Biotransformation of Fluoxetine in Man

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Biotransformation and excretion of fluoxetine were studied in nine patients following administration of known quantities. An average of 58 per cent was exhaled unaltered following anesthesia. Ten per cent of the fluorine administered as fluoxetine was recovered in urine, mainly as trifluoroacetic acid. In contrast to other species, which excrete trifluoroethanol primarily, in man free and conjugated trifluoroethanol accounted for only 0.6 per cent of the administered dose. Fluoride ion excretion in urine did not exceed normal rates of excretion. The fate of 32 per cent of administered fluoxetine remains unknown. (Key words: Anesthetics, volatile: fluoxetine; Biotransformation: fluoxetine.)

FLUOXETINE \( (2,2,2\text{-trifluoroethyl vinyl ether}) \) undergoes biotransformation in the mouse, dog,¹ and monkey.² Trifluoroethanol (TFE) and trifluoroacetic acid (TFAA) have been identified as the urinary metabolites of the laboratory animals,³ with TFE predominating.

Fluoxetine has been found to be highly toxic to mice,² dogs, cats, and rabbits, but not to man.⁴ In the 20 years since its introduction, there have been only two reports of death from hepatic and hepatoportal failure following fluoxetine anesthesia where no other presumptive cause was identified.⁵,⁶ In both cases there were histories of drug exposure which might have altered unfavorably the metabolic fate of fluoxetine.

The present study was undertaken to measure and to identify the metabolites of fluoxetine and to study the kinetics of uptake and excretion of fluoxetine and its metabolites in man.

Method

The subjects of the study (table 1) were nine informed surgical patients, eight women and one man, mean age 40 years (range 23 to 66 years), mean weight 75 kg (range 48 to 100 kg), who underwent eight elective gynecologic and one orthopedic procedure. After preoxygenation, anesthesia was induced with thiopental (average 5.2 mg/kg). The trachea was intubated with a cuffed endotracheal tube following administration of succinylcholine (1 mg/kg). A closed-circle absorption system was then attached and anesthesia was maintained with fluoxetine in oxygen and intravenous administration of relaxants, as previously described.⁷ The breathing circuit was constructed of metal and plastics having low solubility for fluoxetine. The Baralyme carbon dioxide absorbent was thoroughly moistened with water to minimize absorption of fluoxetine. Consumption of fluoxetine by the circuit was negligible (less than 0.1 per cent of uptake by the patient) and the circuit was tested before each study for leaks. Flows of oxygen into the system averaged 200 ml/min (range 150 to 320 ml/min). Respirations were controlled with an Ohio anesthesia ventilator.

Liquid fluoxetine was injected into the circuit by a Harvard infusion pump, the speed of which was controlled by a Datatrak curve follower programmed to maintain a constant alveolar concentration of approximately 3.3 per cent (MAC = 3.4 per cent).⁸,⁹ “Alveolar” concentrations of fluoxetine were measured in end-expired gas samples collected every 10 minutes through a polyethylene catheter passed through the tracheal end of the endotracheal tube.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (Years)</th>
<th>ASA Status</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Body Fat (Per Cent)</th>
<th>Ventilation (L/min)</th>
<th>Operation</th>
<th>Duration (min)</th>
<th>Inh.</th>
<th>Dose (µg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1 ▼</td>
<td>35</td>
<td>II</td>
<td>157</td>
<td>63</td>
<td>11.3</td>
<td>6.6 ± 2.0</td>
<td>Expl. laparotomy</td>
<td>77</td>
<td>17.8</td>
<td>0.28</td>
</tr>
<tr>
<td>Patient 2 ▲</td>
<td>66</td>
<td>II</td>
<td>157</td>
<td>80</td>
<td>19.9</td>
<td>6.7 ± 1.1</td>
<td>Vag. hysterectomy; A &amp; P repair</td>
<td>97</td>
<td>24.7</td>
<td>0.31</td>
</tr>
<tr>
<td>Patient 3 △</td>
<td>23</td>
<td>I*</td>
<td>170</td>
<td>61</td>
<td>4.5</td>
<td>11.6 ± 4.1</td>
<td>Open reduction of fractured femur</td>
<td>104</td>
<td>21.1</td>
<td>0.35</td>
</tr>
<tr>
<td>Patient 4 ▲</td>
<td>37</td>
<td>I</td>
<td>165</td>
<td>100</td>
<td>23.4</td>
<td>8.7 ± 3.4</td>
<td>D &amp; C; total abd. hysterect.; bil. salp. oophorect.</td>
<td>128</td>
<td>34.8</td>
<td>0.35</td>
</tr>
<tr>
<td>Patient 5 ▲</td>
<td>31</td>
<td>I</td>
<td>157</td>
<td>48</td>
<td>2.3</td>
<td>6.3 ± 1.7</td>
<td>D &amp; C; vag. hysterectomy</td>
<td>135</td>
<td>22.3</td>
<td>0.46</td>
</tr>
<tr>
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<td>42</td>
<td>I</td>
<td>165</td>
<td>83</td>
<td>17.6</td>
<td>10.9 ± 6.6</td>
<td>D &amp; C; vag. hysterectomy</td>
<td>151</td>
<td>40.0</td>
<td>0.48</td>
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<tr>
<td>Patient 7 ▼</td>
<td>38</td>
<td>I</td>
<td>160</td>
<td>86</td>
<td>20.7</td>
<td>7.3 ± 1.4</td>
<td>Total abd. hysterect.; Bilat. salpingo-oophorect.</td>
<td>178</td>
<td>42.8</td>
<td>0.50</td>
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<tr>
<td>Patient 8 ▲</td>
<td>44</td>
<td>I</td>
<td>155</td>
<td>59</td>
<td>9.9</td>
<td>6.3 ± 1.5</td>
<td>Radical hysterectomy</td>
<td>195</td>
<td>44.8</td>
<td>0.76</td>
</tr>
<tr>
<td>Patient 9 ▲</td>
<td>48</td>
<td>II</td>
<td>160</td>
<td>100</td>
<td>25.8</td>
<td>6.9 ± 1.6</td>
<td>D &amp; C; total abd. hysterectomy</td>
<td>210</td>
<td>39.6</td>
<td>0.40</td>
</tr>
<tr>
<td>Mean</td>
<td>40</td>
<td></td>
<td>161</td>
<td>76</td>
<td>15.0</td>
<td>7.9</td>
<td></td>
<td>142</td>
<td>32</td>
<td>0.43</td>
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<tr>
<td>SD</td>
<td>12</td>
<td></td>
<td>5</td>
<td>10</td>
<td>8.4</td>
<td>2.0</td>
<td></td>
<td>46</td>
<td>10</td>
<td>0.14</td>
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<tr>
<td>SEM</td>
<td>4</td>
<td></td>
<td>1.7</td>
<td>6.2</td>
<td>2.8</td>
<td>0.7</td>
<td></td>
<td>15.3</td>
<td>3.5</td>
<td>0.048</td>
</tr>
</tbody>
</table>

* Drug addict.
At the end of operation, administration of fluoxetine was discontinued and relaxant effects were reversed. When emergence became evident, the patient was extubated and promptly connected by mask to a nonrebreathing system for collection of all exhaled air for the first hour after anesthesia. Exhaled gases were collected as 5-10-minute samples in laminated mylar and aluminum bags.\footnote{Bioscience Laboratory, Fort Lee, N. J.} Collections were continued at hourly intervals for six hours and, thereafter, from the first to the fifth postoperative days, two or three times daily. The volume of exhaled air and concentration of fluoxetine in each collection bag were measured to calculate minute ventilation and rate of excretion of fluoxetine by the lungs.

The quantity of fluoxetine absorbed by the patient was estimated from the amount injected into the circle, corrected for vapor remaining in the circuit and rate of vapor loss from the circuit during a test run before each study.\footnote{Bioscience Laboratory, Fort Lee, N. J.}

All urine was collected in polyethylene bottles from 24 hours prior to anesthesia until the tenth postoperative day, in approximately 12-hour fractions. Urine volumes and times of collection were noted.

**Analytical Procedures**

**ANALYSIS OF GAS SAMPLES**

An Aerograph HIFI Model A-600C gas chromatograph, equipped with hydrogen flame ionization detector and a 31 cm × 6 mm copper column of 10 per cent diisodecyl phthalate on Chromosorb P 60/80 mesh was used to analyze for fluoxetine. Column temperature was 30°C and carrier gas was nitrogen, flowing at 40 ml/min.

**Analyses of Urine**

Inorganic fluoride and total nonvolatile urinary fluorine were analyzed with a specific fluoride-ion electrode as described previously.\footnote{Bioscience Laboratory, Fort Lee, N. J.} Total urinary fluorine content was determined in three cases by a wet combustion method.\footnote{Bioscience Laboratory, Fort Lee, N. J.} The difference between total fluorine and inorganic fluoride represented the organic fluorine.

Identification and measurement of trifluoroacetic acid (TFAA) and glucuronides were achieved by paper chromatography.\footnote{Bioscience Laboratory, Fort Lee, N. J.} One hundred to 200 μl of urine adjusted to pH 9 were spotted on Whatman paper #1. Chromatograms were developed by descending chromatography with a mixture of propanol: water: ammonia (80:18:2), or a mixture of isopropanol: ammonia (4:1). Bromocresol green\footnote{Bioscience Laboratory, Fort Lee, N. J.} was used for detection of TFAA and β-naphthoresorcinol for detection of glucuronides.\footnote{Bioscience Laboratory, Fort Lee, N. J.} The areas corresponding to trifluoroacetic acid (RF 0.72 with the first mixture) and those corresponding to glucuronides (RF 0.12 with the second mixture) were cut out, combusted in a Schoeniger flask, and analyzed for fluoride. When TFAA was added to urine, 90 to 100 per cent of the fluoride was recovered from the corresponding spot. Identification by thin-layer chromatography on Eastman Chromatogram sheets (6061 Silica gel) yielded similar results.

Identification of trifluoroethanol (TFE) was accomplished by gas chromatography and mass spectrum analysis. One-microliter samples of all 24-hour urine specimens from eight patients were injected directly onto a gas chromatograph column and the peaks compared with a water standard of TFE. TFE standard solutions were prepared by addition of 1 μl TFE (2,2,2-trifluoroethanol, spectro grade, Eastman organic chemicals Lot No. 681) to 5 ml distilled water. To eliminate the interfering water peak, the carrier gas, nitrogen, was prehumidified by passage through a 180-cm-by-6-mm column of Chromosorb W, which was moistened every six hours of operation with 1 ml water. Four resolution columns, 3 m × 3 mm, packed with liquid phases of different polarities, were used to establish the coincidence of a peak obtained from a urine sample with that obtained from standard solutions of TFE. The columns were: 10 per cent disisodecylphthalate on Chromosorb P at 70°C; 10 per cent Carbowax 4000 on Chromosorb W at 45°C; 5 per cent SE-30 on Chromosorb W at 60°C; 5 per cent OV-17 on Chromosorb W at 25°C. Identification was confirmed by injections of mixtures of urine and the standard, and demonstration of a single peak with the appropriate retention time.
Mass spectral analyses were performed by employing both direct probe introduction and combined gas chromatographic–mass spectrometric (GC-MS) analysis on a Perkin-Elmer 270 combined GC-MS double-focusing low-resolution mass spectrometer.

Approximately 2 l of urine, collected during 48 hours following fluroxene anesthesia, were adjusted to pH 7.2 and concentrated in a flash evaporator to a volume of 20 ml. The concentrate was acidified with 5 ml of sulfuric acid containing 0.25 g of paraformaldehyde and heated in a sealed test tube in a boiling-water bath for 30 min to hydrolyze TFE conjugates. The hydrolysate was cooled to room temperature and filtered; TFE was extracted in 5 ml carbon disulfide. The extract was washed with 2 ml of a saturated water solution of K₂CO₃.

Gas chromatographic separations of 3-μl samples of CS₂ urine extract were achieved on a coiled glass column, 180 cm × 3 mm O.D., packed with 15 per cent Carbowax 20M on 60/70 mesh Gas Chrom-P. Helium carrier gas flow rates were maintained at approximately 8 ml/min. Injector and isothermal oven temperatures were maintained at 150 and 112 °C, respectively. Injections (3 μl) of standard TFE in carbon disulfide representing 5 μg of TFE were employed for comparison.

The following electron impact source conditions were maintained: electron energy, 80 ev; target voltage 120 v; accelerating voltage 2.0 kv; emission current 100 amp; manifold and gas inlet temperatures, 172 and 208 °C, respectively; ion source housing temperature 158 °C; target temperature 182 °C; collector slit 1.0 mil; electron multiplier detector 2.5 kv (gain 10⁶). Chromatograms were recorded on a dual-pen strip chart recorder from the total ion current monitor (TIM) located between the electrostatic and magnetic sectors. Mass
### Table 2. Fraction of Uptake (Percentage)

<table>
<thead>
<tr>
<th></th>
<th>Exhaled Air</th>
<th>TFAA</th>
<th>Urinary</th>
<th>TFE</th>
<th>Other</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Free</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td>48</td>
<td>9.4</td>
<td>0.30</td>
<td>0.08</td>
<td>0.38</td>
<td>3.5</td>
</tr>
<tr>
<td>Patient 2</td>
<td>69</td>
<td>0.08</td>
<td>0.18</td>
<td>0.26</td>
<td>*</td>
<td>**</td>
</tr>
<tr>
<td>Patient 3</td>
<td>64</td>
<td>10.7</td>
<td>0.44</td>
<td>0.96</td>
<td>1.40</td>
<td>0.0</td>
</tr>
<tr>
<td>Patient 4</td>
<td>66</td>
<td>4.7</td>
<td>0.16</td>
<td>0.17</td>
<td>0.33</td>
<td>6.9</td>
</tr>
<tr>
<td>Patient 5</td>
<td>77</td>
<td>4.5</td>
<td>0.48</td>
<td>0.22</td>
<td>0.70</td>
<td>6.2</td>
</tr>
<tr>
<td>Patient 6</td>
<td>62</td>
<td>4.6</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>0.8</td>
</tr>
<tr>
<td>Patient 7</td>
<td>40</td>
<td>8.0</td>
<td>0.22</td>
<td>0.12</td>
<td>0.34</td>
<td>0.8</td>
</tr>
<tr>
<td>Patient 8</td>
<td>50</td>
<td>*</td>
<td>0.32</td>
<td>0.43</td>
<td>0.75</td>
<td>*</td>
</tr>
<tr>
<td>Patient 9</td>
<td>46</td>
<td>8.2</td>
<td>0.15</td>
<td>0.45</td>
<td>0.60</td>
<td>0.0</td>
</tr>
<tr>
<td>Average</td>
<td>58</td>
<td>7.2</td>
<td>0.27</td>
<td>0.33</td>
<td>0.60</td>
<td>2.6</td>
</tr>
<tr>
<td>SEM</td>
<td>4.1</td>
<td>1.0</td>
<td>0.05</td>
<td>0.10</td>
<td>0.13</td>
<td>1.1</td>
</tr>
</tbody>
</table>

* Not determined.
† Does not include free TFE.

Spectra were scanned magnetically from m/e 20–200 at a rate of 10 sec/dec.

Quantitative measurements of TFE were performed by GC using a prehumidifying Chromosorb W column and 5 per cent OV-17 on Chromosorb W (80–100 mesh) at 25°C as the resolution column. One μl of untreated urine was injected on column to determine free TFE. To determine conjugated TFE, 1-μl amounts of hydrolyzed samples were injected on the column. Peak heights in response to a water standard of TFE were linear between 0.03 and 0.12 μg, and recovery rates of TFE added to the urine samples ranged from 95 to 106 per cent.

Hydrolysis with sulfuric acid: .1 ml of 5 per cent paraformaldehyde in concentrated H₂SO₄ was added to 0.5 ml of urine in a glass ampule. The ampule was sealed and placed in a boiling-water bath for 10 hours. The sample was cooled in ice water, neutralized with saturated NaOH, and analyzed by gas chromatography for TFE (total TFE).

Hydrolysis with beta-glucuronidase: 2.5 ml

![Fig. 2. Correlation between body fat and fraction of fluoxetine exhaled with the longest time constant.](image)

\[
\% = 100 \frac{a_3}{k_3} - \frac{a_1 + a_2 + a_3}{k_1 + k_2 + k_3}
\]

where a's are intercepts of the three exponential functions with the ordinate of the desaturation curve (fig. 1), and k's are their slopes (rate constants).
Fig. 3. Urinary excretion of fluorinated metabolites. The ordinate is the excretion rate of fluorine (mg/h), abscissa the time after the start of anesthesia (hours). The points are experimental data. Symbols represent the same patients as in figure 1.
of urine were deproteinized with 1 ml of 10 per cent trichloroacetic acid and centrifuged. The supernatant was adjusted with acetate—NaOH buffer to pH 4.5–5.0. Forty milligrams of beta-glucuronidase (beta-glucuronidase—GL Bovine liver, Main Research Laboratories Division of Becton, Dickinson) were added and the sealed sample was incubated overnight at 37 C.

Results

Exhaled Air

Information about the patients, operations and anesthesia is summarized in table 1. The patients are listed according to duration of anesthesia. Anesthesia lasted an average of 142 min (range 77 to 210 min). The quantities of fluroxene taken up by the patients averaged 32.0 g (range 17.8–44.8 g). During anesthesia the end-expired concentrations of fluroxene averaged 3.3 vol per cent (SD 0.4).

The pulmonary desaturation of unaltered fluroxene was assumed to be characterized by three exponential functions. The constants of the functions were obtained by seeking an optimal fit to our experimental data by the method of least squares. The measured exhalation rates of fluroxene at different times after the end of anesthesia were used to compute the parameters of a best-fitting curve for each patient (IBM 360/65 computer, NONLIN** program). The correlation coefficients averaged 0.952 (SEM 0.049). A representative desaturation curve (fig. 1) was calculated using the data (186 values) from all nine subjects:

\[ a = 260e^{-0.05t} + 60e^{-0.0005} + 3e^{-0.0005t} \]  

(1)

where “a” is excretion rate in mg/min and “t” is time in minutes after the end of anesthesia. The correlation coefficient relating the curve representing equation 1 to the experimental points is 0.905. The total quantity of fluroxene exhaled by this “representative” subject was calculated to be 18.7 g, or 58 per cent of the average dose administered. By individual integration of the three exponential functions, it was estimated that an aver-

** NONLIN is a program for parameter estimation supplied through the courtesy of Dr. C. M. Metzler of the Upjohn Company.
age of 28 per cent of the exhaled fluoxetine was contributed by the most rapidly exchanging excretion process. Similarly, the second function contributed approximately 40 per cent, and the third, the slowest, contributed 32 per cent.

Data from each subject were used similarly to calculate the total quantity exhaled by each (table 2), and to estimate the contribution of each of the three exponential functions to the total exhaled. The fraction of total body weight ascribable to body fat was calculated from the body weight and height of each subject. Figure 2 illustrates the close correlation between body fat and the contribution of the third term of equation 1 to the total quantity exhaled.

**URINE**

Excretion in urine of inorganic fluoride following anesthesia did not increase above normal rates of approximately 1 mg per day. Nonvolatile fluorinated metabolites appeared in urine after anesthesia, reaching a maximum excretion rate 34 hours (SD 9.9) after the end of anesthesia. Excretion then declined in five patients as a single exponential function with a half-life of approximately 23 hours (fig. 3, above), and in four patients as a biphasic exponential function with half-lives of 11 hours and 48 hours (fig. 3, below, table 3). The total quantities of organic fluoride excreted, calculated as the sum of nonvolatile fluoride and free TFE, averaged 10.6 (SD 2.6) per cent of the amount of fluoxetine taken up during anesthesia (table 2). At least 75 per cent of the organic fluoride had the same RF on paper and thin-layer chromatograms as TFMA.

**Total urinary fluorine** excretion of three patients was measured. It exceeded nonvolatile fluoride to a measurable extent in the samples collected during the first two post-exposure days only. The volatile fluorinated metabolite measured by this method accounted for approximately 0.73 per cent of the fluoxetine retained during anesthesia. Fluoxetine was present in traces (0–12 mg/l) in urines collected during the first 24 hours, and was absent thereafter. The presence of fluorine-containing urinary glucuronide was established by paper and thin-layer chromatography in two of seven cases studied.

**Identification of TFE.** The major peak in urine had the same retention time as that of a known aqueous solution of TFE in each of the four columns employed in these studies. Identification was confirmed by mass spectrography. Mass spectral analysis of the standard TFE in CS2 resulted in a fragmentation pattern typical of fluorinated low-molecular-weight alcohols. Major fragment ions produced, their m/e values, and their relative peak intensities were essentially similar to those previously reported for TFE. Observation of the molecular ion of m/e 100, and major fragment peaks of m/e 83, (M–OH)+; m/e 69, CF3+; m/e 61, (M–HF–F)+; m/e 51, HCF2+; and m/e 31, CH2OH+ and CF+, proved the presence of TFE in the urine extract.

**Urinary excretion of TFE.** Both free and conjugated TFE were present in urine obtained during and after anesthesia. Figure 4 compares the kinetics of excretion of free and conjugated TFE with TFMA excretion in a typical case. The maximal urinary excretion rate of conjugated TFE occurred an average of 6 hours (3–11 hours) after the end of anesthesia, and that of free TFE after 11 hours (3–15 hours). Afterward, the excretion curves were exponential; the mean half-time for free TFE was 17 hours (SEM 3.3 hours) and that for conjugated TFE was 15 hours (SEM 4.8 hours). Tables 2 and 3 summarize the data from nine patients. An average of 0.6 per cent of the fluoxetine uptake was converted to TFE; almost half of it was excreted in urine as free TFE. The rest was conjugated. Approximately 30 per cent of the conjugate was hydrolyzable by beta-glucuronidase.

**Discussion**

The lung is the principal excretory pathway of fluoxetine, as predictable from its high vapor pressure and low blood–gas partition coefficient. Obese persons had greater uptakes and exhaled larger quantities than non-obese patients (fig. 1). The correlation between amount of body fat and fraction of fluoxetine exhaled with the longest time constant (fig. 2) supports the contention that the third term of equation 1 represents washout.
from poorly perfused lipid depots. Fluoxetine released from fat storage depots is partly exhaled and partly carried by the blood to tissues, in some of which it is subject to metabolism by microsomal enzymes.\textsuperscript{17-19} In the present studies, a significant fraction, 10.6 per cent, of absorbed fluoxetine was metabolized and excreted in the urine. Maximum excretion rates of organic fluorine occurred during the first postoperative day. After the maximum excretion rate was reached, the urinary excretion curves of five patients appeared to represent a single exponential function, whereas those of the remaining four patients appeared to be the sum of two exponential functions. These two patterns of urinary excretion did not correlate with differences in body habitus, duration of anesthesia, or extent of biotransformation; they remain unexplained. Decremental halftime approximated the longest half-time characterizing excretion of unaltered fluoxetine in exhaled air (table 3).

Van Dyke and Chenoweth\textsuperscript{17-19} state that fluoxetine, like halothane, undergoes very little carbon-fluorine-bond cleavage, but that the remainder of the molecule is extensively metabolized. In mice, the ether linkage is cleaved, the vinyl moiety is completely degraded, and the trifluoroethyl group is converted primarily to TFE and to smaller amounts of TFAA.\textsuperscript{1}

TFAA is the major urinary metabolite in man, in contrast to experimental animals.\textsuperscript{1} It comprised at least 72 per cent of the total fluorinated organic material excreted in the urine. TFE accounted for 0.6 per cent of the uptake, of which half is excreted un conjugated.

Acute toxicity of TFE is seven times greater than that of TFAA,\textsuperscript{20,21} and 15 times greater than that of fluoxetine, in laboratory animals (Yoshimura, N., and FiserovaBergerova, V., unpublished data). TFE is presumably responsible for the toxicity of fluoxetine in laboratory animals, since it is the major metabolite\textsuperscript{1} in all species tested except man. The small amount of TFE formed in man may explain the usual lack of delayed toxicity of fluoxetine.

An average of 68 per cent of the measured uptake of fluoxetine was recovered in exhaled air and urine. The fate of the remaining third is unknown. Two mechanisms which would have escaped detection by our methods are possible: excretion by a route or routes other than exhalation or urinary excretion, and incorporation of the drug or its products of biotransformation in the body in a form that is released too slowly to be detected by our methods.

Percutaneous losses\textsuperscript{22} and fecal excretion of fluoxetine and its metabolites\textsuperscript{1} have been reported to represent an insignificant fraction of the total uptake. In this study, it appeared that the longer anesthesia lasted, the smaller the fraction of uptake recovered. Losses from bleeding and exposure of serous surfaces to room air are mechanisms fitting this criteria. The physical properties of fluoxetine (high vapor pressure, low tissue-air partition coefficient) favor evaporation from exposed tissue surfaces. During these studies, operative blood losses never exceeded a liter, and could have accounted for no more than 4 per cent of the unrecovered fluoxetine.

The second possible mechanism, long-term incorporation of fluorine-containing compounds in body tissues, warrants further study. It has been established that halothane is oxidized to trifluoroacetic acid,\textsuperscript{12} and that nonvolatile metabolites of halothane persist in the liver for a long time.\textsuperscript{23,24} It is possible that a significant fraction of a metabolite of fluoxetine is covalently bound to fixed cellular elements and retained in the body beyond the period of the present study. It is also
possible that the 32 per cent of unrecovered fluroxene is responsible for its occasional delayed toxicity in man.

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