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Discussion

Dr. William Silen (Boston): I think Dr. Thompson has indeed validated an excellent assay for CCK. We certainly look forward to further studies from his very productive laboratory showing us the interactions between CCK, gastrin and soon perhaps even secretin.

I did note on some of his slides that the CCK concentrations were elevated for as long as six hours after a meal. I wonder whether Dr. Thompson has any data on the concentration of CCK at which we get physiologic effects in man. In other words, can we expect at those high levels to show how stimulation of contraction of the gallbladder or increase in pancreatic enzyme output perhaps that hasn't been studied yet.

It is of some interest that these levels are very high even at six hours.

Of particular interest, I think, are the elevations noted in the Zollinger-Ellison patients. Perhaps here we have another example of a tumor which might indeed elaborate in addition to gastrin, another hormone.

In the diabetic patients, I would ask whether there's any information

on the gastric function of these patients since certainly the changes in CCK which were seen in the blood might reflect some changes in motility or secretion which is known to occur in diabetic patients.

Finally, do we have any evidence of the disappearance rate of what might be called big CCK since we know that big gastrin, for example, has a much longer half-life than normal or little gastrin.

DR. JAMES C. THOMPSON (Closing discussion): Dr. Silen asked why levels of CCK persist so high so long post-prandially and I don't know. I know the gastrin levels also persist for a long time post-prandially. It may well be that these levels are due to persistence of forms that are metabolically inactive.

For example, after a meal gastrin levels are high for a long time and yet gastric secretion falls off. We suspect that the persistence of these high levels is due to the protection from catabolism of the larger forms of gastrin which are still recognized by the immunoassay (big, big gastrin and a form of gastrin called by Rehfeld component I) apparently do not stimulate gastric secretion. They are apparently resistant to catabolism and yet they continue to be picked up by the radioimmunoassay. I think it will be necessary for us to learn to distinguish between molecular forms of these polypeptide hormones before we can correlate their radioimmunoassay levels of bioactivity.

He asked in what kind of levels in dogs and man do we see physiologic actions. In dogs we get gallbladder contraction and secretion of pancreatic enzymes at about 400 pgm. We have correlated these in dose response studies to intra-duodenally administered amino acids.

We have not done gastric function studies in these diabetic patients, but have studied other diabetic patients and have confirmed that, in general, diabetic patients show a slower pattern of gastric emptying and diminished gastric acid formation. Why they should have such a rapid rise in cholecystokinin is not at all clear. Duodenal ulcer patients of course have rapid gastric emptying. You would anticipate this liquid meal would get into the duodenum early and would cause release of cholecystokinin. Diabetic patients on the other hand tend to empty their stomachs slowly. All individuals empty liquids at a different rate than solids, as Keith Kelly has shown so many times. It may be that diabetics handle this liquid meal differently. We do not know that.

The next question was what is the half-life of a large cholecystokinin-39 or 39 amino acid form of cholecystokinin. I don't know.

I'm quite sure that we could extrapolate that endogenously, that is naturally released cholecystokinin will in all probability be a mixture of the various forms which have different rates of setting, physiologic mechanisms in the motion and also they have different susceptibility to catabolism.

The larger forms seem to be released more slowly, to be less biologically active, and to be more resistant to catabolism and they apparently function as sort of a reserve form.

No one has yet indicated that the larger forms of the molecules can be converted to the smaller forms in circulation, but they certainly must be converted in the mucosa.

Now, we have not been able to correlate some of these studies in dogs because of the peculiarity that we cannot secure the endogenous release of cholecystokinin in anesthetized animals, which, of course, frustrates any experiments we want to do acutely in dogs.

It's particularly strange since both secretin and gastrin and glucagon and calcitonin and almost any other polypeptide hormone is released at the same rate in the anesthetized animals as they are in asleep animals, yet with CCK, the release is blunted so that only about 10% of CCK—we only get about 10% release of CCK in animals that are asleep. That may have some particular significance about the mechanisms of release. They may be highly dependent upon exogenous innervation. We don't know that.