Table 1 Tissue levels of phospholipids, chlorimipramine (CI) and desmethylchlorimipramine (DMCI) in rats chronically treated with CI

Tissue	*Total Phospholipids** *mg/g of lipid-free dry tissue*	*% of control*	*CI†* *μg/g of wet tissue*	*DMCI†*
Lung	187	246	3.3 ± 0.9	131 ± 27
Liver	130	119	1.5 ± 0.3	25 ± 2
Kidney	128	114	1.7 ± 0.1	41 ± 10
Spleen	82	137	1.4 ± 0.2	47 ± 10
Heart	81	92	0.7 ± 0.1	17 ± 5

* CI was given orally in a daily dose of 150 mg/kg body wt and rats were killed after one week (Group A). Values represent the content measured in the homogenate of pooled organs from 5 rats.
† CI was given orally in a daily dose of 90 mg/kg body wt and rats were killed after one week (Group B). Values are mean ± s.e. mean derived from 5 animals.

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Correlation between the rise in acute phase proteins and histological evidence of ulceration in the rat following indomethacin treatment

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An increase in the plasma concentration of the acute phase proteins (APP) accompanies the tissue damage associated with most forms of trauma. These APP changes have been used to determine the severity and duration of various inflammatory reactions in animals (Lowe, 1964; Glenn, Bowman & Koslowske, 1968; Billingham & Gordon, 1976) and man (Crockson, Ratcliffe, Payne & Soothill, 1966). The APP have also been used to demonstrate the therapeutic effects of anti-inflammatory and anti-rheumatic drugs (Glenn, *et al.*, 1968; McConkey, Crockson, Crockson & Wilkinson, 1973). Apart from their therapeutic effects however, anti-inflammatory drugs also produce gastro-intestinal irritation and ulceration, especially at high dosage.

We have investigated the changes in plasma concentration of an acute phase protein, α-glycoprotein (α-GP), to establish whether serial measurements of α-GP were a useful, non-invasive means of determining the severity and duration of the gastro-intestinal damage produced by indomethacin.

Male, Wistar derived rats of the Alderley Park strain weighing 170 ± 10 g were used. Indomethacin (Sigma, suspended in 0.5% tween 80) was given as a single oral dose, at various levels, to rats which had been fasted for twelve hours. After treatment, groups of four rats were sacrificed at various times, up to fifteen days. Body weight and α-GP levels were determined at each time and, after sacrifice, one of us (M.J.T.) examined each gastro-intestinal tract macroscopically and microscopically for evidence of ulceration. Blood samples were taken from the caudal vein and α-GP levels determined by radial immunodiffusion (Mancini, Carbonara & Heremans, 1965).

Results are shown in Table 1, which demonstrates the relationship between changes in body weight and α-GP levels, and the histological evidence of ulceration.

The increase in plasma α-GP levels correlated closely with the severity of the gastro-intestinal

Table 1 Relationship between α-GP levels, body weight changes and histological evidence of ulceration following indomethacin treatment

Treatment Indomethacin (mg/kg)	*α-GP level (area of diffusion ring mm²) Means + s.e. Time (days) after single treatment with indomethacin*				*Body weight (g) Means*				*Histology scored 0–10 in arbitrary scale for severity of ulceration (total score for group of 4 rats)*			
	0	*3*	*5*	*10*	*0*	*3*	*5*	*10*	*0*	*3*	*5*	*10*
5	15 ± 1	18 ± 3	17 ± 2	16 ± 1	165	207	217	256	0	0	0	0
10	16 ± 1	111 ± 14	87 ± 20	24 ± 4	164	173	187	231	0	12	10	0
15	16 ± 2	164 ± 12	112 ± 19	48 ± 24	164	152	167	221	0	24	28	4
20	14 ± 1	146 ± 7	167 ± 11	100 ± 20	166	147	143	177	0	26	38	12*
Vehicle control	16 ± 1	13 ± 1	16 ± 2	13 ± 1	162	206	220	258	—	—	—	—

* Two rats died in this group.

damage produced by indomethacin, as determined histologically and in body weight changes (Table 1) and thus proved to be a useful means of following, non-invasively, the time course of the ulcerative process.

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Effects of β-adrenoceptor antagonists on the hepatic mixed-function oxygenases in the rat

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Following reports that the β-adrenoceptor blocking agents, pronethalol and propranolol exhibited tumorigenic properties in certain strains of mice (Paget, 1963; Alcock & Bond, 1964; Howe, 1965; Smith & Butler, 1978), some concern has been expressed over the potential carcinogenicity of this whole group of drugs.

It is known that chemical carcinogens may initiate malignancy through alkylation of DNA, or may potentiate malignant cell transformations by epigenetic mechanisms. Whereas there are many mutagenic tests for monitoring chemical damage to DNA, there are very few short-term tests for studying epigenetic mechanisms. Chemical carcinogens modify the liver microsomal haemoproteins, leading to the formation of cytochrome P-448 which catalyses the de-ethylation of ethoxyresorufin (Burke & Mayer, 1975), and the 2-hydroxylation of biphenyl (Burke & Mayer, 1975; Atlas & Nebert, 1976). In the present study, the effects of 5 β-adrenoceptor blocking agents (propranolol, practolol, pronethalol, acebutolol, atenolol) on the activities of rat liver microsomal biphenyl-2-hydroxylase, ethoxyresorufin de-ethylase and other mixed-function oxidase enzymes were investigated.

Male Wistar albino rats received single daily oral doses (5, 50 and 150 mg kg^{-1} day^{-1}) of a β-adreno-