The results indicate that diazinon undergoes a dual oxidative metabolism similar to parathion, i.e. activation to diazoxon and degradation to diethyl phosphorothioic acid. Oxidative degradation by microsomes is not, therefore, limited to 4-nitrophenyl analogs of parathion, but probably occurs with many phosphorothioate insecticides. Furthermore, such oxidative degradation may be a common metabolic pathway to most P=S compounds. Our preliminary experiments have shown that ^{35}S-malathion (both S atoms labeled) (S-[1,2-*bis*(ethoxycarbonyl)ethyl] *O,O*-dimethyl phosphorodithioate) is also degraded oxidatively by rat liver microsomes (unpublished results); a requirement *in vitro* for oxygen and reduced pyridine nucleotide cofactors has been demonstrated, but the cleavage site (P—S bond or S—C bond) is yet to be determined. (The ^{35}S-malathion was a gift of the World Health Organization, Geneva, Switzerland.) Oxidative cleavage also occurs with at least one P=O compound, *n*-propyl paraoxon (*O,O*-di-*n*-propyl *O*-4-nitrophenyl phosphate).[8] These results emphasize the importance of microsomal oxidation in the degradation of organophosphorus esters. Many of the so-called phosphatase products or hydrolysis products may actually be oxidative metabolites. Existing concepts on organophosphate metabolism may have to be modified considerably.

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Effect of sugars and sugar derivatives on plasma free fatty acid in rats*

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THE INHIBITION of free fatty acid (FFA) release from adipose tissue can be achieved in two ways: by the use of nicotinic acid[1] or pyrazole derivatives[2, 3] which inhibit the lipolytic activity of adipose tissue, or by the administration of compounds such as simple sugars which compete with FFA as energy sources and promote reesterification of FFA in adipose tissue.[4] This study was carried out to test the effects of a number of sugar alcohols and of methylglucamine upon circulating FFA levels. Glucose and fructose were used as controls. In some experiments, partially hydrolyzed starch (Amidex) was also used.

Male Sprague–Dawley rats (150 g) were fasted, and the test compounds were administered orally or i.v. At intervals of 15–240 min, plasma FFA, blood glucose and liver triglycerides were determined

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Plasma FFA were estimated by the method of Dole[5] with minor modifications; washings of the heptane phase were carried out according to Trout.[6] Liver triglycerides were determined by the Van Handel and Zilversmit technique,[7] using an aliquot of a chloroform–methanol (2:1) extract of liver. Blood glucose was determined with the Biochemical Test Kit (hexokinase/glucose-6-phosphate dehydrogenase) of Boehringer & Sons, Mannheim.

Table 1 summarizes the results of an experiment in which the effects of glucose and fructose wer compared. Glucose administration, as expected, decreased the plasma FFA level. As in the case of

TABLE 1. INFLUENCE OF AN ORAL DOSE OF GLUCOSE OR FRUCTOSE ON PLASMA FFA, BLOOD GLUCOSE AND LIVER TRIGLYCERIDES OF RATS
(5 rats/gp)

Treatment 3 g/kg	Time (min)	Plasma FFA μequiv./l. ± S.E.	Blood Glucose mg/100 ml ± S.E.	Liver Triglycerides mg/100 g ± S.E.
Controls		955 ± 31	82 ± 1	849 ± 38
Glucose	30	565 ± 69*	121 ± 2*	551 ± 65†
Glucose	60	554 ± 66*	127 ± 4*	400 ± 45†
Glucose	90	302 ± 68*	124 ± 6*	265 ± 36*
Glucose	120	611 ± 17*	98 ± 4	325 ± 15*
Controls		646 ± 79	88 ± 1	414 ± 43
Fructose	30	735 ± 52	111 ± 5†	484 ± 41
Fructose	60	608 ± 61	111 ± 3	614 ± 32†
Fructose	120	470 ± 28	112 ± 1	602 ± 12
Fructose	240	481 ± 8	102 ± 1	615 ± 56

Significance (vs. control):
* $P < 0.001$.
† $P < 0.01$.

nicotinic acid or 5-carboxyl-3-methylpyrazole administration,[8] the inhibition of FFA influx into the liver resulted in a lowering of liver triglyceride levels. Fructose administration did not affect plasma FFA levels until 120 min after oral administration. The levels of glucose rose, however, as did the liver triglycerides. These findings are consonant with the observation that fructose feeding causes hypertriglyceridemia,[9] which may be due to an enhanced rate of hepatic lipogenesis from fructose. The differences between glucose and fructose may also be due to differences in the release of lipoprotein lipase.[10]

The oral administration of dulcitol, sorbitol, mannitol, lactitol, 1-4-anhydro-D-glucitol, 1-4,3-6 dianhydro-D-glucitol or of methylglucamine did not affect any of the parameters under observation (Table 2). Amidex did exercise a slight effect on plasma FFA and liver triglyceride levels ($P < 0.05$)

TABLE 2. INFLUENCE OF AN ORAL DOSE OF VARIOUS SUGAR DERIVATIVES ON PLASMA FFA, BLOOD GLUCOSE AND LIVER TRIGLYCERIDES IN RATS
(5 rats/gp)

Treatment 3 g/kg	Plasma FFA* μequiv./l. ± S.E.	Blood Glucose* mg/100 ml ± S.E.	Liver Triglycerides* mg/100 g ± S.E.
Controls	813 ± 73	103 ± 1	464 ± 43
Dulcitol	787 ± 70	92 ± 3	558 ± 31
Sorbitol	702 ± 50	96 ± 3	544 ± 48
Mannitol	784 ± 72	91 ± 1	578 ± 32
Lactitol	787 ± 66	92 ± 1	601 ± 31
Controls	647 ± 68	78 ± 2	362 ± 30
1-4-Anhydro-D-glucitol	760 ± 28	91 ± 1	420 ± 36
1-4,3-6,Dianhydro-D-glucitol	678 ± 68	92 ± 6	392 ± 42
Methylglucamine	562 ± 137	90 ± 3	407 ± 62
Amidex	388 ± 66	118 ± 4	566 ± 69

* Determinations made after 120 min.

and a marked effect on blood glucose ($P < 0.001$). These findings might be expected, since Amidex would be hydrolyzed to glucose. In order to ascertain whether the results reported in Table 2 may have been due to difficulties in absorption of the various sugar derivatives, another experiment was carried out in which the various test compounds were administered i.v. Under these conditions (Table 3)

TABLE 3. INFLUENCE OF I.V. ADMINISTRATION OF SUGAR DERIVATIVES ON PLASMA FFA AND BLOOD GLUCOSE IN RATS
(5 rats/gp)

Treatment	Dose g/kg	Plasma FFA* μequiv./l. ± S.E.	Blood Glucose mg/100 ml ± S.E.
Control	1·0	559 ± 48	81 ± 1
Glucose	1·0	210 ± 27†	185 ± 5†
Dulcitol	1·0	513 ± 67	85 ± 2
Sorbitol	1·0	304 ± 56‡	117 ± 3†
Mannitol	1·0	646 ± 43	75 ± 2
1-4-Anhydro-D-glucitol	1·0	524 ± 41	84 ± 1
1-4,3-6,Dianhydro-D-glucitol	1·0	632 ± 39	84 ± 1
Amidex	1·0	377 ± 14‡	145 ± 3†
Control		920 ± 64	83 ± 2
Sorbitol	0·50	896 ± 64	94 ± 1†
Sorbitol	0·25	936 ± 40	100 ± 1†
Methylglucamine	0·50	1066 ± 44	90 ± 1‡
Methylglucamine	0·25	980 ± 110	86 ± 1

* Determinations made after 15 min. Significance (compared to controls):
† $P < 0.001$.
‡ $P < 0.01$.

glucose, sorbitol and Amidex all significantly reduced plasma FFA and significantly raised blood glucose levels. Among the various sugar alcohols only sorbitol, by i.v. administration, decreases plasma FFA. It is possible that sorbitol exerts this effect either by being transformed into glucose[11] or fructose.[12]

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