rate of oxidation of GSH in the presence of microsomes was enhanced slightly by NADPH, but GSH had no effect on the rate of kidney microsome-catalyzed NADPH oxidation (data not presented). Prior to this report, neither γ-glutamyltranspeptidase nor thiol oxidase has been implicated as participating in the process of thiol-promoted peroxidation, although it has been reported that certain thiols had a proxidant effect on lipid peroxidation in a reconstituted unsaturated lipid model membrane system containing relatively high concentrations of exogenous metal ions [28, 29]. Additionally, it has been suggested that the stimulation of microsomal peroxidation by cysteine results from nonenzymatic reactions between iron and the cysteine sulfhydryl group [30].

In conclusion, GSH greatly enhanced both endogenous and Adriamycin-stimulated NAD(P)H-dependent kidney microsomal lipid peroxidation, although, in contrast, liver microsomal peroxidation was inhibited potently by GSH. The enhancement of kidney lipid peroxidation by GSH was concentration dependent, significant within physiological concentrations, synergistic with either NADPH or NADH, and appeared to require enzymatic activity in that peroxidation was prevented by prior heat-inactivation of the kidney microsomes. The effect of GSH may involve GSH oxidation products resulting from renal γ-glutamyltranspeptidase or thiol oxidase activity or the interaction of GSH with NADPH–cytochrome P-450 reductase-generated oxyradicals. These results suggest that GSH-enhanced peroxidation may have toxicological significance in kidney if a similar process occurs *in vivo*; thus, it may play a significant role in the nephrotoxicity of Adriamycin and other nephrotoxicants.

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Allopurinol as an inhibitor of the *in vivo* formation of acyclovir from desciclovir

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Desciclovir (2-[(2-amino-9*H*-purin-9-yl)methoxy]ethanol), currently in clinical trials, is a prodrug of the antitherpetic agent acyclovir (9-[(2-hydroxyethoxy)methyl]guanine, ZOVIRAX) [1, 2]. The advantage of this prodrug over acyclovir is its greater bioavailability by oral administration. After absorption, desciclovir is oxidized to acyclovir, presumably by xanthine oxidase (EC 1.2.3.2). The basis for this proposed route of enzymatic activation is the ability of xanthine oxidase purified from bovine milk [1] and human liver [3] to catalyze the conversion of desciclovir to acyclovir. However, the possibility exists that, *in vivo*, other enzymes might be involved. Consequently, this study was undertaken to elucidate the effects of the xanthine oxidase inhibitor allopurinol (4-hydroxypyrazolo[3,4-*d*]pyrimidine, ZYLOPRIM) [4] on the renal elimination of desciclovir and acyclovir in the rat.

Materials and methods

Animals. Male Long–Evans rats were obtained from Blue Spruce Farms, Inc. Animals were housed in nalgene metabolism cages that separated urine from feces; all animals had free access to food and water. Each cage contained two rats. Urine from each group of two rats was collected after 8 hr and 24 hr.

Dosing. A single dose of desciclovir (20 mg/kg) was administered by stomach tube to all rats. After a 48-hr

Table 1. Recovery of acyclovir (ACV) and desciclovir (DCV) in the urine of rats*

Drug Adm.†	Time (hr)	Mean U.A./Cr‡	Mean Allan/Cr‡	ACV (Mean % dose recovered)	DCV (Mean % dose recovered)	24 hr Total	Mean ratio ACV/DCV
DCV	0–8	0.20	5.3	34.6	5.6		6.1
	8–24	0.15	4.1	12.4	1.8	54.4	7.6
Allopurinol and DCV	0–8	0.05	3.2	13.3	37.8		0.4
	8–24	0.18	3.9	6.6	7.1	64.8	0.8

* N = two groups, two rats (Long–Evans) per group.
† Desciclovir (20 mg/kg, p.o.), was given first. Forty-eight hours later, 25 mg/kg allopurinol was administered i.p. 30 min before and 4 hr after a single dose of desciclovir (20 mg/kg, p.o.).
‡ U.A. = uric acid; Allan = allantoin; and Cr = creatinine.

wash-out period, the same animals were dosed with 25 mg/kg allopurinol (in the form of sodium allopurinol) intraperitoneally; 30 min later, the rats were orally dosed with 20 mg/kg desciclovir. A second 25 mg/kg dose of allopurinol was administered 4 hr later.

Assays. Concentrations of acyclovir and desciclovir in each urine collection were determined by a radioimmunoassay specific for each drug [5, 6]. Neither drug cross-reacted with allopurinol in the assay.

Uric acid was determined by the uricase method modified for a CentrifiChem Analyzer (Baker Instrument Co.) [7]. Allantoin was determined by a modification of the Rimini–Schryver reaction [8]. Creatinine was determined by the Jaffe reaction modified for a CentrifiChem Analyzer [9].

Results and discussion

Allopurinol markedly affected the ratio of acyclovir to desciclovir in the urine of desciclovir-treated rats (Table 1). With allopurinol treatment, this ratio decreased 15-fold during the first 8 hr of urine collection and 10-fold during the remaining 16 hr of collection. The mean percent dose recovered in urine in 24 hr as acyclovir and its unchanged prodrug was 54% without allopurinol. Treatment with allopurinol did not greatly affect this value.

The results of the determination of uric acid and allantoin (end product of purine excretion in lower mammals) normalized by creatinine concentration in the urine samples (Table 1) indicated that *in vivo* oxidation of xanthine to uric acid by xanthine oxidase was inhibited by allopurinol. In the first 8 hr of urine collection, uric acid levels declined by 75% and allantoin decreased by 40% after treatment with allopurinol plus desciclovir compared to desciclovir given alone. As expected, greater excretion of uric acid and allantoin occurred during the later collection period after allopurinol dosing.

The fact that allopurinol decreased the ratio of acyclovir to desciclovir 10- to 15-fold in the rat implies that xanthine oxidase is a major pathway of conversion of this prodrug to acyclovir in this species.

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In summary. The data presented indicate that the formation of acyclovir from its prodrug desciclovir can be decreased in the rat by the xanthine oxidase inhibitor allopurinol. This *in vivo* result is consistent with the *in vitro* data that indicate xanthine oxidase is instrumental in the conversion of desciclovir to acyclovir.

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