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Letters to the Editor

New Concepts in Understanding the Pathophysiology of Chronic Pancreatitis

To the Editor:

The recently published paper entitled "New Concepts in Understanding the Pathophysiology of Chronic Pancreatitis" by S. Freedman summarizes "the current research knowledge" on the pathophysiology of chronic pancreatitis *(1)*. With respect to the formation of intraductal plugs and pancreatic stones, we would like to comment on these concepts, since evidence from recent literature has not been incorporated.

Two secretory pancreatic proteins have been identified as components of intraductal plugs: pancreatic stone protein (PSP) and GP-2, a membrane-anchored glycoprotein that is released into the juice during the secretion process. The presence of GP-2 in plugs has been associated with an acidification of the centroacinar lumen. However, aggregate formation has not been achieved in vitro by simple acidification *(1)*. PSP, reportedly the predominant protein component of pancreatic plugs and stones *(2–5)*, on the other hand, may be rendered insoluble through "partial activation of pancreatic zymogens within smaller ducts," since minimal amounts of active trypsin suffice to cleave PSP, thereby shortening the protein by 11 amino acids and leading to spontaneous precipitation of the product *(5)*. In our own work with recombinant rat PSP *(6)*, we were able to reproduce this finding in vitro *(7)*. In our view, PSP is still the best-documented protein component of pancreatic plugs or stones.

Further in his paper, Freedman recapitulates the issue "pancreatic stones." There he selectively cites Mul-tigner et al.'s paper *(8)* on the capacity of PSP (="lithostathine") to prevent calcium carbonate precipitation in vitro. However, the experimental basis of the "lithostathine hypothesis" was seriously questioned by our own group in 1997 *(9)*. The in vitro activity reported by Sarles' group according to our experiments, merely turned out to be a nonspecific effect of a protein at micromolar concentrations, an effect that PSP shared with many other randomly chosen proteins and furthermore with phosphate ions, thus an effect that does not deserve to be called a functional activity. We therefore consider the "lithostathine hypothesis" unsupportable and the name "lithostathine" misleading. We have recently found support for our view in a paper published by DeReggi et al. *(10)*. Freedman mentions only the still unresolved controversy regarding PSP levels in pancreatic juice of different groups of patients, but fails to discuss that the function of PSP/*reg* has not been clarified, which makes interpretations of fluctuations in PSP levels highly speculative.

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