be obtained by plotting crushing strength *versus* input values (Fig. 5). The graphs allow a visual determination of mixtures for which the crushing strength can be increased without significantly reducing the input value. Mixtures A, E, and B, for which an increase in crushing strength does not correspond to a marked decrease in input values, are easy to handle. For mixtures C and G, the increase of crushing strength corresponds to a concomitant marked reduction of input values, as evidenced by curve slopes. Mixtures F and D show a limiting value of crushing strength above which a little increase causes a large decrease of the input value.

The shape parameter b (Eq. 1) seems to be linked to the disintegration process in the following way:

1. An S-shaped disintegrating force development curve ($b > 1$) indicates the presence of an initial obstacle to water penetration linked to the surface conditions of the tablet.
2. A steeper initial slope in the disintegrating force development curve ($b < 1$) can indicate the presence of an obstacle to water penetration arising inside the tablet.
3. An exponential disintegrating force development curve ($b = 1$) indicates a regular fluid penetration.

The situation relative to $b < 1$ is more critical, since resistence to fluid penetration arising inside the tablet may lead to considerable delay in disintegration, whereas for $b > 1$, the small values of time lag found in the cases examined indicate that the tablet surface conditions do not influence disintegration time too much.

For the mixtures examined, b values depend on compression force and reflect the changes in compact structure. Mixture G shows b values constantly <1, thus enabling the presumption that disintegrator gelatinization enhances the resistance to fluid penetration. Mixtures D, F, B, and E show b values of ~ 1, thus indicating a regular disintegrating force development. Mixtures A and C show the opposite behavior. For the former, b values decrease as compression force increases. This is consistent with the product compression behavior, *i.e.*, starch granules deformed by compression readily absorb water forming a viscosity-increasing gel[3]. For the latter, the poor absorption is likely to be influenced by porosity conditions, thus enhancing the initial hindrance to water penetration. The results obtained indicate that, of the various mixtures examined, A, B, and E show the best overall performances.

CONCLUSIONS

The measurement of disintegrating force provides a deeper insight into the tablet structure obtained by processing a given formula. Whereas a "static" structure evaluation can be obtained through porosity, pore size distribution, *etc.*, disintegrating force measurements allow a "dynamic" evaluation of the structure itself, linked to the disintegration process and consequent active ingredient liberation. The input value, *i.e.*, the disintegrating force development rate at time $t = t_0 + \tau_d$, can be employed as a new parameter for tablet formulation. It is very sensitive to formulation and tablet structure changes and, if correlated with the crushing strength, allows an overall evaluation of the formula examined. The measure of the shape parameter b is a good reflection of the conditions of the compact and completes the structural information on tablet structure. On the basis of the results obtained, it seems justified to propose the measure of the disintegrating force as a very useful and decisive means for formulation evaluation.

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Disposition of Ibuprofen in Nephrectomized Dogs

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Abstract □ The pharmacokinetics of ibuprofen were studied in four nephrectomized and three normal dogs after administration of 214.3–227.6 mg iv of ibuprofen. Blood samples were collected at various time intervals for up to 10 h and serum concentrations of ibuprofen were assayed by an HPLC method. The elimination of serum ibuprofen followed first-order kinetics, with mean half-lives of 2.51 ± 1.10 and 2.81 ± 0.72 h in normal and nephrectomized dogs, respectively. Mean serum clearance of ibuprofen in nephrectomized dogs, 31.0 ± 5.2 mL/h/kg, was higher than that in normal dogs, 12.2 ± 8.6 mL/h/kg, ($p < 0.02$). The difference may be attributed to the greater volume of distribution for ibuprofen in nephrectomized dogs, 125.2 ± 39.0 (88.8–160.4) mL/kg as compared with 53.4 ± 57.8 (26.0–119.9) mL/kg in the normal group ($p < 0.2$).

Keyphrases □ Ibuprofen—disposition in nephrectomized dogs, pharmacokinetics □ Disposition—ibuprofen, nephrectomized dogs, pharmacokinetics □ Pharmacokinetics—disposition of ibuprofen in nephrectomized dogs

Ibuprofen, (±)-2-(*p*-isobutylphenyl)propionic acid (I), is a nonsteroidal anti-inflammatory agent indicated primarily for rheumatic diseases (1). The pharmacokinetics of I have been studied in normal volunteers. The drug is readily absorbed orally, and plasma peak levels are reached within 2 h of administration. The elimination of I from plasma is first order with apparent half-lives of 1.4–2.5 h (2–6). Similar half-lives are observed in arthritic patients, suggestive of no tissue accumulation of I in rheumatic patients (2). Patients with chronic circulatory insufficiency exhibit pharmacokinetic parameter values comparable with those of healthy subjects (7).

The metabolism of I has been studied in humans and several

Table I—Description of Normal and Nephrectomized Dogs

Dog	Sex	Weight, kg	Physiological Status[a]	Dose, mg iv
1	M	20.0	N	223.5
2	M	18.6	N	227.6
3	F	20.5	N	223.0
4	M	16.0	SN	214.3
5	M	16.8	SN	216.0
6	M	20.6	SN	216.0
7	M	17.4	SN	214.3

[a] Key: (N) normal; (SN) surgically nephrectomized.

animal species, including rats, baboons, and dogs (8, 9). Two major metabolites, the hydroxylated and the carboxylated derivatives of I, were identified in the plasma of the rat, baboon, and human, but not in dog plasma (9, 10). Both metabolites were found in the urine of all four species (9). All species, except the baboon, excreted >50% of the single oral dose in the urine. Of particular interest is the observation in dogs that 46% of the ibuprofen dose appeared in the urine as conjugated and unconjugated metabolites, while no metabolites were detected in plasma, indicating a slow formation but rapid excretion of the metabolites (9). In humans, urinary excretion of I was complete within 24 h following a single oral 200-mg dose (11). In dogs, measurements of total radioactivity in urine and feces accounted for 60% of dose eliminated in 24 h, 80–100% in 3–5 d. The ratio of excreted ibuprofen in urine and feces was on the order of 2:1 (10, 11). In addition, biliary excretion in dogs within 3 h of administration accounted for 25% of a single intravenous dose (9, 10). Ibuprofen (I) is highly bound (~99%) to serum albumin in humans and experimental animals (9). Because of the extensive protein binding, I is characterized by a small volume of distribution, 0.12–0.13 L/kg and 0.18 L/kg in humans (12, 13) and in normal dogs (14), respectively. Half-lives of I ranged from 3 to 3.81 h (14, 15), serum clearance was ~0.5 mL/kg/min (14) in normal dogs.

The pharmacokinetics of I in subjects with renal insufficiency has not yet been reported. Brogard *et al.* (16) recently investigated the pharmacokinetics of benoxaprofen, an analogue of I with a normal half-life of 28 h, and reported a prolonged half-life of up to 69 h in patients with end-stage renal failure. Dosage reduction of benoxaprofen in patients with renal impairment was thus recommended. It is not clear whether I is similarly affected in the renal disease state.

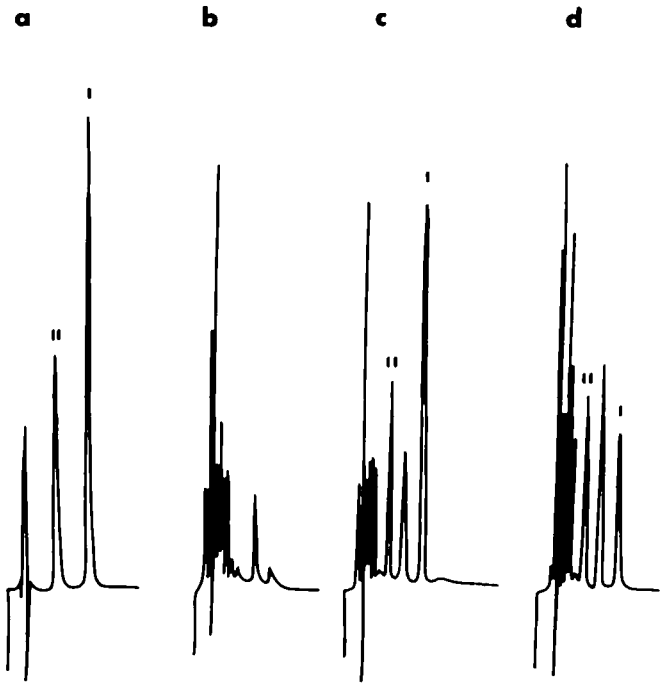
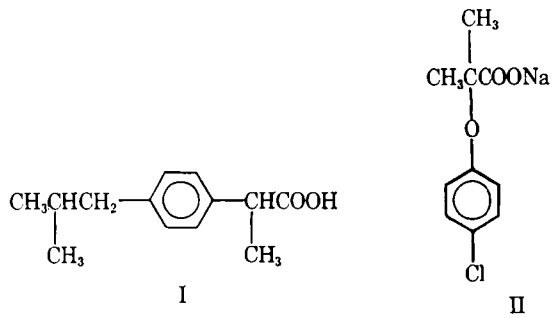


Figure 1 *Typical chromatograms of I and II. Key: (a) standard solution; (b) dog serum blank; (c) spiked sample; (d) dog serum sample.*

Table II—Pharmacokinetic Parameters of I in Normal Dogs Administered a Single Intravenous Dose

Dog	β, h^{-1}	$t_{1/2,\beta}$, h	CL_T, mL/h/kg	Vd_β, mL/kg
1	0.184	3.76	22.1	119.9
2	0.336	2.06	8.7	26.0
3	0.408	1.70	5.9	14.5
Mean	0.309	2.51	12.2	53.4
SD	0.114	1.10	8.6	57.8

Pharmacokinetic information of I in renal failure is of clinical importance, since a majority of patients with rheumatic arthritis are often the elderly who may be renally insufficient. This study was undertaken to investigate the effect of renal failure in pharmacokinetics of I using a nephrectomized dog model.



EXPERIMENTAL

Materials—Ibuprofen(I) was supplied as free acid[1]. Sodium clofibrate[2] (II) was used as an internal standard for the assay of I. HPLC-grade methanol[3] and acetonitrile[3] were glass-distilled and filtered before use.

Seven beagle dogs, 6 male and 1 female (weighing 16.0–20.6 kg), were used in the study. Specific dog data are shown in Table I. Four dogs were bilaterally nephrectomized, while three normal dogs served as the control. All dogs were catheterized at the radial and jugular veins to facilitate drug administration and blood collection, respectively.

Drug Administration and Sampling Schedule—Doses of I were administered as 5-mL aliquots of a 50% ethanolic solution in normal saline *via* the catheterized radial vein of the forearm. Blood samples, 3–5 mL each, were drawn from a cannula in the jugular vein at 0 (blank), 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, 480, 540, and 600 min following the intravenous administration. Samples were allowed to clot in the evacuated tubes, and sera were collected and stored at −20°C until assayed.

Assay—Serum samples of appropriate size, to which 2 μg of II was added, were acidified with 400 μL of 1 M HCl followed by extraction with 8 mL of ether. The ether extract was separated after centrifugation and evaporated to dryness under a nitrogen stream. The residue was reconstituted in 200 μL of methanol and subjected to HPLC analysis.

A chromatograph[4] equipped with a 100-μL sample loop[5], a variable-wavelength UV detector[6], and a microparticulate reverse-phase octyl column[7] (250 mm × 4.6 mm i.d.) was used for the HPLC analysis. The system was operated at ambient temperature with acetonitrile–water as the mobile phase (50:50, v/v, pH 2.5 as adjusted with phosphoric acid[8]). The flow rate was

[1] U-18,573, Lot No. R-51316; kindly supplied by The Upjohn Co., Kalamzoo, Mich.
[2] ICI, Great Britain.
[3] Omnisolv solvents; MCB Mfg. Chemicals Inc., Gibbstown, N.J.
[4] Consta Metric II; Laboratory Data Control, Riviera Beach, Fla.
[5] Model SV-7; Glenco Scientific Inc., Houston, Tex.
[6] Spectro Monitor III; Laboratory Data Control, Riviera Beach, Fla.
[7] Spherisorb; Custom LC Inc., Houston, Tex.
[8] ACS reagent; MCB Mfg. Chemicals Inc., Gibbstown, N.J.

Table III—Pharmacokinetic Parameters of I in Nephrectomized Dogs Administered a Single Intravenous Dose

Dog	β, h^{-1}	$t_{1/2,\beta}$, h	CL_T, mL/h/kg	Vd_β, mL/kg
4	0.336	1.89	34.5	94.3
5	0.217	3.20	34.7	160.4
6	0.266	2.61	23.6	88.8
7	0.197	3.52	31.0	157.5
Mean	0.262	2.81	31.0	125.2
SD	0.075	0.72	5.2	39.0

maintained at 2.0 mL/min, and the effluent was measured at 225 nm for absorbance.

Protein Binding Study—Protein binding of I was determined by the equilibrium dialysis method. Serum samples were spiked with known amounts of I to yield concentrations of 5, 10, and 20 μg/mL and incubated at 37°C for 16 h. The spiked samples were dialyzed against isotonic phosphate-saline buffer, consisting of 154 mM NaCl, 0.44 mM KH_2PO_4, and 2.20 mM K_2HPO_4 (pH 7.4) at 37°C for 6 h. After the equilibrium dialysis, the concentrations of I in the serum and the dialysate were measured by the HPLC assay. Dialysate samples were concentrated by lyophilization to raise the concentrations above the detection limit of the assay procedure.

Data Treatment—Serum concentration–time data were fitted to a two-compartment model using the NONLIN program (17). A series of pharmacokinetic parameters were obtained, of which β, the overall elimination rate constant, was further used for area calculation. The area under the concentration–time curve (AUC) was calculated by $AUC_{0\to\infty} = AUC_{0\to t} + C_t/\beta$, where C_t is the last measured serum concentration and $AUC_{0\to t}$ is the area covering the time interval 0 to t, which was calculated by the trapezoidal method. Half-life ($t_{1/2,\beta}$), total clearance (CL_T), and volume of distribution (Vd_β) were subsequently calculated as: $t_{1/2,\beta} = 0.693/\beta$, CL_T = Dose/$AUC_{0\to\infty}$, and $Vd_\beta = CL_T/\beta$. The significance of difference in mean parameter values between normal and nephrectomized groups, including $t_{1/2,\beta}$, CL_T, and Vd_β, were tested by a nonpaired Student's t test.

RESULTS AND DISCUSSION

The HPLC procedures described herein provided adequate sensitivity and good reproducibility for the analysis of I. Figure 1 depicts typical chromatograms, in which I and II exhibited retention times of 7.0 and 4.0 min, respectively. Baseline resolution was achieved without interference of endogenous substances from the blank dog serum. The typical calibration curve, constructed at a concentration range of 0.5–10 μg/mL, yielded a linearity of $y = 0.311x - 0.045$, $r^2 = 0.999$. The mean coefficient of variation was 3.7 ± 1.4% (n = 5), indicating a satisfactory reproducibility of the assay procedure.

Table IV—Unbound Fractions of I in the Sera of Dogs and Humans

Conc. of I, μg/mL	Percent Unbound to Serum Protein			
	Dog		Human	
	Nephrectomized[a]	Normal[b]	Uremic[c]	Normal[c]
5	7.2	0.9	11.0 ± 2.8	4.5 ± 0.3
10	7.5	1.5	10.9 ± 2.4	5.5 ± 0.1
20	5.6	1.4	10.0 ± 2.3	4.6 ± 1.3
Mean	6.8	1.3	10.6	4.9
SD	1.0	0.3	4.4	1.3

[a] Dog 7. [b] Dog 3. [c] n = 3.

Serum concentration profiles for I are shown in Figs. 2 and 3 for normal and nephrectomized dogs, respectively. First-order elimination of I was apparent in all dogs following the single-dose intravenous drug administration. The pharmacokinetic parameters of I in normal and nephrectomized dogs are reported in Tables II and III, respectively. The mean half-life was 2.51 ± 1.10 h for the normal group and 2.81 ± 0.72 h for the nephrectomized group; the difference was not significant ($p > 0.6$). The total clearance of I in nephrectomized dogs ranged from 23.6 to 34.5 mL/h/kg (mean, 31.0 ± 5.2 mL/h/kg), and that in normal dogs averaged 12.2 ± 8.6 mL/h/kg (range, 5.9–22.1 mL/h/kg). Nephrectomized dogs exhibited significantly higher total clearance than normal dogs ($p < 0.02$). The volume of distribution in nephrectomized dogs, 125.2 ± 39.0 mL/kg, was slightly greater than that in normal dogs, 53.4 ± 57.8 mL/kg; the difference was marginally significant ($p < 0.2$). Wide within-group variations were observed for total clearance and volume of distribution in dogs, indicating intersubject variability in the disposition of I.

Half-lives of I in normal dogs, 2.51 ± 1.10 h, as obtained in this study, were comparable with those reported by Kearns and Wilson, 3.81 h (14), and by Fujise, 3 h (15). The total clearance (12.2 ± 8.6 mL/h/kg) and the volume of distribution (53.4 ± 57.8 mL/kg), however, were smaller than the corresponding literature values, 30.1 mL/h/kg and 180 mL/kg (14). It should be

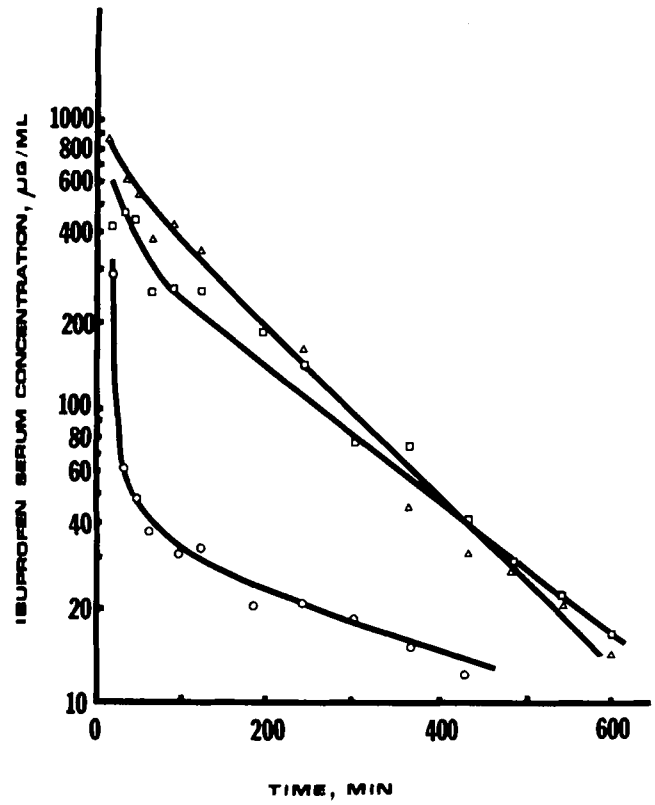


Figure 2—*Time profile of serum concentrations of I in normal dogs. Key: (○) dog 1; (□) dog 2; (△) dog 3.*

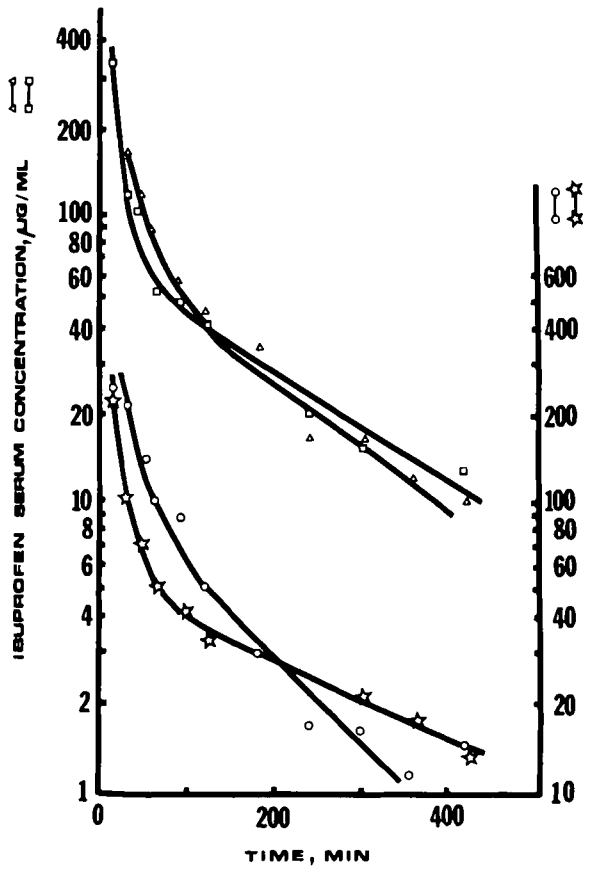


Figure 3—*Time profile of serum concentrations of I in nephrectomized dogs. Key: (○) dog 4; (△) dog 5; (□) dog 6; (☆) dog 7.*

noted that the parameter values reported by Kearns and Wilson were derived from a one-dog study.

No literature information regarding the pharmacokinetics of I in nephrectomized dogs is available. In this study, serum concentrations of I in nephrectomized dogs were lower than the corresponding concentrations in the normal ones. This observation suggests a greater volume of distribution for the nephrectomized dogs, which could be attributable to a reduced protein binding of I in the nephrectomized state. Reduced binding of highly bound organic acid to uremic plasma protein has been demonstrated for phenytoin, resulting in an increased volume of distribution (18). A similar mechanism may be suggested for I, which is also an organic acid with extensive protein binding (9). The reduction in binding of I to serum protein on nephrectomy is shown in Table IV for two dogs, one normal and the other nephrectomized. The protein binding was independent of concentration in the range of 5–20 μg/mL. The percentage of I unbound to serum protein in the nephrectomized dog, 6.8 ± 1.0%, was significantly greater than that in the normal dog, 1.3 ± 0.3% ($p < 0.001$). In a separate binding study of I in uremic patients (19), the fraction of free I in uremic plasma was also found to be higher than that in normal plasma (Table IV). The dogs used for this investigation were nephrectomized 3 d prior to the study and presumably were approaching the chronic uremic state.

Nephrectomy did not significantly alter the half-life of I in dogs; however, increases in both the volume of distribution and total clearance were apparent. Since <8% of the dose is excreted intact in the urine (9, 20), the lack of effect of nephrectomy on the half-life of I was anticipated. Nephrectomy induced increases in the total clearance and volume of distribution. The increased volume of distribution could result from a decreased protein binding of I in the nephrectomized state (Table IV), leaving more free drug available for distribution into the body tissue. The increase in total clearance is secondary to the increase in volume of distribution.

The effects of renal failure on the disposition of I in dogs and those of benoxaprofen in humans (16) are disparate. In dogs, the half-life of I remained unchanged, whereas the volume of distribution and total clearance increased. In humans the half-life of benoxaprofen was significantly prolonged with no distinct changes in other pharmacokinetic parameters. The disparity cautions against the extrapolation of conclusions from one drug analogue to another and from animal model to human subject.

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COMMUNICATIONS

Dynamic Method for Estimating the Extent of Plasma Protein Binding in a Dialysis Experiment

Keyphrases □ Plasma protein binding—dialysis, experimental time □ Dialysis—plasma protein binding, experimental time

To the Editor:

In a protein binding experiment one has a choice between two initial conditions: to place the drug in the plasma or in the buffer. Recent analyses (1, 2) of a linear system with a constant extent of plasma protein have revealed that it takes less time for the buffer drug concentration to reach a given limit of the equilibrium value when the drug is initially placed in the plasma rather than the buffer. This conclusion is also valid for a nonlinear system in which the number of binding sites is finite (3).

Despite the advantage of placing the drug initially in the plasma, a long experimental time may still be needed if permeation of the drug through the dialysis membrane is slow. This may cause some difficulties particularly in maintaining a constant volume in both compartments. In this report, a simple strategy is proposed to shorten the experimental time. The strategy requires two experiments: one with the drug initially placed in the buffer and the other with the drug initially placed in the plasma. The equilibrium value is derived from buffer drug concentrations measured at any given time during these two experiments. Experimental error notwithstanding, the estimate is exact provided the extent of protein binding is constant over the concentration range studied. The errors in applying the proposed method to a nonlinear situation are also considered. This is demonstrated by applying the method to a set of data simulated according to a model with saturable protein binding.

In the following discussion, we consider a dialysis experiment using a membrane with a mass transfer coefficient, M. The mass transfer coefficient is the product of the membrane permeability and the surface area. It has a dimension of volume per unit time. The volumes of the buffer in compartment 1 and the plasma in compartment 2 are V_1 and V_2, respectively. It is assumed that there is no material loss from the solution system and that there are no volume changes in either com-

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