Hepatic metabolism of aminopyrine in patients with chronic renal failure

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Summary

1. To evaluate potential alterations in hepatic metabolism of drugs occurring in patients with renal insufficiency the fate of aminopyrine was studied in 17 patients with chronic renal failure and in 27 normal subjects.

2. Although patients with chronic renal failure exhibited large variations, their aminopyrine plasma disappearance times (mean 0·62 ± sd 0·24 h⁻¹) were significantly higher than those found in normal subjects (0·30 ± 0·07 h⁻¹, P < 0·002).

3. ¹⁴CO₂ derived from [dimethylamine-¹⁴C]aminopyrine disappeared from breath more rapidly in patients with chronic renal failure and a history of analgesic abuse (0·40 ± 0·04 h⁻¹) than in control subjects (0·22 ± 0·03 h⁻¹, P < 0·01) and in other patients with chronic renal failure (0·24 ± 0·04 h⁻¹).

4. Dialysis treatment and serum creatinine concentrations were not correlated with the rates of aminopyrine metabolism. Two additional patients, however, with combined renal and hepatic disease, exhibited markedly slowed rates of aminopyrine demethylation.

5. Although chronic renal failure by itself might not alter microsomal drug metabolism it is concluded that, in patients with a history of abuse of phenacetin-containing analgesics, marked acceleration in aminopyrine N-demethylation may be observed.

Key words: aminopyrine metabolism, analgesics abuse, breath test, chronic renal failure, ¹⁴CO₂ breath analysis, drug metabolism, microsomal aminopyrine demethylation, phenacetin abuse, renal failure.

Introduction

In patients with chronic renal failure, choice of an optimum dose of drug may be difficult. Many compounds which are eliminated by the kidneys have therefore been studied in such patients and guidelines for reductions in dose have been published (Dettli, 1976); in contrast, there is uncertainty as to whether the dose should be adjusted for compounds which are primarily eliminated by metabolism. Studies with antipyrine (Maddocks, Wake & Harber, 1975; Lichter, Black & Arias, 1973), diphenylhydantoin (Odar-Cederlöf & Borga, 1974; Letteri, Mellk, Louis, Kutt, Durante & Glazko, 1971), propranolol (Thompson, Joekes & Foulkes, 1972), digitoxin (Vöhringer, Rietbrock, Spurny, Kuhlmann, Hampl & Baethke, 1976; Rasmussen, Jervell, Storstein & Gjerdrum, 1972) and pentobarbital (Reidenberg, Lowenthal, Briggs & Gasparo, 1976) suggest that hepatic clearances may be normal or elevated in chronic renal failure. Studies in uraemic rats suggest that there is no change (Mezey, Vestal, Potter & Rowe, 1975) or a decrease (Leber & Schütterle, 1972) in activity of hepatic aminopyrine demethylase. This uncertainty prompted our study of aminopyrine metabolism in patients with chronic renal failure and in normal control subjects.

Aminopyrine was used, as its pharmacokinetics and its metabolism are well known, it being well absorbed from the intestine, distributed in a space corresponding to the body water and almost entirely metabolized before renal elimination (Brodie & Axelrod, 1950). Less than 5% of unchanged aminopyrine is found in the urine (Brodie & Axelrod, 1950). Newer methods allow simultaneous investigation of two aspects of its biotransformation, for after administration of specifically labelled aminopyrine, breath analysis of
$^{14}$CO$_2$ is expected to reflect only N-demethylation, whereas the plasma clearance may be regarded as an overall measure for the sum of the different pathways responsible for the removal of aminopyrine from blood.

**Materials and methods**

**Subjects**

**Patients.** Group 1A and B was composed of 17 patients with established chronic renal failure (five males, 12 females; ages 27–64 years) but without clinical or laboratory evidence of liver disease (Table 1). Serum glutamate-oxaloacetate transaminase activities, total bile acids, prothrombin times and hepatitis-B antigen titres were normal. Serum creatinine concentrations ranged from 0.33 to 1.4 mmol/l. Six patients were on a chronic haemodialysis programme. The diagnoses were established by standard clinical and laboratory criteria. Histological confirmation was available in three patients. Six patients (nos. 12–17, group 1B) admitted to abuse of large quantities of Saridon (propyphenazone, 150 mg; phenacetin, 250 mg; dihyprylone, 50 mg; caffeine, 50 mg) for many years. Whether they were taking analgesics at the time of the study could not be adequately ascertained.

In each patient the renal failure was managed according to standard practice, with potassium and sodium restriction and oral administration of phosphate-binding aluminum hydroxide preparations. Protein intake was restricted in nondialysed patients. Treatment for hypertension, hyperuricaemia, alterations in calcium metabolism, urinary tract infection, prevention of arteriovenous-shunt thrombosis and transplant rejection was administered as clinically indicated (Table 1).

**Control subjects.** This group (2) was composed of 27 volunteer subjects (22 males, five females; ages 20–66 years), with no clinical or laboratory evidence of kidney or liver disease. Serum creatinine concentrations, blood urea nitrogen concentrations, alkaline phosphatase activities, total proteins and serum electrophoresis and the tests performed in group 1 patients were normal. None was taking drugs during the week before the test.

All patients and normal subjects gave informed consent to the studies.

**Procedures**

All subjects were allowed a breakfast of toast and tea. Thereafter, aminopyrine (39 μmol/kg), including 2 μCi of $[^{14}$C]aminopyrine, dissolved in water, was given orally. $[^{14}$C]Aminopyrine, labelled specifically at the two N-methyl groups, was obtained from The Radiochemical Centre, (Amersham, Bucks., U.K.) and stored dissolved in a stock solution of physiological sodium chloride solution at 4°C. Breath samples were collected at intervals of 15 min to 2 h for 8 h after the administration of aminopyrine. The subjects were requested to blow through a valve directly into radioactivity counting vials containing 2 mmol of Hyamine in 4 ml of methanol/ethanol (1:1, v/v), and phenolphthalein as indicator, until the pink colour of phenolphthalein had completely disappeared. Whenever possible plasma aminopyrine concentrations were measured. For this purpose heparinized blood samples were obtained at intervals of 15–120 min for 6 h. Plasma samples were stored at −18°C.

**Analytical methods**

$^{14}$C radioactivity in breath samples was counted in a Packard Tri-Carb Liquid Scintillation counter 3380 after the addition of 5 ml of scintillation cocktail consisting of 800 ml of toluene, 200 ml of Triton X-100, 5-0 g of 2,5-diphenyloxazole (POPOP; Merck, Darmstadt, FRG) and 100 mg of 1,4-bis-(5-phenyloxazol-2-yl)benzene (POPOP; Merck, Darmstadt, FRG). The counting efficiency of about 80% was determined by the channel ratio method with an external standard. To permit aminopyrine analysis in small samples of blood obtained from anaemic patients, a gas–liquid-chromatographic method was developed. As internal standard 100 μl of mepyramine maleate in aqueous solution (75 μmol/l) was added to 500 μl of plasma diluted with 1 ml of distilled water. The samples were deproteinized with 1 ml of trichloroacetic acid (10%, w/v). After centrifugation for 10 min, the supernatant was made alkaline with 200 μl of sodium hydroxide (3.0 mol/l) and extracted with 5 ml of chloroform. After addition of 50 μl of freshly distilled hexanol to the chloroform phase, the samples were evaporated under vacuum and the residue was redissolved in 20 μl of chloroform. Portions were assayed by a Perkin–Elmer model 3920 gas chromatograph with flame ionization detector coupled to an Infotronics model 208 integrator and a Perkin–Elmer model 56 recorder. The 6 feet glass columns (lumen diameter 2 mm) were packed with Chromosorb W AW 80/100 mesh coated with SE 30 10%. The injection
**TABLE 1. Clinical characteristics of examined patients and results of aminopyrine studies**

Group 1: patients in chronic renal failure without (A) and with (B) history of analgesic abuse.

Group 2: normal control subjects (n = 27). Significance of difference of values from control value: *P < 0.01; **P < 0.002. $V_d =$ volume of distribution; $k_{plasma} =$ disappearance rate constant of aminopyrine from plasma; $k_{breath} =$ disappearance rate constant of $^4$CO$_2$ from breath.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Dialysis</th>
<th>Serum creatinine (mmol/l)</th>
<th>Serum albumin (g/100 ml)</th>
<th>$V_d$ (ml/kg)</th>
<th>$k_{plasma}$ (h$^{-1}$)</th>
<th>$k_{breath}$ (h$^{-1}$)</th>
<th>Drug therapy</th>
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<td>1.06</td>
<td>2.79</td>
<td>889</td>
<td>0.383</td>
<td>0.197</td>
<td></td>
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<td>0.365</td>
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<td>3.74</td>
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<td>1.19</td>
<td>2.58</td>
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<td>—</td>
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<td>—</td>
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<td>4.54</td>
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<td>—</td>
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<td>40.8</td>
<td>±13.4</td>
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<td> </td>
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<td>3.36</td>
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<td></td>
<td></td>
<td>±0.346</td>
<td>±0.66</td>
<td>±332</td>
<td>±0.181*</td>
<td>±0.036</td>
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<td>4.06</td>
<td>—</td>
<td>—</td>
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<tr>
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<td>4.60</td>
<td>832</td>
<td>0.894</td>
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</tr>
<tr>
<td>Mean</td>
<td>44.3</td>
<td>±4.8</td>
<td> </td>
<td> </td>
<td>±0.278</td>
<td>±0.69</td>
<td>±0.557</td>
<td>±0.199</td>
<td>±0.044</td>
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<tr>
<td>Group 1 A + B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.832</td>
<td>3.51</td>
<td>997</td>
<td>0.615</td>
<td>0.295</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>42.1</td>
<td>±11.0</td>
<td> </td>
<td> </td>
<td>±0.359</td>
<td>±0.68</td>
<td>±425</td>
<td>±0.235**</td>
<td>±0.088*</td>
<td></td>
</tr>
</tbody>
</table>

Group 2

| Mean        | 30.7        | 5F |           |         | <0.1 | 4.57 | 814 | 0.300 | 0.222 |
| Mean        | 30.7        | ±12.2 | 22M |         | ±0.35 | ±132 | ±0.066 | ±0.032 |

Dihydrallazine, oxprenolol, α-methyldopa
Propranolol, guanethidine, thiethylperazine, diazoxide, co-trimoxazole, frusemide
Propranolol, oxprenolol, allopurinol, frusemide
Allopurinol
Propranolol, sulphinpyrazone, salazosulphapyridine
α-Methyldopa, frusemide
α-Methyldopa, frusemide
Lanatoside C. clonidine, frusemide
Hexestrol, flavoxomesterone, frusemide
Azathioprine, predniisolone, frusemide
Clonidine, dihydrallazine, oxprenolol
Frusemide
Clonidine, propranolol, sulphinpyrazone, frusemide
Nalidixic acid, ampiillin, frusemide
Allopurinol, cephalaxin bromazepam, frusemide
Etilefrine, frusemide
Thiamphenicol, dihydrotachysterol

**Notes:**
- $V_d =$ volume of distribution
- $k_{plasma} =$ disappearance rate constant of aminopyrine from plasma
- $k_{breath} =$ disappearance rate constant of $^4$CO$_2$ from breath
- Significance of difference from control value: *P < 0.01; **P < 0.002
port and the flame ionization detector temperatures were 250°C and 300°C respectively. The column temperature was 220°C. The standard curve was made by plotting the ratio of the analysis peak area to the internal standard peak area against the standard values. During preparation of the sample for gas–liquid chromatography recovery of [14C]aminopyrine added to plasma was more than 90%. Linear standard curves were obtained down to a concentration of 4 μmol/l. Duplicates could be reproduced within ±7%.

Calculations

The disappearance rate constants of 14CO2 in breath (k_breath) and of aminopyrine in plasma (k_plasma) were analysed graphically by plotting the logarithm of the specific radioactivity of 14CO2 in breath and of the plasma concentrations of aminopyrine respectively against time and were calculated by semilogarithmic least-square regression analysis. Equations (1)–(3) were used.

Area under the curve

\[
\text{AUC} = \int_0^T C \cdot dt + \frac{C_T}{k_{\text{plasma}}} \tag{1}
\]

\(C_T\) corresponds to the last measured plasma concentration. The term \(C \cdot dt\) was calculated by means of the trapezoid rule.

Volume of distribution (V_d) = \(\frac{\text{oral dose}}{k_{\text{plasma}} \cdot \text{AUC}}\) \(\tag{2}\)

\(\text{Clearance} = \frac{\text{oral dose}}{\text{AUC}}\) \(\tag{3}\)

Group comparisons are based on the non-parametric two-sample rank test of Mann and Whitney. Correlations were judged by Spearman's rank correlation coefficient. Results are presented as mean ±SD in text, Figures and Tables. \(P < 0.05\) was regarded as statistically significant.

Results

Plasma concentrations of aminopyrine

In all subjects the aminopyrine plasma concentrations increased to a maximum within the first hour after aminopyrine administration and, thereafter, declined in an apparently single exponential manner (Fig. 1). In patients with chronic renal failure peak plasma concentrations tended to be lower and plasma disappearance rates were significantly more rapid than in control subjects. Consequently, the apparent volumes of distribution for aminopyrine (997 ± 425 ml/kg) were slightly higher in patients than in normal subjects (814 ± 132 ml/kg) (Table 1). All plasma disappearance rate constants (k_plasma) obtained in patients with chronic renal failure (range 0.339–1.037 h⁻¹) were above the normal mean of 0.300 h⁻¹ (Table 1). These data resulted in aminopyrine clearances of 9.99 ± 5.15 ml min⁻¹ kg⁻¹ in patients, which were significantly higher than in normal control subjects (4.04 ± 0.97 ml min⁻¹ kg⁻¹, \(P < 0.002\)).

FIG. 1. Examples of (a) aminopyrine plasma disappearance curves and of (b) the corresponding specific radioactivities of 14CO2, (as % dose kg⁻¹ mmol⁻¹ of 14CO2) in breath in patient no. 8 (■) with chronic renal failure and in a normal subject (●).
Aminopyrine in chronic renal failure

Exhalation of $^{14}$CO$_2$ in breath

The specific radioactivity of $^{14}$CO$_2$ in breath usually rose slightly slower than aminopyrine in plasma. Peak activities occurred within 2 h after aminopyrine administration and, thereafter, also declined in an apparently single exponential fashion for at least 8 h. All disappearance rate constants for $^{14}$CO$_2$ from breath ($k_{\text{breath}}$) were smaller than the corresponding $k_{\text{plasma}}$ value (Table 1). Overall the $k_{\text{breath}}$ was significantly higher in patients (0.295 ± 0.088 h$^{-1}$) than in normal control subjects (0.222 ± 0.032 h$^{-1}$, $P < 0.01$) even though the difference between the two groups is less pronounced than for $k_{\text{plasma}}$.

Aminopyrine metabolism in clinical subgroups

There were no significant differences in aminopyrine metabolism in patients with chronic glomerulonephritis, pyelonephritis, polycystic kidneys, nephrosclerosis or transplant rejection as the cause for chronic renal failure. However, six cases with analgesic abuse had significantly higher $k_{\text{breath}}$ (0.399 ± 0.044 h$^{-1}$) compared with the other patients with chronic renal failure (0.239 ± 0.036 h$^{-1}$, $P < 0.002$) and with the control subjects (0.222 ± 0.032 h$^{-1}$, $P < 0.002$). When the six patients with analgesic abuse were removed from the group of patients with chronic renal failure, $k_{\text{breath}}$ in the remaining cases was found comparable with that of normal subjects ($P > 0.20$).

In patients with abuse of phenacetin-containing analgesics $k_{\text{plasma}}$ (0.773 ± 0.199 h$^{-1}$) was higher than in the other patients (0.483 ± 0.181 h$^{-1}$), although the difference was not statistically significant. The plasma clearances were 12.6 ± 5.1 (n = 5) and 7.8 ± 4.4 ml min$^{-1}$ kg$^{-1}$ (n = 6) in groups 1B and 1A respectively ($P > 0.05$). No effect of regular dialysis treatment on aminopyrine metabolism was apparent: excluding the patients with analgesic abuse the mean $k_{\text{breath}}$ in six dialysed patients was 0.246 ± 0.033 h$^{-1}$, compared with 0.230 ± 0.042 h$^{-1}$ in five patients not requiring regular dialysis treatment. There was no significant correlation between $k_{\text{plasma}}$, $k_{\text{breath}}$ and serum creatinine or serum albumin, whether the patients with analgesic abuse were considered separately or not.

Combined renal and liver disease

Two additional patients with chronic renal failure and evidence of liver disease were also examined. The diagnosis of chronic glomerulonephritis was made in one and chronic interstitial nephritis in the other. Both were chronic alcoholics, had enlarged firm livers, and some abnormal results with liver-function tests including fasting serum bile acids. No liver biopsies were obtained. Their $k_{\text{breath}}$ were 0.100 and 0.117 h$^{-1}$ respectively, values distinctly below the range for normal subjects.

Discussion

This study has shown that aminopyrine metabolism may be altered in many patients with chronic renal failure. Interpretation of the findings requires consideration of pharmacokinetic details. Although absorption, distribution and metabolism of aminopyrine have been extensively studied (Brodie & Axelrod, 1950), inferences from plasma disappearance curves obtained after oral administration of the drug are hampered by first-pass effects, which may decrease the amount of aminopyrine available to blood and peripheral tissues. Calculated volumes of distribution may be inaccurate. An attempt was therefore made to correct these volumes, assuming a hepatic blood flow of 20 ml min$^{-1}$ kg$^{-1}$ body weight (Caesar, Shaldon, Chandussi, Guevara & Sherlock, 1961) as detailed in the Appendix. The corrected volumes were 652 ± 204 ml/kg in the patients with chronic renal failure and 676 ± 101 ml/kg in normal subjects (Fig. 2). These values are consistent with the assumption that aminopyrine essentially distributes evenly throughout the body water (Brodie & Axelrod, 1950). The lack of a difference between normal subjects and the patients agrees with results obtained with antipyrine by Maddocks et al. (1975). Since the volumes of distribution are practically equal in the patients and in normal subjects the aminopyrine plasma disappearance rates may be considered actually to reflect hepatic clearances.

The above assumptions also allowed the calculation of hepatic extraction ratios (Fig. 2), which were 0.316 ± 0.108 in patients with chronic renal failure and 0.167 ± 0.034 in normal subjects ($P < 0.002$). The latter corresponds to the value of 0.168 measured during cardiac catheterization in one subject with normal liver and kidney function in our laboratory. According to these calculations, in some patients with chronic renal failure 40–50% of the aminopyrine reaching the liver was removed in a single passage. These extraction ratios suggest that in some patients the first-pass effect may have been very high and the systemic availability of aminopyrine correspondingly decreased.
Breath analysis of aminopyrine $N$-demethylation has been well established (Hepner & Vesell, 1974; Hepner & Vesell, 1975; Lauterburg & Bircher, 1976). Nevertheless, consistency between $k_{\text{plasma}}$ and $k_{\text{breath}}$ was not as complete as in the previously studied cirrhotic patients (Bircher, Küpfer, Gikalov & Preisig, 1976). This may result from the fact that $^{14}$CO$_2$ in breath can be derived only from aminopyrine $N$-demethylation, whereas aminopyrine may disappear from plasma also through other unknown metabolic routes (Brodie & Axelrod, 1950). Furthermore, the two methyl groups probably are removed from the aminopyrine molecule at differing rates (La Du, Gaudette, Trousof & Brodie, 1955; Gram, Wilson & Fouts, 1968). Alterations in formaldehyde, formate and CO$_2$ metabolism also may affect the breath data. It is conceivable that formaldehyde oxidation to CO$_2$ became partially rate-limiting at the markedly accelerated demethylation rates of our patients. Studies to define the pharmacokinetics of the demethylation breath test are in progress, [$^{14}$C]glycodiazine being used as a more suitable test substance as it has only a single methyl group. Despite some discrepancies in individual patients both methods agree in showing that hepatic aminopyrine metabolism may be normal or accelerated in patients with chronic renal failure.

Although efforts have been made to define factors that may be responsible for increased rates of drug metabolism, we cannot explain why aminopyrine $N$-demethylation or plasma disappearance of the drug was accelerated in some cases. The different diagnoses, long-term dialysis treatment, serum creatinine or serum albumin concentrations were not related to the indices of aminopyrine metabolism, except for nephropathy associated with phenacetin-containing analgesic abuse. We cannot say if enzyme induction due to analgesics may be responsible for the extremely rapid rates of aminopyrine metabolism in these cases, or whether constitutionally rapid rates of drug metabolism predispose to nephropathy in patients with analgesic abuse. Furthermore all patients studied received enough different drugs (Table 1) to modify potentially their microsomal enzyme system (Vesell, Passananti & Greene, 1970; Conney, 1967; Koch-Weser & Sellers, 1971; Verbeck, Tjandramaga, Verberckmoes & De Schepper, 1976; O'Malley, Stevenson & Crooks, 1972; Herz, Haemmerli, Koelz, Benes & Blum, 1976). We cannot therefore draw conclusions as to how chronic renal failure by itself affects the microsomal enzyme system of the liver.

The opportunity to study two patients with combined chronic renal failure and liver disease suggests that the rates of drug metabolism may be strikingly reduced in such cases. Their values for $k_{\text{breath}}$ were in the range that we have found in patients with cirrhosis of the liver (Bircher et al., 1976; Hepner & Vesell, 1975).

If our findings with aminopyrine are representative for the microsomal biotransformation system as a whole, alterations of this system may be expected in many patients with chronic renal failure. Indeed, pharmacokinetic studies with other drugs such as antipyrine (Maddocks et al., 1975; Lichter et al., 1973), diphenylhydantoin (Odar-Cederlöf & Borga, 1974; Letteri et al., 1971), propranolol (Thompson, Joekes & Foulkes, 1972), digitoxin (Vöhinger et al., 1976; Rasmussen et al., 1972) and pentobarbital (Reidenberg et al., 1976) suggest that hepatic drug clearance may be increased at least in some patients. However, other reports have shown that in patients with advanced chronic renal failure the extrarenal elimination of rolitetracyclin (Reubi & Münger, 1968) and ampicillin (Reubi & Vorburger, 1969) is not increased. Since factors other than the microsomal enzyme system, such as binding to plasma proteins, may also affect rates of drug metabolism in vivo, results obtained with aminopyrine cannot be extrapolated a priori to other drugs. Further studies are needed to clarify the clinical significance of the observed changes.

It is conceivable that the accelerated rates of aminopyrine metabolism may be associated with correspondingly high rates of biotransformation of vitamin D and with the vitamin D-resistant osteomalacia seen in patients with chronic renal failure. Avioli, Birge & Lee (1968) found a twofold increase in turnover of radioactive vitamin D$_3$ with simultaneous accumulation of inactive metabolites in such cases. It would be interesting to know if
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References


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