after implantation we have observed some tissue erosion with white cell 'clumping' in the damaged area. These lesions have not been examined histologically. No significant problems have been encountered with the venous catheter. We have not adopted any protocol for regular flushing of implanted catheters for two reasons:

(i) We have been unable so far to find a suitable rapid method for frequent flushing. Conventional unsealing and re-sealing of each catheter for daily flushing damages the wall of the exteriorized portion of the catheter, thereby shortening its useful life.

(ii) We hold 50–60 catheterized animals at any given time and frequent flushing by conventional methods would be a time-consuming and, therefore, expensive exercise. In terms of cost-effectiveness we prefer to accept a small proportion of catheter failures and leave the animals undisturbed between time of implantation and time of usage (1–2 days) and between times of usage (2–3 days).

This technique has been used routinely in our laboratory for a considerble period with a low proportion of failures.

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The hydroxylation of *p*-tyramine in man

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Normal human urine contains *p*-hydroxymandelic acid, a metabolite of octopamine (Kakimoto & Armstrong, 1962). The production of octopamine from *p*-tyramine has been demonstrated in several animal tissues, including brain, and is particularly associated with the sympathetic nervous system (Carlsson & Waldeck, 1963; Brandau & Axelrod, 1972; Boulton & Wu, 1973). In rabbits after intraperitoneal injection of [^{14}C]-*p*-tyramine 7% of the radioactivity recovered in the urine was in the form of *p*-hydroxymandelic acid (Lemberger, Klutch & Kuntzman, 1966). In man, an increase in urinary *p*-hydroxymandelic acid after intravenous *p*-tyramine has been noted but it was not possible to determine whether this increase was due directly to conversion of infused tyramine to octopamine or to the release of endogenous octopamine stores (Bonham-Carter, Karoum & others, 1970). Surprisingly, no radioactive *p*-hydroxymandelic acid could be detected in the urine of four subjects receiving [1-^{14}C]-*p*-tyramine intravenously (Tacker, Creaven & McIsaac, 1972) suggesting that in man exogenous tyramine could not serve as a precursor for octopamine. We are investigating the metabolism of deuterium labelled *p*-tyramine in man using gas chromatography-mass spectrometry and report here the incorporation of label into both *p*-hydroxymandelic acid and 3,4-dihydroxyphenylacetic acid.

Two normal subjects (1 male, 1 female) were given 3,5-[$^2H_2$]-*p*-tyramine hydrochloride twice, once by mouth and once several weeks later intravenously. Urine was collected hourly for at least 3 h before the loads and at least 4 h afterwards; later collections were 2-hourly or overnight. Two subjects with manic-depressive psychosis were given intravenous tyramine only. The urinary acidic metabolites were extracted into ether and converted to the trimethylsilyl derivatives by standard methods (Dalgliesh, Horning & others, 1966). Gas chromatography-mass spectrometry with repetitive scanning was carried out using a modified Perkin-Elmer 270 instrument. Unlabelled compounds or $\alpha\,\alpha$,3,5-[$^2H_4$]-*p*-hydroxyphenylacetic acid, 3,5-[$^2H_2$]-*p*-hydroxymandelic acid and $\alpha\,\alpha$,2,5,6-[$^2H_5$]-3,4-dihydroxyphenylacetic acid were used as internal standards for quantitation. The identity of the metabolites rests on coincidence with either natural or deuterium labelled internal standards on at least three stationary phases (OV3, OV17 and OV225). The deuterated compounds emerge a few seconds before the natural compounds. The *p*-hydroxyphenylacetic acid was monitored using the *m/e* 296 fragment and the *p*-hydroxymandelic and 3,4-dihydroxyphenyl acetic acids using *m/e* 267 and 384 respectively.

Results for the two normal subjects are summarized in Table 1 and Fig. 1. The two patients gave similar results on the intravenous load, with incorporation of label into *p*-hydroxymandelic acid and 3,4-dihydroxyphenylacetic acid. With the 3,4-dihydroxyphenylacetic acid, low levels of labelling could not be measured accurately on our machine as the large peak at *m/e* 385 in the natural compound coincides with the M^+ peak of the deuterium labelled compound. The presence of only one deuterium atom in the labelled 3,4-dihydroxyphenylacetic acid agrees with the findings of Nagatsu, Levitt & Udenfriend (1964) that the NIH-shift does not occur between the 3 and 2 positions during the hydroxylation of tyrosine.

* Correspondence.

Table 1. *Recoveries of deuterium labelled metabolites in urine, as % of administered dose.*

	p-OH phenyl-acetic acid	*p*-OH mand-elic acid	3,4-DiOH phenyl-acetic acid
Subject 1			
Oral, 103 mg	62	0·10	0·02
Intravenous, 12 mg/10 min	79	0·91	0·23
Subject 2			
Oral, 103 mg	58	0·15	0·07
Intravenous, 31 mg/28 min	89	0·83	0·49

Tyramine dose is expressed as the hydrochloride.

The side-chain hydroxylation of *p*-tyramine probably involves the action of dopamine-β-hydroxylase (Brandau & Axelrod, 1972). Ring hydroxylation of *p*-tyramine to dopamine can be brought about by a relatively non-specific microsomal enzyme found in the liver of various species (Lemberger, Kuntzman & others, 1965). This reaction does not seem to have been demonstrated *in vivo* though injected [2-^{14}C]-*p*-tyramine is incorporated into urinary normetanephrine in rats (Creveling, Levitt & Udenfriend, 1962).

The discrepancy between the present results and those of Tacker & others (1972) is not easy to explain. The doses given by these workers were much smaller than those used in the present study and it could be that in man some threshold concentration needs to be exceeded before the tyramine enters the noradrenergic nerve endings where it can be β-hydroxylated. In mice, however, a reverse situation exists and a larger proportion of tyramine is converted to octopamine for low doses than for high (Waldeck, 1971).

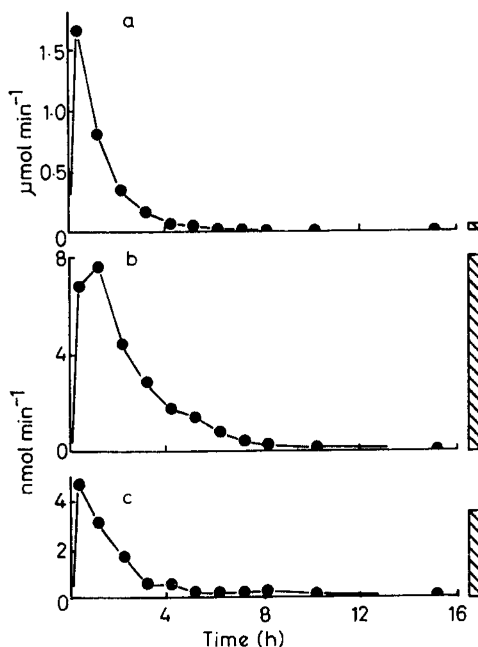

FIG. 1. Excretion of deuterium labelled metabolites in subject 2 following intravenous [$^2H_2$]tyramine load starting at time 0. The hatched bars on the right indicate the average excretion of the unlabelled metabolites during the experimental period. a—*p*-hydroxyphenylacetic acid, b—*p*-hydroxymandelic acid, c—3,4-dihydroxyphenylacetic acid.

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