CHEMICAL MESSENGERS—A SPECIAL CONSIDERATION

Those Known to Play a Direct Rôle in Digestion

BY

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In the realm of physics we may look upon heat, light, sound, and electricity as *physical messengers.* They may be produced at a certain point and through the agency of an appropriate transmitting medium may be conducted to a distant point to produce an effect. In the realm of biology, we know that a specialized group of cells may produce a specific organic substance that is transmitted by the blood or lymph to distant cell groups or organs to produce a specific reaction in them. Biologists refer to this group of substances as *chemical messengers.* Technically they are referred to as internal secretions or autocoids (self-remedy). The glands or group of cells that form them are called glands of internal secretion or endocrine glands (separate within). If the autocoid or internal secretion has a stimulating action, it is called a hormone (to excite). If it has a depressing action, it is called a chalone (to inhibit).

This biological concept is not old. The expression "internal secretion" was first used by Claude Bernard in 1857. He used the term to describe the sugar which is passed into the blood by the liver cells, although now we use the term in a more restricted sense. Brown-Sequard in 1889 was the first scientist to test out and to give an impetus to the idea that a chemical messenger might be stored in a tissue and hence might be extractable and available as a therapeutic agent. In the same year V. Mering and Minkowski found that extirpation of the pancreas would result in experimental diabetes and were the first to excite the interest of physiologists in extirpation experiments, although Schiff in 1884 had described convulsive seizures following removal of the parathyroid glands and Brown-Sequard had attempted to extirpate the adrenals in 1856. Although much pioneer work had been done prior to the year 1902, it was not until this date that the terms chemical messenger (1902) and hormone (Starling, 1906) were coined by Bayliss and Starling.

The exact mechanism by which the chemical messengers or autocoids act is not known. But it is known that they regulate and govern

not only many different types of physiological activity but also morphological development. Some play a vital rôle; others do not.

As our information in regard to the endocrine glands increases, it becomes more evident that the number of active principles or internal secretions is greater than was formerly suspected and that an interrelation exists between them.

I shall list the effects of the anterior lobe of the hypophysis as an example of the diverse action that some of these glands have. Experiments on animals have shown that the anterior lobe has the following distinct effects: (1) stimulation of growth, (2) stimulation of gonad development and ripening of ovarian follicles, (3) stimulation of the lutein cells, which prevents ovulation, (4) stimulation of metabolism by increasing the specific dynamic action of foods, (5) stimulation of the thyroid, prevents thyroid atrophy, (6) stimulation of lactation, (7) initiation of the bleeding of menstruation.

Through the use of chemical methods and procedures, a number of these autocoids are now available for therapeutic purposes. Thyroxin, the active principle of the thyroid, and epinephrine, the active principle of the medulla of the adrenals have been crystalized and synthesized. Insulin, the active principle of the islet cells of the pancreas, and estrin, the active principle of the follicular fluid of the ovaries, have been crystalized. Oxytocin and vaso-pressin of the post-lobe of the hypophysis, parathormone of the parathyroids, emmenin of the placenta, prolan of the anterior lobe, cortin of the adrenal cortex, gastrin, secretin and cholecystokinin, the hormones of the gastro-intestinal tract, and possibly others have been sufficiently "purified" to use in man and animals without producing marked toxic reactions.

The author and his colleagues have been primarily interested in the physiological proof of the existence of hormones related to the activity of the digestive organs and the chemical isolation of these hormones.

In order to prove the existence of a hormone, it is not sufficient to show that an extract of a certain tissue yields a principle which has certain pharmacological actions. One of the other required points of evidence is that it must be shown that the active principle actually gets into the blood or lymph under physiological conditions in sufficient amounts to produce an effect. For this purpose a number of methods are available. The methods which have served us effectively in our work in demonstrating the existence of hormones which excite the digestive organs, are (1) the method of cross-circulation and (2) the method of transplantation.

I shall tell you first of our work on gastrin, the hormone that is concerned in causing the gastric glands to secrete.

A number of years ago (1903) Edkins made an extract of the pyloric gastric mucosa which when injected into cats or dogs stimulated gastric secretion. He called the active principle gastrin. Subsequently a number of workers showed that such an active principle could be extracted from a number of other tissues and even plants, a fact that was interpreted as discrediting the gastrin theory of Edkins. However, several years ago, Ivy and Farrell transplanted a small pouch of the stomach subcutaneously and found that when the animal was fed, the transplanted gastric pouch secreted acid gastric juice. This observation which has been confirmed by others shows that when the animal eats, something enters the blood which excites the gastric glands. This something may be either the hormone gastrin or substances which the physiologist calls secretagogues and which are present in food or result from the digestion of food. Quite recently, however, Ivy and Kim have shown that a solution containing potent secretagogues may be injected intravenously at a timed rate without exciting gastric secretion. This we believe proves that the active principle circulating in the blood after eating is the hormone gastrin. Further, we (Sacks, Burgess, Ivy and Vandolah) have been working on the chemistry of gastrin and believe that it is histamine. This is a significant and pertinent statement, because some have thought that the "gastrin effect" was due to histamine, a non-specific substance. Our experiments indicate that histamine has a specific relation to gastro-intestinal physiology.

Bayliss and Starling coined the word *chemical messenger* and later Starling created the word *hormone,* as a result of their discovery of secretin. Secretin is a hormone that is produced by the mucosa of the upper intestine and on being carried to the pancreas by the blood causes it to secrete pancreatic juice. Bayliss and Starling found (1) that dilute acid applied to the duodenum caused the pancreas to secrete even after they had attempted to sever its nerve supply, and (2) that extracts of the duodenal mucosa when injected would cause the pancreas to secrete. They advanced what is known in the texts as the "secretin theory" of pancreatic secretion. Subsequently this theory was argued pro and con by experimentors. Several years ago, Ivy, Farrell, and Lueth transplanted the tail or a portion of the pancreas subcutaneously and found that when the animal ingested a meal the pancreatic transplant was stimulated to secrete. They then transplanted two loops of small intestine (jejunum) under the skin in an animal with a pancreatic transplant and found that the application of dilute hydrochloric acid or gastric juice to the transplanted intestine caused

the transplanted pancreas to secrete. This procedure ruled out a secretagogue action, inasmuch as acid intravenously was ineffective, and showed that a hormone was elaborated when the acid came into contact with the intestinal mucosa. Further, it has been shown that when the blood of a fed animal is vivi-dialyzed, an excitant of pancreatic secretion is obtained in the dialysate (Lim and Necheles). We have shown recently that the "specific pancreatic secretin" of duodenal mucosa is not present in other tissues, and have been able to concentrate secretin so that 0.1 milligram injected intravenously will cause the pancreas to secrete.

We (Ivy and Oldberg) next directed our attention to the gall bladder. We were impressed by the facts (1) that fat stimulated the pancreas to secrete, (2) that fat caused the gall bladder to evacuate, and (3) that bile played an important rôle in the digestion and absorption of fat. The correlation of these facts suggested that fatty acids caused secretin to be formed as was already known, and that the secretin formed not only caused the pancreas to secrete but also caused the gall bladder to contract. We tested out this theory and found that the gall bladder is caused to contract and evacuate by a hormone closely related to secretin, but as we now believe, not identical with it. We have named this hormone cholecystokinin.

We have shown that when the gall bladder is connected to an apparatus for recording intra-gall bladder pressure, an injection of cholecystokinin will cause the gall bladder to contract, increasing the pressure from 1 to 11 centimeters of bile pressure. When several injections are made at ten minute intervals, the pressure within the gall bladder may rise as high as 26 centimeters of bile pressure. It has also been shown that when the gall bladder is filled with an x-ray opaque material such as iodized oil, or is "visualized" with tetraiodophenolphthalein (Graham-Cole), an injection of cholecystokinin at ten minute intervals will cause evacuation of the gall bladder. By cross-circulating two dogs (i. e., so that the blood of one dog mixed with the blood of the other) it was found that the introduction of dilute acid into the duodenum of one dog caused this dog's gall bladder to contract within two minutes and the gall bladder of the other to contract from six to ten minutes later. Finally, we have been able to concentrate or "purify" cholecystokinin to the extent that 1 milligram of the dry powder will cause a contration of the gall bladder. Cholecystokinin is effective in man, but no more effective than egg-yolk and cream taken by mouth.