NERVOUS AND NEUROHUMORAL REGULATION OF INTESTINAL MOTILITY

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PREFACE

The present status of knowledge concerning the role of extrinsic nerves of the small intestine in the regulation of intestinal motility is summarized in this monograph. My interest in this subject was aroused in 1935 by the studies of W. J. Meek and R. C. Herrin, in which they demonstrated the role of extrinsic nerves in the production of death by distention of Thiry fistulas in unanesthetized dogs. The studies during the period from 1935 to 1938, at the University of Wisconsin, were facilitated by the availability of a number of animals which they had prepared and by their numerous helpful suggestions. The studies on intestinal motility have been continued at the University of Oregon Medical School from 1938 until the present. During most of the latter period the research has been aided by grants from the John and Mary R. Markle Foundation.

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CHAPTER I

INTRODUCTION

I. Terminology

There is a lack of uniformity in the terminology applied to autonomic physiology and pharmacology; therefore, it is necessary to indicate the sense in which various terms will be used.

The active principle of the adrenal medulla will be called *adrenaline* or *epinephrine.* Following Cannon's usage (2), the term *adrenine* will be used when referring to the substance liberated into the circulation from the adrenal medulla or at nerve endings; and adrenaline or epinephrine will be used when referring to chemical preparations. On the basis of present information, there is no objection to considering that adrenine is the substance produced as the chemical mediator at all of the postganglionic autonomic nerve endings that have an adrenaline-like action on the effectors supplied. The substance that enters the circulation after the action of adrenine (the mediator) on the effector cell may be called sympathin, without necessarily implying by the use of another name that sympathin is different from adrenine; or it may be called adrenine, if there is no evidence that the mediator is modified by the effector cell into a compound differing from the mediator.

The term *autonomic* will be used to refer to the general visceral efferent system; *sympathetic* will apply to the thoracolumbar division, and *parasympathetic* to the craniosacral division. These terms are used only in the anatomic sense. The *visceral afferent* system will be referred to as such; and for differentiation, afferent fibers are subdivided into *vagal afferents* and *thoracolumbar afferents.*

Following Dale's usage (3), the term *adrenergic* will refer to the autonomic nerves which liberate adrenine, or an adrenine-like substance, as the chemical mediator. Postganglionic adrenergic nerves may be found in both the sympathetic and parasympathetic systems. The term *cholinergic* will refer to the nerves which liberate acetylcholine as the chemical mediator. Preganglionic and postganglionic cholinergic fibers are found in both the sympathetic and parasympathetic systems. This terminology will be used only in the physiologic sense and never to refer to anatomic divisions of the autonomic system.

The earlier concept that the sympathetic and parasympathetic systems are antagonistic or reciprocally acting systems is an oversimplification. This is true only for certain visceral effectors, and there are so many exceptions that the generalization is misleading. Some visceral effectors have only a single innervation. Other effectors are innervated by only one anatomic division of the autonomic system, and this division supplies both adrenergic and cholinergic fibers. Some effectors which are innervated by both the sympathetic and parasympathetic divisions of the autonomic system receive adrenergic and cholinergic fibers from one or both of these divisions. The terms *sympathomimetic, sympatholytic, parasympathomimetic* and *parasympatholytic* are products of this oversimplification. Therefore, *adrenolytic* will be used in preference to sympatholytic; and *adrenomimetic, cholinomimetic* and *cholinolytic* are suggested for use in preference to sympathomimetic, parasympathomimetic, and parasympatholytic, respectively.

II. Physiologic Types of Smooth Muscle

In a recent review, Fischer (4) states that our understanding of the physiology of smooth muscle is improving as a result of recognition of the fact that this tissue is not a biologic unity. The subdivision of mammalian smooth muscle into two types, multi-unit and visceral, is quite useful (1). The multi-unit type is exemplified by the piloerector muscles, nictitating membrane, and radial and circular muscles of the pupils. Intestinal smooth muscle is an example of the visceral type. Each of these two main types contains an undetermined number of subtypes. In general, the multi-unit type is singly innervated by excitatory nerves, does not contain nerve plexuses, and contracts in response to impulses reaching it over its extrinsic nerves. In these respects, this type of muscle resembles skeletal muscle more than intestinal smooth muscle. It is obvious, therefore, that results obtained from a study of either type of smooth muscle cannot necessarily be applied to the other type. Actually, it is not safe to assume that the physiologic properties of intestinal smooth muscle are the same as those of any other smooth muscle.

A classification of smooth muscle into various subtypes may be made on the basis of whether the *direct* effect of acetylcholine or adrenaline is to produce relaxation, contraction, or no response. Apparently, examples of four types of smooth muscle can be listed on the basis of this method of differentiation alone, and it is not unlikely that examples of some of the remaining five types, which are theoretic possibilities, will be found. These facts are cited to emphasize that at present there is not enough information for a complete classification of smooth muscle on a physiologic basis.

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CHAPTER II

RECORDING OF INTESTINAL MOTILITY AND INTERPRETATION OF RECORDS

Most of the techniques for studying intestinal motility are included in four general categories: (*1*) direct visualization, (*2*) indirect visualization by the use of radiologic methods, (*3*) recording of rate of propulsion of contents, and (*4*) recording of changes in pressure or volume in the intestinal lumen. The majority of the methods involve subjecting the intestine to unusual conditions and have either a stimulatory or inhibitory influence on intestinal motility. The choice of these must be determined by the purposes of the study. The best method for observing all effects upon motility is one which allows an intermediate level of motility. Excitatory influences cannot be detected when the bowel is already quite stimulated. On the other hand, a method which is moderately stimulatory may prove preferable when inhibitory influences are being studied.

A complete description of intestinal motility requires separate consideration of tonus, propulsive motility, and nonpropulsive motility. The term "tonus" has been used in more than one sense in connection with muscle in tubular organs. The complexity of the problem is indicated in the discussion by Krueger (8). The term will be used here in a nontechnical sense, as follows: a decreased pressure in the presence of a constant volume, or an increase in volume in the presence of no increase in pressure, is referred to as a decrease in tonus. In most balloon methods of recording motility, a decrease in tonus is associated with a lower position of the writing point during the relaxation phase of the rhythmic contractions.

I. Direct Visualization

Methods involving direct visualization include (*1*) exposure of the intestine by laparatomy in anesthetized animals; (*2*) chronic experiments in which transparent abdominal windows are used; (*3*) subcutaneous transplantation or exteriorization of intestinal segments; (*4*) cases of ventral hernia in which, as illustrated in Figure 1, the abdominal wall is thin enough to allow visualization

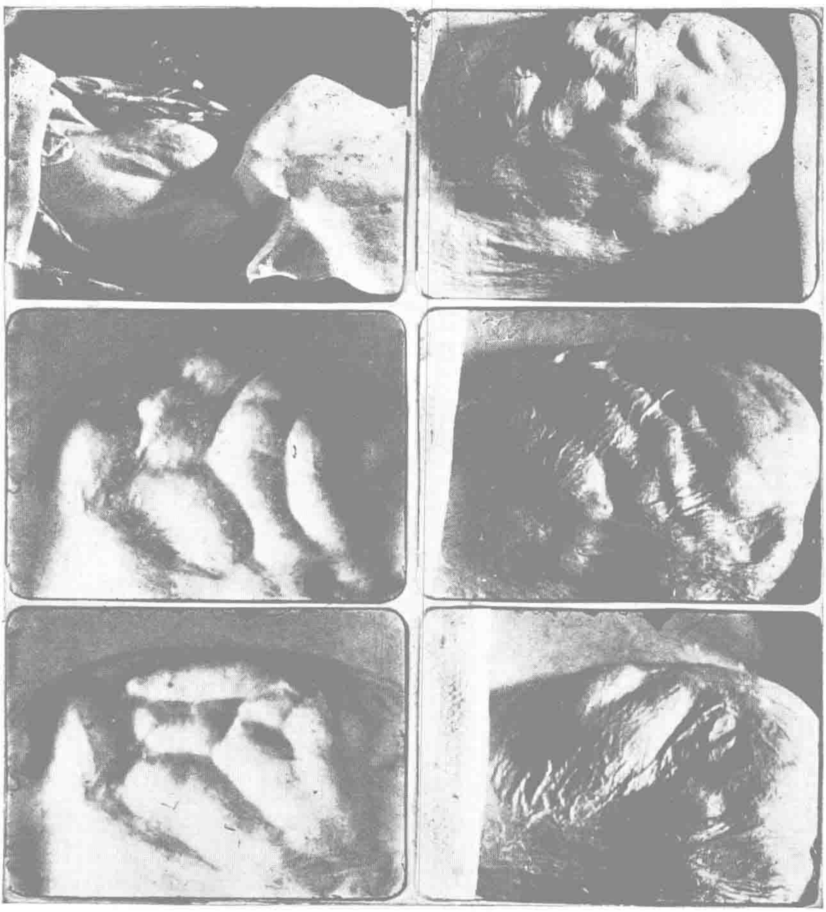

Fig. 1. Loops of small bowel clearly visible under atrophic skin in a patient with a large ventral hernia (12).

of loops of bowel; (*5*) observation of the bowel through fistulas; and (*6*) observing and recording motility of segments of intestine isolated in appropriate solutions. Each of these methods is suitable for some studies and unsuited to others; for example, the anesthetized animal which has been subjected to abdominal surgery is not suitable for the study of the normal level of intestinal motility and its control. Obviously, such a preparation is required for studying the effects of anesthesia and abdominal surgery on intestinal motility. Several methods may be required to gain an understanding of mechanisms involved; for example, the response of isolated intestine to a given substance, such as acetylcholine, may be similar or opposite to the response of the intestine *in situ* following intravenous injection of the substance. The knowledge of what the compound does in both types of preparation affords a basis for conclusions that would not be possible if motility had been studied by a single method.

II. Radiologic Methods

Cannon (1) introduced the fluoroscopic technique for the study of gastro-intestinal motility. The method has two great advantages: it is applicable to human subjects, and the environment of the intestine remains essentially normal. A major disadvantage of the method is the difficulty in obtaining an objective analysis of the results, unless gross phenomena such as initial and final emptying time of the stomach are being studied. It is necessary to depend upon impressions gained by the observer, and often there are little available data. However, radiologic methods are of great value and make possible the accumulation of information that at present can be obtained in no other way.

III. Recording of Propulsive Motility

Peristaltic waves may be observed by direct visualization and in radiologic studies. They produce characteristic patterns in balloon records of intestinal motility. The bolus propulsion method provides an objective means of detecting alterations in the ability of the intestine to propel contents. In this method, the