Some Recent Advances in the Physiology of the Alimentary Tract*

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IT is obviously impossible in a fifteen-minute presentation to present even a bird's-eye view of the recent advances in the physiology of the alimentary tract. The number of physiologists and clinicians contributing to this field has increased remarkably in the past fifteen years. Prior to that time it was rare to have more than ten papers in the field presented at the meetings of the American Physiological Society. At the recent meetings of this Society in Chicago some sixty papers dealing with the alimentary tract were presented, the majority of which were important contributions and worthy of citation on this occasion.

THE GASTRO-INTESTINAL AUTACOIDS

Since this morning we shall have presented a series of papers dealing with substances present in the mucosa of the upper intestine and the urine which affect gastric activities, it is appropriate to review in outline form the present status of the problem of the gastro-intestinal hormones. It will be observed that the alimentary tract ranks close to the anterior lobe of the hypophysis in regard to the number of active principles it is supposed to elaborate.

The existence of three gastro-intestinal autacoids or hormones can be considered to be well established by physiological evidence which has been adequately confirmed. These are *secretin*, *cholecystokinin*, and *enterogastrone*. In regard to enterogastrone, which inhibits gastric secretion and motility (1), it is problematic whether only one substance is concerned, or whether two substances are concerned, one which inhibits secretion and another which inhibits motility. If enterogastrone does consist of two substances, both at present appear to be closely related chemically.

The diagnostic or therapeutic usefulness of these three autacoids has not been established. Evidence is accumulating which at present indicates that *secretin* may prove to be useful as a test of the exocrine function of the pancreas (2). It appears that secretin will be as valuable in determining the capacity of the pancreas to secrete, as histamine is in determining the capacity of the stomach to secrete. Though there is little evidence available at present, it is reasonable to hope that *cholecystokinin* may be useful in diagnosing categorically the presence of biliary dyskinesia. At least, when it becomes available in quantity for intravenous injection into man, we shall then have a constant and potent excitant of the gall bladder musculature. It may even be possible to differentiate between the alleged hyperkinetic and atonic types of dyskinesia. Since *enterogastrone* inhibits the gastric secretory response to histamine, which atropine does not do effectively, it should be useful in controlling the hypercontinuous secretion of the stomach which occurs in a number of patients, particularly with duodenal ulcer, who at present are rather difficult to manage. This possibility is supported by the recent observation that the injection of enterogastrone three times daily into Mann-Williamson dogs has a marked prophylactic value in the prevention of the post-operative ulcer that so uniformly occurs in untreated animals (3).

There are two other gastro-intestinal hormones, the existence of which appears to have been established by physiological methods. Their existence cannot be considered as definitely established, since further study and confirmation is required. One of these is *gastrin*, and the other is *enterocrinin*. Though histamine may be extracted from the gastric mucosa in crystalline form (4), it does not follow that gastrin is histamine. Recent evidence indicates that alcohol applied to the gastric mucosa liberates histamine (5), but the application of the secretagogues in liver or meat extract does not. Enterocrinin is a hormone elaborated by the intestinal mucosa which stimulates the secretion of succus entericus (6).

The usefulness of histamine is generally recognized. If a gastrin other than histamine should be found, it would represent perhaps a more physiological way of testing the capacity of the gastric glands to secrete. The possible usefulness of enterocrinin is even more conjectural; however, its existence is of considerable scientific interest.

Two other hormones have been claimed to be produced by the intestinal mucosa. They are *villikinin*, which stimulates the movements of the villi (7), and *enterocin*, which stimulates the movements of the intestine. That these hormones represent specific substances has not been established. For example, these motor excitants may be nothing more than cholecystokinin, or some non-specific substance present in extracts of intestinal mucosa (8). Even the existence of enterocin is very doubtful in my opinion. However, investigators should not overlook them in their efforts to advance medical science. It may be conjectured that villikinin may in part be the solution to the problem of celiac disease and of idiopathic steatorrhea, since the movements of the villi play a role in absorption, and that enterocin may be of value in paralytic ileus.

Duodenin, incretin or *insuloptropic hormone* are terms applied to a substance or substances supposed to be present in intestinal mucosa, and to play a role in providing for the deposition or utilization of the sugar that is absorbed from the intestine. In other words, this hormone is supposed to assist in the regulation of the blood sugar level. One view holds that duodenin is elaborated when sugar or acid gastric juice is present in the intestine and stimulates the islets of Langerhans to secrete insulin. Practically

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all the evidence, on which the existence of this hormone has been claimed to exist, has been seriously challenged (9). Nevertheless, the possibility that the intestinal mucosa produces an "insulin-synergist or adjuvant" has not been excluded.

Parasympathin and *sympathin,* which are produced by visceral motor nerve endings, are not specific to the visceral motor nerve endings of the alimentary tract. It has been found, for example, that the distension of the colon will inhibit the movements of a denervated loop of bowel (10). This suggested that the distension of the colon caused sympathin to be released by the sympathetic nerve endings. The released sympathin, on being carried to the denervated loop by the blood stream, caused inhibition of motor activity. The possibility of sympathin being involved has to be considered when any condition causing inhibition of motility or secretion is observed.

Referring again to enterogastrone, one should not obtain the idea that enterogastrone is the only mechanism by which *the upper intestine regulates the rate of evacuation of the stomach.* The intestine possesses two general means of preventing too rapid evacuation of the stomach. One is enterogastrone, or a humoral mechanism, which operates in the case of fats and sugar; the other is nervous, which operates via the enterogastric reflex in the case of acid, peptones, and distension (11). In addition, one must not forget the myenteric plexus, and in the case of noxious stimuli, the splanchnic nerves.

THE METABOLISM OF THE GASTRO-INTESTINAL HORMONES

The problem of the metabolism of the gastro-intestinal hormones is a relatively new field of investigation.

The gastro-intestinal hormones must be metabolized; if they were not metabolized, they would accumulate in the body and produce disastrous results. To prevent their accumulation, the hormones must either (a) be excreted in the secretion, or (b) in the urine, or (c) be used up in the chemical process of the formation of the secretion, or (d) be destroyed by an enzyme.

The possibility of the excretion of enterogastrone in the urine will be considered in the symposium this morning. A substance has been found in human and canine urine which inhibits gastric secretion markedly, and gastric motility slightly (12). This has been referred to as "urogastrone," since its source is unknown. It would appear that the urine may contain more than one substance which directly or indirectly inhibits the secretion of gastric and also of pancreatic juice (13). It also appears that the urine contains a substance which prevents the development of experimental jejunal ulcer (14).

More recently our laboratory has directed attention to the metabolism of secretin. Not being able to find secretin in the urine, we attempted to ascertain whether it is destroyed by the blood or the tissues. It was found that the blood plasma of human and canine subjects contains a substance of the nature of an enzyme which inactivates secretin. This enzyme has been referred to as *secretinase* (15). To what extent variations in the secretinase activity of the plasma varies in health and disease remains to be determined.

It should be emphasized that the investigation of the autacoids of the gastro-intestinal tract is beset with difficulties. It is easy to think wishfully in this field, but it is difficult to devise crucial experiments, to set up adequate control experiments, to assay active products, to differentiate between specific and non-specific effects, and to visualize and to examine all of the possibilities that may be concerned in the causation of a response. The chemical purification and isolation of the active principles is especially difficult in the case of the gastro-intestinal hormones, because they are relatively unstable or easily inactivated. This is unlike the sex hormones which are relatively stable and easily extracted. This is mentioned to indicate that the clinician must expect a considerable period of time to elapse between the discovery and clinical application of these active principles. For example, the concept of internal secretions was first definitely introduced by Claude Bernard about the middle of the last century. It was not until 1890 that Von Mering and Minkowski demonstrated that the pancreas produced an internal secretion. Insulin was rendered available for clinical use in 1923 and crystallized in 1926. Thus, a third of a century elapsed between the physiological demonstration of the possible existence of insulin and its clinical application. The same is true of secretin. It was discovered in 1902 (16), at which time the word hormone was coined and a clear-cut proof for the existence of a hormone was first provided. Secretin was used on human subjects and crystallized only a few years ago (17). Hence, we must not be too impatient regarding the clinical application of the gastro-intestinal hormones.

An analogy exists between the initial discovery of a hormone and its concrete application in practice and the appreciation of the need and merit of a medical specialty and the general recognition of that need and merit by the medical profession. It should be appropriate in concluding this Address, as it is in all Presidential Addresses, to make a few remarks regarding the past, present, and future of our Association.

The object of our Association is "to study the normal and abnormal conditions of the digestive organs and problems connected with metabolism, and to conduct scientific research and investigation related to or connected with the digestive organs and the problems connected with metabolism."

Our Association was founded in 1897. By 1904 it had shown but little growth. Dr. S. J. Meltzer, who was at that time president of the Association and one of the leaders in medicine and physiology in our country, ascribed the retarded growth to two factors:

First, the formation of a specialty of gastro-enterology was not favored by many physicians because the diagnosis and treatment of diseases of the digestive tract was an essential part of the activities of the general practitioner. However, such opposition has been counteracted to a large extent by the remarkable progress that has occurred in the last half century in the science and practice of gastro-enterology. This has been recently recognized in a concrete manner by the American Board of Internal Medicine which has recognized gastro-enterology as one of four specialties for certification. The other three special-

ties that have been so recognized are tuberculosis, allergy and cardiovascular disease. The first examination for certification of such specialties was held recently in Boston.

This accomplishment represents a definite milestone in the history of our Association and much credit is due Doctor Andresen and his associates for devoting much time, energy and wisdom toward this meritorious cause. It should be emphasized, however, that the gastro-enterologist must first be qualified and certified as an internist, just as the gastro-intestinal physiologist must first be a physiologist.

In addition, during the past eighteen months, our Association, through the efforts and wisdom of Dr. John L. Kantor, Chairman of our Committee on Military Preparedness, has helped define and mold the status of gastro-enterology in the Medical Department of the United States Army. This represents probably the first official recognition, chronologically, of our specialty.

The second factor that retarded the early growth of our Association was that many practitioners, without adequate training, had pronounced themselves "stomach specialists," a movement which discredited gastro-enterology as a specialty. Since history is prone to repeat itself, this factor constantly challenges us and will continue to do so in the future.

How was this challenge met in 1904? It was not met by lowering the standards of admission to membership so that anyone who called himself a "stomach specialist" could join the Association. It was met by dispelling distrust in the appellation, "gastro-enterologist." Such distrust was dispelled by attracting men and women whose solid work and true interest in the field bore witness to their basic desire to contribute to the progress and welfare of gastro-enterology. That such distrust has been dispelled to a large extent by members of our Association has been attested by recent events.

Nevertheless, we should recognize that interest in gastro-enterology is growing, the number of solid contributions is increasing, the number of well-trained young physicians entering the field is enlarging, and the increase in nominations for membership in our Association is considerable. The Governing Board of your Association is cognizant of these facts. To insure a healthy growth of high quality, a committee under the chairmanship of Dr. Victor Myers has been making a study. Among various items studied, they have made a survey of the United States and Canada to ascertain the number and distribution of pure scientists and physicians whose prime field of interest in research and practice is gastro-enterology. The problem is to steer a clear course between the Charybdis of mediocrity and the Scylla of a mutual admiration society, to continue to select a membership that will maintain the ideals of the Association and command the respect of our colleagues in medical science and practice.

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Enterogastrone—Significant Steps in Development of the Present Conceptions*

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EWALD and Boas, 1886 — observed that olive oil added to starch paste inhibited gastric secretion and delayed evacuation. This observation initiated countless investigations designed to confirm, expand and explain this phenomenon.. "It was the face which launched a thousand ships." Some of the ships were captioned by the masters of g.i. physiology—Pavlov, Cannon, Carlson, Ivy, but lesser sailors have also left port on the same mission.

Eight years later Khizhim reported that the output of acid by the stomach was decreased if fat was added to a meal. In 1896, Lobosov noted under similar conditions, a decrease in pepsin output. Kasanki, 1903, found that fat inhibited the psychic secretion of gastric juice and it has subsequently been shown that the inhibition is sufficiently effective to depress the stimulatory effect of sham feeding, histamine or insulin administration. The evidence up to this time was interpreted as showing that fats exerted their inhibition *while in the stomach.*

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