Discussion

Dr. Harry A. Oberhelman, Jr. (Palo Alto): We have also been interested in the problems of the metabolism or deactivation of gastrin over the past several years. Although my colleagues and I did not repeat the experiments in the liver in which Grossman and Gillespie had failed to show inactivation of gastrin, we, therefore, looked to other organs as possible deactivation sites. We know that the incidence of peptic ulcer is increased in certain pulmonary diseases and it has been shown that the lung can act as a metabolic organ and can inactivate such substances as histamine, serotonin and other agents.

Additionally, it has been observed that in the Zollinger-Ellison syndrome that gastrin has been recovered in the urine in some of these patients. We, therefore, looked to the lungs and the kidneys in two separate types of experiments to see whether gastrin was deactivated via these routes.

In rats, using the pyloric ligated stomach preparation with vagotomy, we found no significant changes in the gastric secretory output to varying doses of gastrin after nephrectomy. I am sure this does not, in itself, rule out the kidney as a possible site for deactivation but at least in this rat preparation we were unable to note any difference from the controls.

And similarly, in Heidenhain pouch animal preparations, we alternately infused human synthetic gastrin into the right and left atria through implanted catheters and again found no significant difference in the response to gastrin whether it was infused into the left or right atrium.

This study, I think, is one of the first bits of evidence that the liver may play a role in the inactivation of gastrin.

Dr. Edward R. Woodward (Gainesville): We have noticed in our studies with gastrin and with the synthetic pentapeptide that with a single intravenous injection the duration of effect seems to be the same. I wonder if Dr. Thompson has observed this same thing. One would think that perhaps the whole molecule would have a longer action. We have studied the effect on gastric motility; gastrin is a very strong stimulant of gastric motility but a single injection of either synthetic human gastrin or pentapeptide lasts only about 3 minutes.

Dr. Walter F. Ballinger (St. Louis): My associates at Washington University have been interested in the physiology of gastrin for some time since the pioneering work of Dr. McGuigan in developing an immuno-assay technic for its measurement, and they reviewed with me the abstract with great interest when it appeared in the program of the American Surgical Association.

We had three questions to ask Dr. Thompson. The first question asked by Drs. McGuigan, Jaffe, and Newton, I think, has been resolved by Dr. Thompson since the submission of the abstract, since the data show now approximately the same loss of secretory potency upon intraportal injection of gastrin as the supposed loss of measured gastrin following hepatic transfer, that is approximately 50 per cent.

We had two other questions, however, that Dr. Thompson could help us with. First, we believe that Dr. Thompson is talking about loss or dilution of gastrin rather than inactivation of gastrin. We know that inulin is lost very slowly in its passage across the liver or through any other vascular space for that matter, but that gastrin diffuses rather rapidly from any vascular space in the body, including the liver. So perhaps Dr. Thompson has measured dilution or loss of gastrin but not inactivation by this technic.

Secondly, Dr. Grossman in California, with some rather neat experiments which he has recently reconfirmed, using physiologic amounts of gastrin has demonstrated no loss of acid secretory activity of gastrin as it crosses the liver. *In vivo* studies in our laboratory measuring endogenous gastrin in portal and hepatic venous blood by radio-immuno assay showed no definite hepatic inactivation of gastrin. So I wonder whether perhaps pharmacologic rather than physiologic doses of gastrin were used in this experiment as opposed to experiments where endogenous gastrin was stimulated by acetyl choline infusion of the antrum. Perhaps Dr. Thompson could clarify this for us.

President Wangensteen: Dr. Thompson asked me if I would say a word. Some of this technology is a little sophisticated for my orientation.

I would like to comment, however, on the shift of emphasis that is occurring in the surgical literature with reference to vagal influence on secretion and now the gastrin influence.

The influence of vagus, the involuntary nervous system upon gastric secretion, goes back to Schiff (1867) indicated that division of the vagi beneath the diaphragm was well tolerated. Pavlov, a pupil of Heidenhain, developed the innervated isolated gastric pouch, that gave emphasis to the role in gastric secretion, a role that the strides of our own Lester Dragstedt has emphasized.

In 1920 or thereabouts, Dr. Ivy said that if any gastrin exists, it is histamine. The inactivation of histamine by the liver, which Dr. Thompson showed in his slides, Milo Loucks and I observed in 1928 (Arch. Surg., V. 16, p. 1089), finding that the liver detoxified histamine; histamine tolerance was considerably less than when histamine traversed the portal vein. The order of disparity is quite significant, at least as great as Dr. Thompson showed us today.

It is interesting that physiologists for a long time were unable to prove the existence of gastrin. It remained for a surgeon to do this, none other than Sir Henegage Ogilvie. You may remember that he indicated in 1936 (Edinb. Med. J., V. 43, p. 61), concerning a group of cases in which he

suggested there was no observable difference whether a small segment of the antrum is excluded or not.

By 1939 (Lancet, V. 2, p. 295) Ogilvie had changed his mind, finding a telling disparity of neostomal ulcer in patients with the excluded antral segment. The initial suggestion of an antral gastric hormone had been made by Edkins in 1906 (J. Physiol., V. 34, p. 133), and reaffirmed again in the same journal (V. 38, 263, 1908) together with his wife Tweedy. Recently gastrin has come to occupy the attention of physiologists and surgeons.

I would like to make a brief comment on the Maki paper. I am quite willing, Sir, to withdraw the name glorified segmental resection and substitute rightfully in its place the proper name, the Maki gastrectomy.

Dr. Goodale (1968) in my laboratory has made some interesting studies on the Heidenhain pouch, employing the Maki procedure, leaving just a short cuff about a centimeter to a centimeter and a half in length of antral mucosa. Many of you will recall that Drs. Woodward and Bigelow and Dr. Dragstedt first showed, back in 1950, if I remember correctly (*Archives of Physiology,* V. 162, p. 99), that complete excision of the antral mucosa reduced secretion from Heidenhain pouches about 86 per cent. 90 per cent? Is that a new figure Dr. Woodward?

Well, Lester Dragstedt, the second, has published in *Archives of Surgery* last summer; as I remember his observations suggested that acid secretion from Heidenhain pouches was reduced 60 per cent by antral excision. This figure is approximately the same that Dr. Goodale observed employing the Maki operation. Moreover, Goodale (Arch. Surg., In Press) has shown the Maki operation, subtotal excision of the antrum, leaving a short prepyloric segment accompanied by 50 per cent excision of the acid-peptic secreting area, provides protection against the neostomal ulcer attending the Henley-Silverman loop.

It may well be that the Maki operation may come to have a vogue in difficult duodenal ulcers. Time will tell. It has not yet had a clinical trial, at least at our hands. Dr. Goodale's findings suggest that the Maki operation deserves trial not only for gastric but also for duodenal ulcer.

DR. J. C. THOMPSON (Closing): In regard to the points brought up by Dr. Harry Oberhelman, we have studied the effect of transit of secretory stimulants through the lung and we have been surprised to find that we have found some decreases in the concentration of histamine and gastrin itself, on pulmonary transit. These studies are preliminary and we well be able, hopefully, to report them later.

Addressing Dr. Woodward's question about the duration of action. We have been surprised also by the very brisk secretory response to gastrin as well as the very rapid deterioration of this action, suggesting that there is some very potent inactivating mechanism available.

Dr. Ballinger has brought up some extremely important questions, some of which are covered in our discussion in the manuscript.

There are certain problems in this experiment. One of them is that we had to use different concentrations of agents in the secretory experiments as compared to the studies in which we measured the concentrations of agents.

In the secretory studies, we used standard physiologic doses. Histamine, 24 micrograms per kilo per hour; synthetic pentagastrin was administered at the rate of 5 micrograms per kilo per hour and gastrin was injected at the rate of 1.25 micrograms/Kg./hr. These are in our laboratories about half maximal doses for Heindenhain pouch secretion.

The amounts used, however, in the studies on the chemical determination of the concentrations of these agents are quite different, since these technics are not sufficiently sensitive to pick up physiologic levels. The fact that the results in the two studies came out the same, I look upon as a great coincidence. I think it's lucky; it looks very nice, but I don't think it has any great significance.

The question of the semantic approach to the problem of loss, inactivation, sequestration or storage is one, Dr. Ballinger, that has troubled me and all of my associates. My residents have badgered me about using the term, "inactivation," and they will be gleeful that you jumped on it. I don't know what the proper term is. Perhaps "loss," or "sequestration," or "storage" is a better term.

As for the question of the failure of previous investigators to show loss of gastrin on hepatic transit, I believe that all published works have dealt either with crude hog gastrin or with partially purified gastrin. Lick, who worked with partially purified gastrin, suggested that the impurities in partially purified gastrin might block its inactivation.

Lastly, Dr. Wangensteen, you called attention to an interesting shift in emphasis from the vagus to gastrin. I think that medicine is so dependent upon work in parallel fields that we emphasize those things we know something about.

There is a story about a drunk who was found looking for a wallet under a street lamp by a policeman and the policeman asked him what he was doing and he said that he was looking for his lost wallet. The policeman asked, "Well, where did you lose it?" The man said he lost it across the street, over there in the dark. And the policeman said, "What are you doing here, why are you looking for it here?" And the man said, "Because the light's a lot better here."

Actually, that's the way we do a lot of our research. We study things where the light is good and right now the light is fairly good on gastrin so that's what we are working on.