Primary cultures of bovine adrenal medullary chromaffin cells were pulse-labeled with \(^{3}H\)dopamine or \(^{3}H\)norepinephrine and examined for radioactive and total catecholamine contents by high performance liquid chromatography after additional incubations of 15 min to 10 days. \(^{3}H\)Dopamine was rapidly taken up by chromaffin vesicles in situ and converted to norepinephrine within a half-time of approximately 6 h. \(^{3}H\)Norepinephrine taken up by the cells was metabolized in three phases. 1) During its brief transit through the cytoplasm, 20 to 35% of this amine was converted to \(^{3}H\)epinephrine. 2) Following vesicular accumulation, 65 to 70% of the remaining \(^{3}H\)norepinephrine was methylated to form \(^{3}H\)epinephrine with a half-time of approximately 30 h, corresponding to the rate of vesicular catecholamine loss from reserpine-treated cells. 3) The residual \(^{3}H\)norepinephrine decreased with a half-time of 5 days, probably representing loss from norepinephrine-storing cells. \(^{3}H\)Epinephrine formed endogenously had a half-life in the cultures of approximately 15 days. These data suggest that leakage of norepinephrine from chromaffin vesicles into the cytoplasm limits the rate of dopamine conversion to epinephrine in the adrenal medulla. The kinetic data indicate that approximately 18% of the endogenous norepinephrine and 73% of the endogenous dopamine are present in epinephrine cells.
experiments, 8 x 10^6 cells were plated on a 35-mm diameter dish and labeled with 16 μCi of [3H]norepinephrine for 1 h at 37 °C. After two 10-min washes with Locke's solution, the cells were scraped from the dish and homogenized in 1.0 ml of 0.25 M sucrose, 5 mM PIPES, pH 7.0, at 4 °C with 10 strokes of a Potter-Elvehjem homogenizer. The homogenate was placed in 1.5-ml microfuge tubes with adaptors and centrifuged at 1500 rpm for 5 min in a Sorvall SS-34 rotor. The pellet (P1) was rehomogenized as above in 0.5 ml of sucrose buffer, centrifuged at 1500 rpm for 5 min, and the two low speed supernatants combined. The supernatants were then centrifuged at 20,000 rpm for 5 min. The supernatant (S2) was saved for analysis, the pellet (P2) was resuspended in 0.7 ml of 0.5 M sucrose, 5 mM PIPES, and 0.55 ml was layered on a 4.75-m1 linear gradient of 10-40% Renografin containing 0.5 M sucrose, 5 mM PIPES, pH 7.0.

The density gradients were centrifuged in a Beckman SW 50L rotor at 45,000 rpm for 2.5 h. Fractions (0.25 ml) were collected from the bottom of the gradient by puncturing the centrifuge tube. Density was determined by refractive index in a sister gradient run without centrifugation. The chromatographic vesicles were further homogenized and centrifuged at 1500 rpm for 5 min, and the two low speed supernatants combined. The supernatants were then centrifuged at 20,000 rpm for 5 min. The supernatant (S2) was saved for analysis, the pellet (P2) was resuspended in 0.7 ml of 0.5 M sucrose, 5 mM PIPES, and 0.55 ml was layered on a 4.75-m1 linear gradient of 10-40% Renografin containing 0.5 M sucrose, 5 mM PIPES, pH 7.0.

Materials—Tritiated catecholamines were obtained from New England Nuclear: dopamine hydrochloride, 3,4-[3H]-40-60 Ci/mmol; norepinephrine, levo-[3H]-2,5,6,14H], 40-60 Ci/mmol. Renografin-60 was obtained from Squibb.

RESULTS

Subcellular Distribution of Labeled Catecholamines—The subcellular distribution of labeled and endogenous catecholamines was determined immediately after a 2-h labeling period with [3H]norepinephrine or [3H]dopamine by differential and density gradient centrifugation as described under “Experimental Procedures.” In three experiments (Table I) the subcellular distribution of total radioactivity was similar to the distribution of endogenous catecholamines immediately after the labeling period. Most of the catecholamines and radioactivity were present in the P2 fraction which contained the chromaffin vesicles.

To further characterize the distribution of radioactivity in the P2 fraction, it was centrifuged through a continuous Renografin density gradient as described under “Experimental Procedures” to separate chromaffin vesicles from mitochondria and lysosomes. The radioactivity which was identified in dopamine, norepinephrine, and epinephrine by HPLC had the same distribution as chromaffin vesicles. Thus the labeled catecholamines are rapidly taken up by chromaffin vesicles in the intact cells.

Cells Labeled with [3H]Dopamine—Fig. 2 shows the conversion of [3H]dopamine to [3H]norepinephrine and [3H]epinephrine and their turnover over a 10-day period. In this study cells were labeled with [3H]dopamine for a 2-h period and were examined immediately after the wash and at subsequent 24-h intervals. Dopamine was rapidly converted to norepinephrine during the labeling period. In the study shown in Fig. 2, 41% of the total radioactivity present in the cell after the initial wash cycle was norepinephrine and 3% was epinephrine. Since β-hydroxylation of dopamine occurs after it is taken up by the vesicles (4) this indicates that transport of dopamine from the cytoplasm into the vesicles is a relatively rapid process.

Twenty-four h after the pulse, [3H]dopamine had declined to less than 10% of its initial value, and only trace amounts could be detected at 48 h. [3H]Norepinephrine reached a peak at 24 h and then declined exponentially while [3H]epinephrine reached a maximum at 48 h and thereafter declined slowly. The endogenous levels of norepinephrine remained constant throughout the 10-day period while there was an apparent small decline in the epinephrine levels. In other experiments there were no changes in catecholamine levels. The levels of endogenous dopamine were also determined in these studies; they represented 1.0 to 1.5% of the total catecholamine content and remained constant throughout the experimental periods except in those studies in which the cells were treated with reserpine.

Semi-log plots of these data (Fig. 2B) revealed that the decline in [3H]norepinephrine was biphasic and could be resolved into two apparent first order components which fit an equation of the type

\[ N_r = N_0e^{-kt} + N_0'e^{-kt'} \]

where \( N_r \) is the per cent of [3H]norepinephrine remaining at time \( t \), \( N_0 \) and \( N_0' \) are the proportions present in each component at zero time and \( k \) and \( k' \) are the apparent first order reaction rate constants (13). Graphical analysis of these data gave a fast component with a \( t_\alpha \) of 1.3 days and a slow component of 4.8 days. Evidence presented below indicates that the fast component represents the conversion of norepinephrine to epinephrine while the slow component represents the turnover of norepinephrine in norepinephrine cells. The results of this and other similar experiments using different cell preparations are summarized in Table II. The half-life for the turnover of epinephrine was 2- to 3-fold longer than the half-life for the turnover of norepinephrine in norepinephrine cells regardless of whether the cells were labeled with [3H]dopamine or [3H]norepinephrine.

To better evaluate the time course for the conversion of dopamine to norepinephrine and epinephrine, cells were pulse-labeled for 1 h with [3H]dopamine and examined for products at short intervals up to 6 h. The data from one experiment is shown in Fig. 3. At the end of the 1-h labeling period 25% of the radioactivity was present as the β-hydroxylated products norepinephrine and epinephrine. Thereafter [3H]dopamine decreased and norepinephrine and epinephrine increased in an apparent biphasic exponential manner. The fast phase in the decline of [3H]dopamine had a half-life of 30 min and represented 15% of the total [3H]dopamine taken up by the cell. This rapid decline in [3H]dopamine was matched by a similar rapid formation of [3H]norepinephrine. The slow phase in the decline of [3H]dopamine had a half-life...
Catecholamine Flux through Chromaffin Vesicles

FIG. 2. Conversion of [3H]dopamine to [3H]norepinephrine and [3H]epinephrine. Cells were labeled for 2 h with [3H]dopamine and examined immediately after the wash cycle and at the times indicated. A, linear presentation of data. Upper: endogenous catecholamines; O, norepinephrine; □, epinephrine. Lower: Δ, [3H]dopamine; ○, [3H]norepinephrine; △, total 3H-catecholamines. B, semi-logarithmic presentation of data. ○, [3H]norepinephrine, fast component obtained by subtracting extrapolated values of slow component (t∞, 6.5 h) from experimental data points; △, [3H]norepinephrine plus [3H]epinephrine plotted assuming that all of the [3H]dopamine present in the cell at t∞ is converted to β-hydroxylated products (A∞). The amounts of [3H]norepinephrine and [3H]epinephrine present at the end of the labeling period, t∞, have been subtracted from the total amounts present at the experimental time points (At). Inset: O, [3H]norepinephrine; △, [3H]dopamine; □, [3H]epinephrine.

of 6.5 hours and represented 85% of the [3H]dopamine present at the end of the labeling period. There was essentially quantitative conversion of [3H]dopamine to 3H-β-hydroxylated products. In a second experiment the half-life for the disappearance of [3H]dopamine was 5.5 h.

In these studies we specifically sought the presence of [3H]N-methyldopamine which has been proposed as an intermediate in the formation of epinephrine (14) but could not detect a significant radioactive peak at the position at which N-methyldopamine eluted from the HPLC column. From these studies and the work of others (15) we conclude that the formation of epinephrine does not proceed to any significant extent through N-methyldopamine as an intermediate.

Cells Labeled with [3H]Norepinephrine—Long term studies similar to those reported above were carried out with cells

TABLE II

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Label</th>
<th>NE, t∞</th>
<th>NE, t∞</th>
<th>E</th>
<th>[3H]</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>[3H]Dopamine</td>
<td>1.3</td>
<td>4.8</td>
<td>17.3</td>
<td>11.1</td>
</tr>
<tr>
<td>2</td>
<td>[3H]Dopamine</td>
<td>1.4</td>
<td>5.6</td>
<td>9.1</td>
<td>8.5</td>
</tr>
<tr>
<td>3</td>
<td>[3H]Norepinephrine</td>
<td>0.8</td>
<td>4.1</td>
<td>15.8</td>
<td>13.4</td>
</tr>
<tr>
<td>4</td>
<td>[3H]Norepinephrine</td>
<td>1.2</td>
<td>4.7</td>
<td>16.4</td>
<td>10.9</td>
</tr>
</tbody>
</table>

Mean ± S.E. 1.2 ± 0.1 4.8 ± 0.3 14.7 ± 1.9 11.0 ± 1.0
labeled with \[^3H\]norepinephrine. Fig. 4 shows the results of one study. At the end of the 2-h labeling period 38% of the total radioactivity in the cells was \[^3H\]epinephrine indicating that the \[^3H\]norepinephrine was rapidly \(N\)-methylated in its passage from the plasma membrane through the cytoplasm and into the chromaffin vesicle. Graphical analysis of these data (Fig. 4B) revealed a biphasic decline in \[^3H\]norepinephrine similar to that seen in cells loaded with \[^3H\]dopamine with a fast component having a \(t_u\) of 0.8 day and a slow component of 4.1 days. \[^3H\]Epinephrine levels reached a maximum on the second day and after the fourth day declined with a \(t_u\) of 15.8 days. Throughout the time course of this study there was no change in the levels of endogenous catecholamines. Similar results were obtained in a second experiment reported in Table II.

Extrapolation of the slow component of \[^3H\]norepinephrine turnover to the abscissa in Fig. 4B indicates that 36% of the total radioactivity taken up by the cells was in this compartment. However, in two other experiments this compartment contained 19 and 20%, respectively, of the total radioactivity. Similar analysis of Fig. 2B indicates that 24% of the total \[^3H\]dopamine taken up was present in the slow norepinephrine compartment.

To better evaluate the time course of the conversion of vesicular norepinephrine to vesicular epinephrine, shorter time course studies were carried out. Cells were labeled with \[^3H\]norepinephrine for 1 h and examined for \[^3H\]norepinephrine and \[^3H\]epinephrine at time periods up to 48 h. In two studies using different cell preparations \[^3H\]epinephrine reached maximum levels at about 24 h and thereafter remained constant while \[^3H\]norepinephrine declined throughout the course of the study. The results of one study are shown in Fig. 5A. During the first 24 h after labeling there was essentially quantitative conversion of \[^3H\]norepinephrine to \[^3H\]epinephrine. Graphic analysis of the data gave half-lives for the decline of \[^3H\]norepinephrine of 20 to 32 h, respectively, in two experiments with different cell preparations.

**Efflux of Catecholamines from Chromaffin Vesicles**—The studies with \[^3H\]dopamine and \[^3H\]norepinephrine suggested that the rate-limiting step in the conversion of norepinephrine to epinephrine was the efflux of norepinephrine from chromaffin vesicles and not the methylation reaction itself. To examine the time course for the efflux of \(^3H\)-catecholamines

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**Fig. 4. Conversion of norepinephrine to epinephrine.** Cells were labeled for 2 h with \[^3H\]norepinephrine and examined for products immediately after the wash cycle and at the times indicated. *A,* linear presentation of data. Upper, endogenous catecholamines; \(\square\), epinephrine; \(\bullet\), norepinephrine. **Lower,** \[^3H\]-total catecholamines; \(\boxdot\), \[^3H\]epinephrine; \(\bullet\), \[^3H\]norepinephrine. *B,* semi-logarithmic presentation of data: *, total \[^3H\]-catecholamines; \(\square\), \[^3H\]epinephrine; \(\bullet\), \[^3H\]norepinephrine, experimental data points; \(\boxdot\), \[^3H\]norepinephrine, fast component obtained by subtracting extrapolated values of slow component from the experimental data points.

**Fig. 5. Conversion of norepinephrine to epinephrine; effect of reserpine.** Cells were labeled with \[^3H\]norepinephrine and examined immediately after the wash cycle and at the times shown. Reserpine, 0.5 \(\mu M\) (\(\square\)) was added immediately after the wash cycle. **A,** endogenous epinephrine and norepinephrine, respectively; \(\boxdot\), \[^3H\]epinephrine and \[^3H\]norepinephrine, respectively.
Catecholamine Flux through Chromaffin Vesicles

**TABLE III**

<table>
<thead>
<tr>
<th>Cell preparation</th>
<th>Total $^3$H</th>
<th>$^3$H</th>
<th>NE</th>
<th>$^3$H</th>
<th>E</th>
<th>NE</th>
<th>E</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>$t_e$ (h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>36.9 ± 2</td>
<td>23.2 ± 2</td>
<td>24.7 ± 2</td>
<td>35 ± 5</td>
<td>27 ± 3</td>
<td>33 ± 4</td>
<td></td>
</tr>
<tr>
<td>Mean ± S.E.</td>
<td>28 ± 2</td>
<td>24 ± 2</td>
<td>35 ± 5</td>
<td>27 ± 3</td>
<td>33 ± 4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

from the vesicles, cells were treated with 0.5 mM reserpine immediately after the labeling period. Reserpine blocks the uptake of catecholamines into chromaffin vesicles, thus enabling one to determine the unidirectional rate of leakage from the vesicles by measuring the decline in endogenous or labeled catecholamines. Reserpine does not alter the rate of efflux of catecholamines from isolated chromaffin vesicles (13). The amount of reserpine used was adequate to inhibit reuptake of catecholamines. In other studies Wilson and Viveros (18) have shown that 0.1 mM reserpine produced a maximal rate of catecholamine depletion from chromaffin cells. The results of these studies are shown in Fig. 5B.

In the reserpine-treated cells there was a continuous loss of both endogenous and labeled catecholamines which occurred with the same $t_e$. Reserpine effectively prevented the accumulation of newly formed epinephrine. This was indicated by the constant specific activities of $^3$H|norepinephrine and $^3$H|epinephrine. In cells not treated with reserpine the specific activity of $^3$H|norepinephrine declined while that of $^3$H|epinephrine increased to a constant value at 24 h (Fig. 5A). Analysis of the data showed that the decline of both endogenous and labeled catecholamines as well as the decline in total radioactivity were monophasic. The results of this and three similar experiments on the effects of reserpine on catecholamine leakage are summarized in Table III. The half-lives for labeled catecholamines were the same as those for the endogenous amines, approximately 24 h for norepinephrine and 34 h for epinephrine. In all preparations the $t_e$ for epinephrine was consistently longer than the $t_e$ for norepinephrine.

**Effect of Pulse Time on Formation of Products**—To obtain additional information on the formation of products during the pulse period, cells were incubated with either $^3$H|norepinephrine or $^3$H|dopamine for 15, 30, 60, and 120 min and examined at the end of this pulse period the subcellular distribution of $^3$H|catecholamines was the same as the distribution of endogenous amines.

When cells were labeled with $^3$H|norepinephrine a constant proportion of $^3$H|epinephrine was present at the end of the pulse period regardless of its length. In the study reported in Table IV the amount of $^3$H|epinephrine formed, 20% of the total radioactivity present at the end of the incubation period, was somewhat lower than was generally observed throughout the course of the work reported here. In a second similar study $^3$H|epinephrine represented 30% of the total radioactivity present at the end of the pulse period. These results are consistent with the proposal that $^3$H|norepinephrine is rapidly converted to epinephrine in its passage through the cytoplasm into the chromaffin vesicles.

DISCUSSION

The experimental data obtained in these studies allow the estimation of half-lives for a number of the processes in the dopamine-norepinephrine-epinephrine pathway (Table V). The uptake of cytoplasmic catecholamines by chromaffin vesicles occurs rapidly. This is indicated by the following: a) shortly after the labeling period the subcellular distribution of $^3$H|catecholamines is the same as the distribution of endogenous amines; b) at the end of labeling periods with $^3$H|norepinephrine varying from 15 to 120 min a constant proportion of $^3$H|epinephrine was present in the cell accounting for 20 to 35% of the total radioactivity in different experiments; thereafter the conversion of norepinephrine to epinephrine occurred much more slowly indicating that cytoplasmic norepinephrine is both rapidly N-methylated and rapidly taken up by chromaffin vesicles; c) iproniazid, a monoamine oxidase inhibitor, had no effect on the uptake of dopamine and norepinephrine or their conversion to subsequent products during short term experiments suggesting...
Half-lives for the flux of catecholamines through chromaffin vesicles and for the synthesis of norepinephrine and epinephrine in cultured bovine adrenal medullary chromaffin cells

<table>
<thead>
<tr>
<th>Process</th>
<th>(t_h)</th>
<th>(k)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dopamine (\rightarrow) dopamine</td>
<td>Fast (min)</td>
<td></td>
</tr>
<tr>
<td>2. Dopamine (\rightarrow) norepinephrine</td>
<td>5.5-6.5 h</td>
<td>0.126-0.107</td>
</tr>
<tr>
<td>3. Norepinephrine (\rightarrow) norepinephrine</td>
<td>25 h</td>
<td>0.028</td>
</tr>
<tr>
<td>4. Norepinephrine (\rightarrow) epinephrine</td>
<td>Fast (min)</td>
<td></td>
</tr>
<tr>
<td>5. Epinephrine (\rightarrow) epinephrine</td>
<td>Fast (min)</td>
<td></td>
</tr>
<tr>
<td>6. Norepinephrine (\rightarrow) epinephrine</td>
<td>18-30 h</td>
<td>0.039-0.023</td>
</tr>
<tr>
<td>7. Epinephrine (\rightarrow) epinephrine</td>
<td>34 h</td>
<td>0.020</td>
</tr>
<tr>
<td>8. NE turnover in E cells</td>
<td>20-35 h</td>
<td>0.035-0.020</td>
</tr>
<tr>
<td>9. NE turnover in NE cells</td>
<td>4-5 days</td>
<td>0.007-0.006</td>
</tr>
<tr>
<td>10. E turnover</td>
<td>15 days</td>
<td>0.002</td>
</tr>
</tbody>
</table>

* The abbreviations used are: ves, present in chromaffin vesicle; cyt, present in cytoplasm; \(k\), apparent first order reaction rate constant calculated from 0.693/\(t_h\); NE, norepinephrine; E, epinephrine.

TABLE V

The efflux of catecholamines from chromaffin vesicles was studied with the aid of reserpine, a specific inhibitor of the ATP-dependent vesicular catecholamine uptake system (4, 19). Depletion of both endogenous and labeled catecholamines was identical indicating complete mixing. Norepinephrine depletion was somewhat more rapid than epinephrine depletion with average half-times of 24 and 34 h, respectively. These values are similar to that reported by Wilson et al. (20) who found the reserpine caused a depletion of total catecholamines with a half-time of 36 h. These figures can be compared to those for leakage from isolated vesicles in vitro (13), about 17 h in the presence of added Mg-ATP and 3 to 4 h in the absence of Mg-ATP or in the presence of reserpine with or without added Mg-ATP. Thus catecholamines are more stably retained by chromaffin vesicles within intact cells than would be anticipated from studies of the isolated vesicles.

The turnover of \([^{3}H]\)norepinephrine in adrenal medullary cell cultures appears biphasic. One component had a half-time of 19 to 34 h corresponding to the conversion of \([^{3}H]\)norepinephrine to \([^{3}H]\)epinephrine in epinephrine cells and accounting for the metabolism of 65% or more of the \([^{3}H]\)norepinephrine taken up by the cell cultures. The other component had a half-time of 4 to 5 days and may be attributed to the metabolism or loss of norepinephrine from norepinephrine cells. This suggestion is supported by the fact that these cell cultures contain both epinephrine and norepinephrine cells (11). Additionally one can estimate that with an average half-time of 24 h for the conversion of norepinephrine to epinephrine that only about 6% of the \([^{3}H]\)norepinephrine present after the labeling period would remain unchanged after 4 days if it was only in epinephrine cells. However, the \([^{3}H]\)norepinephrine present in cultures 4 days after labeling accounted for 20 to 30% of the \([^{3}H]\)norepinephrine in the cells immediately after labeling.

The pool sizes of dopamine and norepinephrine utilized for epinephrine synthesis and the pool sizes of dopamine and norepinephrine in norepinephrine cells can be estimated assuming steady state conditions. In the steady state the pool size of the substrate is directly proportional to the \(t_h\) of the reaction. In the experiments reported here the average pool sizes of epinephrine, norepinephrine, and dopamine were 67, 31.5, and 1.5% of the total catecholamine content. Assuming that epinephrine is in a single pool and a total catecholamine content of 100 nmol/10^6 cells and using the average \(t_h\) values from Table II of 360 h for the loss of epinephrine, 29 h for the conversion of norepinephrine to epinephrine, and 6 h for the \(\beta\)-hydroxylation of dopamine, we have estimated that 24% of the \([^{3}H]\)dopamine and 36% of the \([^{3}H]\)norepinephrine taken up by the cells was present in norepinephrine cells. 24% of the \([^{3}H]\)norepinephrine and 18% of the norepinephrine is present in epinephrine cells. These values are consistent with two other observations. 1) From Figs. 2B, and 4B and other similar experiments, we have estimated that 24% of the \([^{3}H]\)dopamine and 36% of the \([^{3}H]\)norepinephrine taken up by the cells was present in norepinephrine cells. 2) Centrifugation of freshly isolated bovine adrenal medullary chromaffin cells on a continuous Renografin density gradient demonstrates that epinephrine-containing cells have a higher buoyant density than those containing norepinephrine (21). Although the resolution of these gradients is not sufficient to completely separate the two cell types, the most dense fractions of the gradient have a consistent epinephrine to norepinephrine ratio suggesting that these fractions may contain pure epinephrine cells. The chromaffin cells present in these high density fractions contain 82-85% epinephrine and 15-18% norepinephrine; dopamine levels were not determined.

Assuming the estimates of the pool sizes to be correct we can calculate the \(t_h\) for the \(\beta\)-hydroxylation reaction in norepinephrine cells to be 1.8 h using a \(t_h\) of 115 h for the disappearance of norepinephrine and pool sizes of 26 nmol and 0.4 nmol, respectively, for norepinephrine and dopamine. Considering the complexity of these experiments it is unclear if a pool consisting of 26% of the dopamine with a \(t_h\) of 1.8 h could have been resolved.
The studies reported here provide new information on catecholamine synthesis and flux through chromaffin vesicles in intact cells. Dopamine which is formed in the cytoplasm from tyrosine is rapidly taken up by chromaffin vesicles. Although we do not have a direct measure of the rate of this process we estimate the $t_\alpha$ to be a few minutes. Once within the chromaffin vesicles dopamine is converted to norepinephrine with a $t_\alpha$ of about 6 h. Norepinephrine then only slowly leaves the vesicles with a $t_\alpha$ of approximately 24 h. Within the cytoplasm norepinephrine is rapidly converted to epinephrine, although we do not have a direct measure of the rate of this reaction we estimate the $t_\alpha$ to be On the Order Of 15 to 18 days. These results help explain the observation made a number of years ago that, following depletion of the catecholamine content of cat and rabbit adrenal glands, the recovery of the epinephrine content lags behind the recovery of norepinephrine content by several days (22, 23).

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Flux of catecholamines through chromaffin vesicles in cultured bovine adrenal medullary cells.
J J Corcoran, S P Wilson and N Kirshner


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