The Physiologic Basis of GASTROINTESTINAL THERAPY

SELECTED TOPICS

Heinrich Necheles and Martin M. Kirshen

The Physiologic Basis of GASTROINTESTINAL THERAPY

SELECTED TOPICS

Heinrich Necheles, M.D., Ph.D., F.A.C.P.

Director, Department of Gastro-Intestinal Research, Medical Research Institute of Michael Reese Hospital; Attending Physician, Michael Reese Hospital; Professorial Lecturer in Physiology, University of Chicago, Chicago, Illinois

and

Martin M. Kirshen, M.D., F.A.C.P.

Professor of Clinical Medicine, Chicago Medical School; Attending Physician, Mount Sinai Hospital; Senior Attending Physician, Michael Reese Hospital, Chicago, Illinois

GRUNE & STRATTON 1957

NEW YORK LONDON

Library of Congress Catalog Card No. 57-9624

Printed in U.S.A.

Preface

IN OUR TEACHING of undergraduate and postgraduate students for the last 25 years, we have noticed a great interest in gastroenterology on the one hand and a lack of certain specific types of information in basic and applied physiology on the other. In our experience, the teaching of gastrointestinal physiology seems to be too cursory and inadequate in many aspects to be sufficient for the understanding of the disturbances of normal processes. We have tried, therefore, to fill these gaps with our lectures and at the same time not only to give students a review of the field of gastrointestinal physiology, but also to show the connections between general phenomena and those involved in gastroenterology. After all, gastrointestinal physiology is the application of general and special physiology to one particular field.

We have been encouraged in our work on this book by the desire of many of our students to have our lectures assembled in one volume. We cannot claim that we have touched every aspect of gastrointestinal physiology and of gastroenterology. We feel, however, that we have dealt with the most important chapters and that also we have given the students sufficient references for pursuing topics in which they may be more interested.

The physiology of intestinal motility, innervation and drug action is fundamental for the understanding as well as for the treatment of many gastrointestinal disturbances, and thus we have devoted a relatively large portion to these subjects. On the other hand, the liver offered a particular problem. This organ is presently dealt with in medical schools in the study not only of gastrointestinal physiology, but also of various other aspects of metabolism, endocrinology, etc. Yet, we find that this information is not well integrated in the minds of students and we have attempted, therefore, to unify this knowledge in one large chapter.

Our own interests in secretion, in the functions of the liver and of the pancreas, in peptic ulcer, as well as consti-

pation, diarrhea, and ulcerative colitis, may have swayed us to use relatively more space for these topics. We hope, however, that this personal approach will stimulate and interest the student of gastroenterology. On the whole, we have attempted to show the problems and also the gaps in our knowledge in order to stimulate thinking and further research in our field.

In the beginning of our work on the book we lost a faithful collaborator and friend, Dr. Frank Neuwelt, by a tragic death.

We want to express our gratitude to Miss Gladys Pritchard for her untiring help in the preparation of the manuscript and to Dr. Robert Kirshen for corrections.

The Authors

Contents

(Detailed contents will be found on the first page of each chapter.)

CHAPTER 1

Innervation

TRANSMISSION OF NERVE IMPULSES

Nerve impulses are conducted and transmitted to the effector cells by rapid chemical reactions and permeability changes in the membrane of the nerve fiber (depolarization), and by action currents, followed by restitution to the resting state (repolarization).

Impulses along most nerves of the body and across most synaptic connections apparently are effected by release of acetylcholine. Stimulation of the effector cells in the end organs by the postganglionic end fibers of the nerves is specific in the different nerve systems. Parasympathetic (cholinergic) impulses and impulses from motor nerves to striated muscles are transmitted by the acetylcholine mechanism, while most impulses to the effector cells of the sympathetic nerves involve the release of epinephrine or norepinephrine (adrenergic). There is some evidence that transmitter substances other than acetylcholine and the epinephrines exist (Dale, 1955; Hebb, 1957).

Cannon described two types of sympathetic transmitter substances, which he named excitatory sympathin E and inhibitory sympathin I. We know now that the adrenal medulla, sympathetic ganglia, and most sympathetic nerve endings produce nor-adrenaline (arterenol) and epinephrine, and that noradrenaline is the precursor of epinephrine. The effects of both these hormones vary in different species and in different areas

of the body, but generally nor-adrenaline has a predominantly vasoconstrictor effect, whereas epinephrine has predominantly central nervous and metabolic effects. It seems that both hormones are not purely excitatory agents and that epinephrine appears to be equal to, or even more active as excitatory agent than, nor-adrenaline (Krantz and Carr, 1951). Epinephrine stimulates salivary and possibly gastric secretion. According to Dale (1955), nor-adrenaline appears to be the prevalent transmitter of adrenergic impulses. Commercial adrenalin contains both factors. Both hormones produce variable relaxation of the smooth muscle of the gastrointestinal tract and contraction of the sphincters, and both contract the splanchnic blood vessels.

Not all sympathetic impulses are transmitted to the effector cells by the epinephrines; some are transmitted by acetylcholine, as in the sweat glands.

In order to obtain a more precise terminology, the names sympathetic and parasympathetic nerves and systems have been abandoned, and a new terminology for the characterization of the systems has been introduced, based on the chemical differences in terminal transmission. Nerves which transmit impulses to their effector cells by acetylcholine are termed cholinergic; those which use epinephrines are termed adrenergic. Drugs simulating the effects of the epinephrines are called adrenomimetic, and those simulating acetylcholine effects are called cholinomimetic drugs. Drugs which inhibit the adrenergic or cholinergic systems may act on ganglionic synapses or at the effector cell and are called, respectively, antiadrenergic or adrenolytic and anticholinergic or parasympatholytic.

Transmitter substances are contained in nerves, synapses and nerve endings, as preformed labile compounds (mother substances) which, upon arrival of a nerve impulse, dissociate rapidly. Conduction of impulses along most nerve fibers appears to be caused by an explosive liberation of acetylcholine, traveling along the nerve, similar to a trail of gunpowder ignited at one end.

Once the transmitter substances have been liberated and have achieved the purpose of stimulation, they must be de-

stroyed in order to prevent accumulation, continuously increasing excitation and final paralysis of the effector cells. Acetylcholine is destroyed by acetylcholine esterase, an enzyme present in high concentrations in most nerve sheaths, nerve fibers, at the endings in cholinergic neurones and also in the blood. The epinephrines are destroyed by phenoloxidase.

It is evident, therefore, that a diminished production of acetylcholine or an increased activity of acetylcholine esterase will lead to diminution of tone and contraction of smooth and striated muscle and to a diminished secretory activity. Conversely, increased formation of acetylcholine or diminished activity of acetylcholine esterase will lead to greater and more prolonged muscular contraction and glandular secretion. A similar mechanism probably acts in the adrenergic system. Poisoning or inactivation of the end plates of cholinergic or adrenergic nerves has the same effect as diminished production of acetylcholine or epinephrines or increased activity of the enzymes destroying them, and such mechanism is suspected to exist at the cholinergic innervation of striated muscle in myasthenia gravis. Nerve impulses can be blocked in the central nervous system, at the ganglionic synapse (e.g., stellate ganglion, celiac plexus, etc.), in the course of the nerves, and at the nerve endings.

The precursors of the transmitter substances must be resynthesized after they are broken down, and it appears that acetylcholine is synthesized by the enzyme choline-acetylase, and the epinephrines by an esterase.

Acetylcholine is so rapidly destroyed by the esterase that it cannot be detected in the circulating blood, while the epinephrines are destroyed at a slower rate and, therefore, can be found in the blood. The body seems to be additionally protected against excessive accumulation of acetylcholine and epinephrines through mechanisms by which these substances are able by themselves to inhibit their further liberation (Marrazzi and Marrazzi, 1947).

The cholinergic and adrenergic nerves constitute the two main divisions of what is called the vegetative, autonomic, or involuntary nervous system, with their craniosacral and thoracicolumbar outflows. The cholinergic fibers originate in gan-

glion cells situated at three different levels of the central nervous system: midbrain, medulla, and the sacral spinal cord; the adrenergic fibers originate in cells in the midbrain and the thoracic and lumbar sections of the cord.

Through its widespread activities, the autonomic nervous system plays an important role in the homeostasis of different body functions and the regulation and stability of the internal environment. In addition, it has a dominant influence upon the hypothalamus and upon the master gland of most of the hormonal integration of the living organism, the pituitary, and possibly directly affects other endocrine glands.

The activities of the two divisions of the autonomic nervous system have certain characteristics which led physiologists years ago to speak of the adrenergic nerves as having catabolic functions and of cholinergic nerve function as being of anabolic nature. The teachings of Claude Bernard, Cannon, and Selye seem to support this assumption.

The two systems are anatomically different in two important respects: Adrenergic nerves are more ubiquitous than cholinergic nerves, and the terminal ganglion cells of the cholinergic nerves are near or within the effector organs, while those of the adrenergic nerves are located more distantly. Therefore, the preganglionic fibers of the adrenergic nerves are short and the postganglionic ones are long, whereas the opposite is true of the cholinergic system.

INTRINSIC NERVES

The gastrointestinal tract is innervated by intrinsic (intramural) cholinergic plexuses and by the extrinsic adrenergic and cholinergic nerves.

The functions of the extrinsic nerves consist in coordination of the activities of the different parts of the gastrointestinal tract among themselves, with other organs, and with the central nervous system. Additional integration is provided for by hormones, by the composition and circulation of the blood, etc. (Thomas, 1955).

The intrinsic plexuses are the purveyors of impulses brought to them by the cholinergic nerves and of impulses originating within themselves; by these latter impulses they

are able to coordinate by local reflexes peristaltic activity and tone in limited areas. The contraction of the gut above and the relaxation below a bolus are caused by such a local reflex (Bayliss and Starling's "law of the intestine" or "myenteric" reflex), and the receptors for this reflex can be paralyzed by local application of surface anesthetic drugs to the mucosa. This latter observation is being utilized in the therapy of functional local spasms.

The intrinsic plexuses are divided into subserous, intramuscular (Auerbach's) and submucous (Meissner's) plexuses; they are not, however, separate structures but linked together by connecting nerve fibers. Genetically, the intrinsic nerve plexuses probably represent the primitive nervous system, and their destruction or degeneration may be more serious than the loss of the extrinsic cholinergic nerve supply.

EXTRINSIC NERVES

The cholinergic nerves entering the gastrointestinal tract form synaptic connections with the ganglion cells of the plexuses and exert their effect by activating the ganglion nets. Local reflexes in the plexuses may be sensitized or increased by subthreshold vagal impulses (Thomas, 1953, 1955). The adrenergic nerves do not seem to enter into similar synaptic contacts with the plexuses, but run directly to the cells which they innervate. Therefore, adrenergic transmission of impulses is less vulnerable than transmission of cholinergic ones, which can be abolished by damage to the intrinsic plexuses.

It is generally believed that cholinergic impulses contract the smooth muscles of the gastrointestinal tract and adrenergic impulses relax them, while the opposite occurs with the sphincters, which are supposed to be relaxed by cholinergic impulses and contracted by adrenergic ones. However, this is not a strict rule, and the reverse may occur, depending upon the tone of the stimulated muscle. Stimulation of the left splanchnic nerve may contract a relaxed stomach, vagus stimulation may relax a contracted stomach, while conversely, adrenergic impulses may relax contracted sphincters, and cholinergic impulses may contract relaxed sphincters. These facts demonstrate that nerve impulses by themselves are not specific. Their effects are deter-

mined by their point of origin and by the character and condition of the cell which they innervate, which explains a number of apparently paradoxical reactions of the musculature of the alimentary tract to stimulation and to drugs.

Generally, cholinergic impulses contract the smooth muscle of the gastrointestinal tract, and adrenergic impulses relax it. In the case of the sphincters, generally adrenergic impulses produce contraction, and cholinergic impulses produce relaxation.

AUTONOMIC IMBALANCE

The cholinergic and adrenergic systems have been assumed to maintain normal autonomic functions by a fixed balance of their activities, and it was believed that a disturbance of this balance might produce malfunction or disease. However, the two systems are not always opposed to each other in their effects, but often operate in the same direction. Each system can be affected by factors within itself, and factors outside the two systems can affect each of them separately or both at the same time. It has been therefore proposed to replace the term "autonomic imbalance" by "autonomic dyssynergia," indicating lack of normal cooperation between the two systems, but not assuming antagonism or a fixed imbalance.

SENSORY AND AFFERENT NERVES, PAIN

Somatic pain induces a so-called defense reaction, consisting of an increased output of epinephrine, associated with cardiac acceleration, increase of blood pressure, and vasoconstriction. Visceral pain, on the other hand, has almost exactly opposite effects; it decreases heart rate and blood pressure, produces nausea and vomiting, with an attempt to withdraw to safety (Corbin, 1956).

Individual susceptibility to pain varies. According to Libman (1934), some 20 per cent of the population is hyposensitive for deep pressure pain, and this seems to apply to visceral as well as to skeletal sensation.

Sensory receptors have not been definitely demonstrated in the wall or in the mucosa of the intestine, but they must exist, because strong contraction or distention of the wall of

the gut elicits pain. Reflex and pain receptors can be paralyzed temporarily by surface anesthetic drugs.

Afferent fibers from the gastrointestinal tract are present in both autonomic systems; cholinergic afferent fibers conduct reflex impulses in the main and only a few or no sensory impulses. Almost all sensory fibers from the abdominal organs pass through the splanchnic nerves and, therefore, splanchnic anesthesia may be of value in abdominal operations. Vagotomy does not abolish the gastrointestinal distention reflex, pain, or hunger.

In unanesthetized patients, cutting, application of cold or heat, or cauterization of stomach and intestine do not produce pain. Adequate stimuli for pain production in the gastrointestinal tract are strong contractions, pressure and distention, particularly in areas of ulceration and inflammation. Injection of isotonic saline solution into the submucosa may produce pain. The epigastric pain present in duodenal ulcer seems to correlate better with forceful contractions and spasms of the stomach, pylorus, and probably duodenum than with the degree of gastric acidity. Palmer's hydrochloric acid test for the diagnosis of active peptic ulcer has not been confirmed by others (Meyer, Fetter et al., 1932).

Gastrointestinal pain may often be caused by local edema and ischemia, as, for example, in chronic peptic ulcers surrounded by areas of inflammation and congestion. The benefits of food, atropine, atropine-like drugs, and alkalis (e.g., bicarbonates) may rather be the abolition of spasms, vigorous contractions, increased tone, or antiperistalsis of stomach and duodenum, than their effects on gastric acidity and pepsin. Abolition of spasm may well enhance blood and lymph circulation in the ulcer area and thus diminish hypoxemia and edema, in this way relieving pain. Sodium bicarbonate and oil of peppermint may act beneficially by speeding up gastric emptying (Meyer, Arens et al., 1935; Necheles, 1953).

We do not believe that ulcer pain is mainly caused by excess acidity in the stomach or duodenum. We have seen a patient with gastric ulcer in whom anacidity was present during a prolonged period of time, and in whom a number of stimuli, including a double histamine test, failed to provoke

acid secretion. Despite this anacidity, chronic ulcer pain was present and was abolished by baking soda (Greenspan, Levy et al., 1951). We believe that the occurrence of pain in peptic ulcer correlates better with the presence of spasm, hypermotility and congestion in the area of the ulcer than with the degree of gastric acidity (Necheles, 1949; Bloomfield, 1954).

The parietal peritoneum, the insertions of the diaphragm and the radix of the mesentery with its extensions are innervated by spinal sensory nerves. While pain from the gastrointestinal tract, transmitted through adrenergic nerves, is not well localized and often diffuse (visceral pain), pain in areas innervated by spinal sensory nerves is distinct and well localized (somatic pain).

Frequently, visceral pathology manifests itself by somatic pain in areas distant from the site of the original disturbance, and, vice versa, somatic pain due to irritation of the spinal nerves supplying the abdominal wall may be felt in the abdomen (referred pain). Many operations have been and are still performed in women with a neuralgia of the 12th thoracic and first lumbar nerves, under the diagnosis of appendicitis, adnexitis, chronic oophoritis, etc.

AXON REFLEXES

Axon, spurious, or pseudoreflexes are local phenomena which do not involve ganglion cells. Their reflex arcs in the gastrointestinal tract consist apparently of small branches of afferent, adrenergic fibers which, instead of running centrally, turn back to innervate blood vessels and muscle fibers. Therefore, adequate stimuli may produce spasm or atony of muscle and arterioles in the same area in which they arise, resulting in anoxia, stasis and exudation. Such reflexes may play a role in local reactions of the gastrointestinal tract to inflammation, foreign bodies, polyps, neoplasm, etc., and may increase spasm, exudation, swelling and pain. These reflexes can be interrupted by topical anesthetic drugs.

VAGOTOMY

Vagotomy merits consideration at this point, because of the profound changes in gastric function often following it.

The gastric vagi convey important tonic, motor, vasomotor, and secretory impulses to the stomach and, vice versa, transmit impulses from the stomach to the central nervous system. Certain types of vomiting may be abolished following gastric vagal denervation (Borison and Wang, 1953). Pancreatic secretion was found to be somewhat depressed, but without conspicuous clinical symptomatology (Thistlethwaite, 1951). On occasion, supradiaphragmatic vagotomy can produce cardiospasm, and supra- or infradiaphragmatic vagotomy is followed in a high percentage of cases by gastric atony, even when an additional gastroenterostomy has been performed. This atony can be abolished by left phrenic crush (Necheles and Jefferson, 1952; Jefferson, Dailey et al., 1956).

We seriously doubt whether complete vagotomy is possible. Above and below the diaphragm the vagi have a number of large and small plexus-like branches, some of which enter the esophageal tissue in the chest and run to the stomach inside the esophageal wall. Some of these branches form anastomoses with the ganglion cells of the intrinsic plexuses, from where impulses are transmitted to the stomach. It is also possible that cholinergic fibers enter the stomach together with sympathetic nerves.

The insulin test for ascertaining the completeness of vagotomy, as proposed now, is not entirely reliable, because small changes in acidity are difficult to detect, and because gastric secretion to insulin can be found increased at a later period of time than the one considered by Hollander satisfactory for evidence of complete denervation (Olson and Necheles, 1953, 1955). It seems that, in some cases, even incomplete vagotomy (as evidenced by insulin tests) yields clinical results equally as satisfactory as complete vagotomy (Colp, 1948; Walters, Brownson et al., 1949). Sham vagotomy in the dog (all vagus branches above the diaphragm were detached and elevated carefully, but injury to the nerves was avoided) led to complete and prolonged gastric atony in two out of six animals (Necheles and Jefferson, 1952).

Gastric secretion is not only stimulated by the vagi, but also by pituitary corticotropic hormone (ACTH), cortisones, epinephrine, and the gastrin mechanisms, all of which act

independently of the vagi (Sandweiss, 1951). In view of the possible effects of emotions and vasospastic reflexes on the formation of ulcer, the role of the alarm reaction, of the adrenergic nerves, and of hormones must be seriously considered.

Following vagotomy, the pain of peptic ulcer disappears, apparently immediately. This is not owing to interruption of pain fibers or to an acute depression of acid-pepsin secretion, but to an immediate gastric atony, which abolishes spasm and contractions, thus relieving pressure in the ulcer area. We do believe that peptic ulcer is produced by neurocirculatory disturbances which cannot be remedied by vagotomy, at least not entirely (Necheles, 1949; Bralow, Spellberg et al., 1950).

In some cases of vagotomy, disordered gastric motility, atony, and retention may persist for prolonged periods of time, and in these, Urecholine, Doryl, etc., have been used with relative success to overcome stasis, foul eructations, etc. (Code, Hightower et al., 1952).

We must remember that the surgical approach to the ulcer problem is not ideal, because operations like subtotal gastrectomy or vagotomy do not affect the "ulcer personality" found among many patients with duodenal ulcer, and ailments in other target areas may substitute the former ulcer complaints (Szasz, 1949; Browning and Houseworth, 1953).

Prefrontal lobotomy produces a profound change in emotional reactions, but yet, gastric secretion was reported essentially unchanged (Carpenter, 1951) or increased (Reed, 1948). Lobotomy does not prevent formation or recurrence of ulcers, and a case with recurrence of an ulcer has been reported following bilateral vagotomy and lobotomy (Logan and Pillar, 1955).

PAROXYSMAL ABDOMINAL PAIN

These conditions are considered here, because in most of them disturbances in innervation and motility seem to be related to the pain.

Abdominal Epilepsy (Paroxysmal Abdominal Pain, Visceral Epilepsy)

This symptom complex belongs definitely to the group of epileptic diseases, but in children it is often misdiagnosed as navel colic, mesenteric adenitis, hypoglycemia, behavior dis-

orders, etc. It is rarely seen in adults, more frequently in children, and has been defined as "bouts of abdominal pain . . . due to hypermotility of the bowel, provoked by abnormal discharges of . . . neurons . . . presumably . . . in the premotor and postmotor cerebral cortex and/or the diencephalon" (Moore, 1946). In some children the symptoms may disappear completely, or change to attacks of frank epilepsy. In a high percentage of cases, cerebral trauma was found to precede the disease (Mulder, Daly et al., 1954).

The recognition of the condition and the exclusion of other etiologic factors may be difficult, and unwarranted operations have often been performed. It is interesting that occasionally the occurrence of intussusception during these attacks has been described (Hoefer, Cohen et al., 1951). Many, but unfortunately not all, of these patients respond to treatment with anticonvulsant drugs, such as Dilantin, Mesantoin, phenobarbital, and bromides (Moore, 1950). Dilantin has been found, in addition to its influence on the central nervous system, to have distinct spasmolytic effects (Druckman and Moore, 1955).

Headache, Migraine

Headaches are a frequent symptom encountered by gastroenterologists (Bockus, 1943). Gastrointestinal disturbances during attacks of migraine may occasionally be a minor form of gastrointestinal epilepsy, but common headache is a steady companion of a number of gastrointestinal diseases.

Cranial migraine, abdominal pain and vomiting may occur together, but occasionally abdominal pain or periods of vomiting can appear without migraine (forme fruste—Brams, 1922; Blitzsten and Brams, 1926), and often a family history of migraine, epilepsy, petit mal, etc., can be elicited in such patients. With predominantly abdominal symptoms, the condition may not be recognized and unnecessary operations may be performed. Cyclic vomiting in childhood may be followed by migraine in later life.

Migrainous forms of headaches with abdominal manifestations may be treated with relative success by sedatives and antiepileptic drugs.