LETTERS TO THE EDITOR

Phospholipase A₂ and acute pancreatitis in rats

EDITOR,—Phospholipase A₂ (PLA₂) is an enzyme that cleaves fatty acids from phospholipids, leading to the generation of inflammatory eicosanoids.¹ The group II isoenzyme of phospholipase A₂ (PLA₂-II) is raised in peripheral blood during various inflammatory states.² PLA₂ is induced in vitro and in vivo by the classic acute phase cytokine interleukin 6.^{3,4} Therefore PLA₂-II can be regarded as an acute phase protein. With great interest we read the well designed study of Furue *et al* (*Gut* 1997;41:826-31) who could clearly show that most PLA₂ activity during sodium deoxycholate induced acute pancreatitis in rats is due to the group II isoenzyme. Furue and colleagues suggested that the liver is the main source of this enzyme in their experiments because Nevalainen and coworkers⁵ and Crowl and coworkers⁶ described PLA₂-II activity in human hepatocytes. We agree with the suggestion of Furue *et al* that PLA₂-II is produced in human hepatocytes like classic acute phase proteins. This was also demonstrated by our group,⁷ but we think that the extrapolation of these findings from human tissue to animal experiments, as done by Furue *et al*, requires some clarification. Hatch *et al* were able to show that liver macrophages and not hepatocytes were the main source of PLA₂-II in rats during endotoxin induced acute phase reaction.⁷ As a consequence, liver macrophages but not hepatocytes could also be the main source of PLA₂-II in the animal experiments presented by Furue and collaborators. Therefore an alternative pathogenetic mechanism leading to liver damage in experimental induced acute pancreatitis should be taken into account. Our alternative pathogenetic sequence is that PLA₂-II released by liver macrophages attacks adjacent already damaged liver tissue, thus leading to complete destruction of hepatocytes with subsequent release of aminotransferases into the circulation, as shown by Furue *et al*. In conclusion, we agree that PLA₂-II could be an important mediator of liver failure in acute pancreatitis, but alternative pathomechanisms resulting from different production sites should be discussed.

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- 1 Aufenanger J, Bertsch T. Catalytic phospholipase A₂ assays. In: Uhl W, Nevalainen TJ, Büchler MW, eds. *Phospholipase A₂—Basic and clinical aspects in inflammatory diseases. Progress in surgery*. Basel: Karger, 1997:43-9.
- 2 Prudzenski W, Vadas P. Phospholipase A₂: A mediator between proximal and distal effectors of inflammation. *Immunol Today* 1991;12:143-6.
- 3 Crowl RM, Stoller TJ, Conroy RR, *et al*. Induction of phospholipase A₂ gene expression in human hepatoma cells by mediators of the

acute phase response. *J Biol Chem* 1991;266:2647-51.

- 4 Bertsch T, Banks RE, Forbes MA, *et al*. Phospholipase A₂ activity is induced during treatment with recombinant interleukin-6 in patients with cancer. *Ann Clin Biochem* 1996;33:565-7.
- 5 Nevalainen TJ, Kallajoki M, Pesonen E, *et al*. Origin of circulating group II phospholipase A₂ in hepatocytes in a patient with epitheloid hemangioendothelioma of the liver. *Lab Invest* 1996;74:585-91.
- 6 Bertsch T, Banks RE, Forbes MA, *et al*. Phospholipase A₂ is induced during treatment with recombinant interleukin-6. In: Martin SM, Halloran SP, eds. *Proceedings of the XVI International Congress of Clinical Chemistry*. Cambridge: Pigott, 1996:62.
- 7 Hatch GM, Vance DE, Wilton DC. Rat liver phospholipase A₂ is an endotoxin stimulated membrane-associated enzyme of Kupffer cells which is released during liver perfusion. *Biochem J* 1993;293:143-50.

Reply

EDITOR,—We thank Drs Bertsch and Fischer for their interest in our paper. As group II PLA₂ (PLA₂-II) is known to be produced from a variety of cells upon stimulation with various stimuli, it is still difficult to ascertain the main source of increased levels of this enzyme in the circulation both in animal models of inflammation and in human patients.^{1,2} As Bertsch and Fischer comment, we have to be careful about transferring findings from human tissue to animal experiments. Also of note is that liver macrophages (Kupffer cells) and not hepatocytes could be the main source of PLA₂-II in our experiments on acute pancreatitis in rats. However, in contrast to the findings by Hatch and colleagues³ rat cultured hepatocytes can produce PLA₂-II upon stimulation via chemical hypoxic injury,⁴ suggesting that the production of PLA₂-II depends on both the type of cell and also the type of stimulus used. So we still think that hepatocytes are the main source of PLA₂-II in our experiments. In addition, vascular smooth muscle cells could also be a potential source of PLA₂-II as reported by Nakano and Arita⁵ who found high levels of PLA₂-II transcripts in aorta of endotoxaemic rats. Very recently high levels of PLA₂-II protein and overexpression of its mRNA in vascular tissue were also found in rat adjuvant arthritis.⁶ Therefore, the possible sources of PLA₂-II in our rat acute pancreatitis could be hepatocytes, Kupffer cells and smooth muscle cells, and this enzyme from different type of cells would work in concert to damage liver tissue. Of course, the immunohistochemical study to identify the cellular source of PLA₂-II in our experiments should be performed.

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- 1 Vadas P, Browning J, Edelson, *et al*. Extracellular phospholipase A₂ expression and inflammation: the relationship with associated disease states. *J Lipid Mediat* 1993;8:1-30.

2 Kallajoki M, Nevalainen TJ. Expression of group II phospholipase A₂ in human tissues. In: Uhl W, Nevalainen TJ, Büchler MW, eds. *Phospholipase A₂—Basic and clinical aspects in inflammatory diseases. Progress in Surgery*. Basel: Karger, 1997:8-16.

3 Hatch GM, Vance DE, Wilton DC. Rat liver mitochondrial phospholipase A₂ is an endotoxin-stimulated membrane-associated enzyme of Kupffer cells which is released during liver perfusion. *Biochem J* 1993;293:143-50.

4 Wang H, Harrison-Shostak DC, Lemasters JJ, *et al*. Contribution of pH-dependent group II phospholipase A₂ to chemical hypoxic injury in rat hepatocytes. *FASEB J* 1996;10:1318-25.

5 Nakano T, Arita H. Enhanced expression of group II phospholipase A₂ gene in the tissues of endotoxin shock rats and its suppression by glucocorticoid. *FEBS Lett* 1990;273:23-6.

6 Koo Seen Lin M, Katz A, Van Den Bosch H, *et al*. Induction of secretory phospholipase A₂ confirms the systemic inflammatory nature of adjuvant arthritis. *Inflammation* 1998;22:161-73.

Effect of gastric acid suppressants on human gastric motility

EDITOR,—I read with interest the recent article by Parkman *et al* (*Gut* 1998;42:243-50) who reported on the effects of H₂ receptor antagonists and omeprazole on interdigestive gastroduodenal motility and concluded that these drugs have a motor stimulant effect. This conclusion, however, could be invalidated by the unsatisfactory study design. The basal fasting period of 30 minutes prior to administration of the drug is very short when one considers that the mean duration of the cycle of the interdigestive migrating motor complex is at least three times as long¹; the 30 minute observation period after drug administration is also quite short. Parkman and colleagues could have recorded the phase III that frequently occurs spontaneously when the stress caused by the insertion of the probe has lessened. In addition, omeprazole was given before the insertion of the manometric probe so that no control period was recorded in these subjects. These biases could raise some perplexing questions about the real effectiveness of these acid suppressants in stimulating interdigestive gastroduodenal motility. However, this is a real effect as has been previously and repeatedly demonstrated for ranitidine,² famotidine,³ nizatidine,⁴ and particularly for omeprazole.⁵ Unfortunately these studies were not cited by Parkman *et al*.

The hypothesis of cholinergic activity put forward to explain the strange motor effects of these acid suppressants could be valid for only a few H₂ receptor antagonists. The most probable explanation is that acid suppression removes the inhibition exerted by acid on the initiation of phase III by motilin, as can be inferred from the close relation between the interdigestive motor and secretory activities of the stomach.⁶ However, as some authors have found an increase in plasma motilin after the administration of famotidine,³ I believe that a study on plasma motilin concentrations after the administration of these drugs, especially omeprazole, is desirable in an attempt to clarify the mechanism underlying this unexpected effect of these acid suppressants.

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- 1 Quigley EMM, Donovan JP, Lane MJ, *et al*. Antroduodenal manometry. Usefulness and limitations as an outpatient study. *Dig Dis Sci* 1992;37:20-8.