The work was supported by a grant from the Medical Research Council.

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Increased Concentrations of Malonaldehyde in the Livers of Rats Treated with Carbon Tetrachloride

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The administration of CCl_4 to rats results in numerous biochemical changes in the liver within the first hour after dosing. These changes are particularly evident in the endoplasmic reticulum and have been suggested to be, at least partially, dependent on lipid peroxidation, which, once initiated by free-radical metabolites of the CCl_4 , is an autocatalytic process (Recknagel & Ghoshal, 1966; Slater, 1966).

CCl_4 has been shown to stimulate the NADPH-dependent peroxidation of rat liver microsomal suspensions (Comporti *et al.*, 1965; Ghoshal & Recknagel, 1965; Slater & Sawyer, 1971). CCl_4 has also been shown to initiate the peroxidation of 'microsomal' lipids *in vivo* within 5 min of its administration, as evidenced by diene conjugation absorption (Rao & Recknagel, 1968). However, attempts to detect malonaldehyde (which is an extensively used index of lipid peroxidation) in the livers of rats treated with CCl_4 have failed (Priest *et al.*, 1962; Recknagel & Ghoshal, 1965). In retrospect this is not surprising, since malonaldehyde has been found to be metabolized *in vivo* (Placer *et al.*, 1965). We have overcome this problem by homogenizing a small piece of liver in cold 20% (w/v) trichloroacetic acid in a top-drive Waring Blendor as soon as possible after the animal was killed. The supernatant from the centrifuged homogenate was incubated (at 100°C for 10 min) with thiobarbituric acid. The pink chromogen, which is indicative of malonaldehyde, was extracted into butanol and its E_{535} determined.

The concentrations of malonaldehyde found in rat livers 2 h after the administration of liquid paraffin or a mixture of CCl_4 and liquid paraffin (1:1, v/v) were 1.39 ± 0.11 and 2.97 ± 0.31 nmol/g of liver respectively ($P < 0.001$). The administration of promethazine, an antioxidant that protects CCl_4 -treated rats against the onset of necrosis, decreased the concentrations of malonaldehyde in the livers of untreated rats or of rats that had been dosed with liquid paraffin or with the mixture of CCl_4 and liquid paraffin. However, promethazine did not completely inhibit the stimulation of lipid peroxidation caused

by CCl_4 , as assessed 2 h after dosage with the hepatotoxic agent.

The finding that CCl_4 stimulates lipid peroxidation *in vivo* is consistent with, and lends further support to, the suggestions that CCl_4 stimulates free-radical-motivated reactions in rat liver shortly after administration (Recknagel, 1967; Slater, 1972).

P. J. J. is grateful to the Medical Research Council for a Research Studentship.

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The Absorption of Aliphatic Carbamates by Everted Gut Sacs of Rat

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The everted-gut-sac technique (Wilson & Wiseman, 1954) has been used to study the absorption of a series of carbamates of general structure R-O-CO-NH_2 , where R is an aliphatic group ranging from methyl to *n*-heptyl. These compounds show a wide range of lipophilicity and are not ionized nor hydrolysed in aqueous solution.

Cannulated everted sacs of rat were incubated at 37°C in an oxygenated Krebs-Henseleit medium containing Tween 80 (5%, w/v) and one of the carbamates (10–50 mM). Samples (20 μl) were removed from the interior of the sac every 10 min for 1 h and assayed by g.l.c. on a Porapac P column. No metabolism was evident, recoveries averaging 97%. The results obtained, expressed as % of carbamate of the initial mucosal fluid absorbed/h per cm^2 were as follows: methyl, 2.81; ethyl, 3.37; *n*-propyl, 5.07; *n*-butyl, 6.60; *n*-pentyl, 3.75; *n*-hexyl, 2.25; *n*-heptyl, 0.67. It was found that the presence of Tween 80 did