we describe the conversion of acetanilide to paracetamol by aromatic hydroxylation in volunteers who gave their informed consent and who had been previously phenotyped with respect to their ability to oxidize oral doses of debrisoquine, guanoxan and phenacetin.

The eight healthy adult males (age 22–42) who had previously been phenotyped with debrisoquine, comprised four phenotypically extensive metabolizers (EM)

* Correspondence.

Table 1. Hydroxylation of acetanilide in EM and PM subjects.

Subject	Phenotype*	Hydroxylation (% of dose) at time (h):					
		2	4	6	8	12	24
1	EM	2·8	16·9	33·5	49·0	64·0	81·9
2	EM	8·6	24·2	40·0	55·2	71·7	90·6
3	EM	7·1	29·7	49·3	61·9	79·2	90·2
4	EM	{ 4·7 { 10·4	{ 22·5 { 29·4	{ 45·7 { 52·7	{ 59·5 { 62·4	{ 78·5 { 79·5	{ 97·9 { 95·9
Mean (s.d.)		6·7 (3·0)	24·5 (5·3)	44·2 (7·6)	57·6 (5·6)	74·6 (6·7)	91·1 (6·0)
5	PM	6·9	23·5	38·9	50·1	69·0	87·5
6	PM	10·4	29·7	48·3	62·1	78·5	91·5
7	PM	7·6	24·8	44·6	60·2	77·5	93·6
8	PM	5·9	23·0	43·0	55·5	73·0	94·0
Mean (s.d.)		7·7 (1·9)	25·3 (3·1)	43·7 (3·9)	57·0 (5·4)	74·8 (4·7)	91·7 (3·0)

* Phenotyped with respect to debrisoquine 4-hydroxylation.
EM = extensive metabolizer, PM = poor metabolizer (Mahgoub et al 1977).

Table 2. Kinetic constants for the metabolism and elimination of acetanilide in man.

Subject	Pheno-type	Apparent first order rate constants (h⁻¹).	
		K	k_f
1	EM	0·146	0·126
2	EM	0·115	0·113
3	EM	0·172	0·157
4	EM	{ 0·148 { 0·143	{ 0·144 { 0·139
Mean (s.d.)		0·145 (0·020)	0·136 (0·017)
5	PM	0·133	0·123
6	PM	0·168	0·157
7	PM	0·122	0·115
8	PM	0·130	0·127
Mean (s.d.)		0·138 (0·020)	0·131 (0·018)

and four phenotypically poor metabolizers (PM) (Mahgoub et al 1977). Each subject fasted overnight and then was given by mouth a gelatin capsule containing 500 mg (3·7 μCi) [¹⁴C]acetanilide (radiochemical purity >99·5%, synthesized from [U-¹⁴C] aniline according to Vogel (1951). Urine was collected at 2, 4, 6, 8, 12, 24h and either 26 or 27 h post-dosing. Radiochromatography revealed little or no qualitative difference between urine samples, with paracetamol and its sulphate and glucuronic acid conjugates comprising 95–99% of the urinary ¹⁴C. Neither aniline nor unchanged acetanilide was detected. Accordingly, [¹⁴C]paracetamol production was measured by scintillation counting of total ¹⁴C elimination in urine.

The extent of hydroxylation of acetanilide in four EM and four PM subjects is shown in Table 1. Mean values for each phenotype compare remarkably well, both groups of individuals metabolizing around 90% of the dose of acetanilide within 24 h. Treatment of these data by the kinetic methods of Martin (1967) and Cummings et al (1967) allowed calculation of the minimum esti-

mates of the apparent first-order rate constants for the overall elimination in urine (K) and formation of paracetamol (k_f) which are given in Table 2. There was no discernible inter-phenotype difference in either K or k_f, both groups hydroxylating acetanilide at a rate of 0·13–0·14 h⁻¹.

The hydroxylation of acetanilide in man contrasts greatly with the de-ethylation of phenacetin. In this latter case, paracetamol is produced at only one-third of the rate (0·09 h⁻¹) in PM subjects as in EM subjects (0·28 h⁻¹) (Sloan et al 1978b). In addition, phenotypically poor metabolizers are almost totally unable to perform the aromatic hydroxylation of guanoxan (Sloan et al 1978b) and, by definition, the alicyclic hydroxylation of debrisoquine, where the inter-phenotype difference in k_f is of the order of 40–50 (Sloan et al 1978a).

Thus, the genetic defect in the oxidation of debrisoquine, guanoxan and phenacetin, seen in some 5% of the population, does not occur for acetanilide hydroxylation, indicating that this reaction is mediated by a separate enzyme system to debrisoquine hydroxylation and thus controlled by a different gene complex.

Recent work would seem to corroborate these findings. In a pharmacokinetic investigation of paracetamol appearance in plasma after co-administered oral doses of phenacetin and acetanilide, it was concluded that phenacetin was subject to a significant first-pass effect with resulting drug/metabolite ratios in plasma less than 0·1. In contrast, acetanilide persisted in plasma for the duration of the experiment (6 h) with non-first-pass characteristics (Baty & Robinson 1977). In addition, Sato (1978) has commented that the microsomal fatty acid desaturase system, a non-P450 enzyme, is capable of hydroxylating acetanilide and similar substrates.

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Possible involvement of 5-hydroxytryptamine in dopamine-receptor-mediated hypothermia in the rat

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In most species dopamine agonists cause a fall in core temperature which is specifically antagonized by dopamine antagonists (for review see Cox 1979). In a previous study, the preoptic anterior hypothalamus was shown to be the most responsive site to central injection of dopamine agonists (Cox & Lee 1977). However, since other putative neurotransmitters, such as acetylcholine and 5-hydroxytryptamine (5-HT), are also reported to be present in the hypothalamus and to have an important role in thermoregulation, the relationship between dopamine and other transmitters in thermoregulation has been investigated. In 1974, a cholinergic link in dopamine-receptor-mediated hypothermia in mice was suggested by Glick & Marsanico. They reported that the hypothermia induced by intraperitoneal apomorphine injection was not only blocked by haloperidol, but also by hyoscine. More recently, this proposal received further support from the experiments of Jacob & Suaudeau (1977), who reported that the hypothermic response to intracisternal dopamine injection was significantly reduced by subcutaneous pretreatment with atropine. However, other workers have reported that atropine was ineffective in blocking the hypothermic effect of apomorphine (Fuxe & Sjöqvist 1972). Recently, an involvement of 5-HT in dopamine-receptor-mediated hypothermia has also been suggested. Dopamine agonist-induced hypothermia has been reported to be prevented by either 5,6-hydroxytryptamine or electrolytic lesions of the dorsal raphe nuclei (Maj & Przewlocka 1975; Przewlocki 1977). Further, Grabowska et al (1973) have shown that the hypothermia induced by apomorphine in rodents could be antagonized by lysergic acid diethylamide and butyrophenones. As with acetylcholine, some results contrary to those mentioned above have also

been reported in that methysergide was found to be ineffective against the hypothermic response to the dopamine agonists (Grabowska et al 1973; Burks & Rosenfeld 1977). Therefore in this study, further investigations have been made to determine the relationship, if any, between central cholinergic and 5-hydroxytryptaminergic tracts in dopamine-receptor-mediated hypothermia in the rat.

Male Sprague-Dawley rats, 250 to 300 g, were used at an ambient temperature of 17 ± 1 °C. For the systemic injections, drugs were administered intraperitoneally in 1 ml kg^{-1}; and for central injections, drugs were given in 1 μl down guide cannulae which had been implanted 7 days previously into the preoptic anterior hypothalamus under pentobarbitone (45 mg kg^{-1}, i.p.) anaesthesia. The concurrent control group received the appropriate vehicle injected by the same route. Core temperature was measured by a rectal probe inserted to a depth of 4 cm. At the end of the experiment all the central injection sites were verified histologically.

In this study two types of experiment were performed. In the first series the effect of intrahypothalamic injection of various agonists were compared in controls and in rats pretreated systemically with various antagonists. Unilateral intrahypothalamic injection of the dopamine agonists, apomorphine and dopamine, caused a dose-related fall in core temperature of the rat (Fig. 1a, b). The significant fall in core temperature induced by dopamine (10 μg) or apomorphine (10 μg) was prevented by systemic pretreatment with the dopamine receptor antagonists, pimozide (2 h) and haloperidol (1 h). However, systemic pretreatment with atropine, methysergide and cyproheptadine (all for 1 h) failed to antagonize the hypothermic response to central dopamine agonist injection (Table 1). Oxotremorine (OT) and 5-HT also produced a dose-related fall in core temperature when administered

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