

**NERVOUS AND NEUROHUMORAL
REGULATION OF
INTESTINAL MOTILITY**

W. B. YOUNG
PROFESSOR OF PHYSIOLOGY
UNIVERSITY OF OREGON MEDICAL SCHOOL

1 9 4 9

INTERSCIENCE PUBLISHERS, INC., NEW YORK
INTERSCIENCE PUBLISHERS LTD., LONDON

Copyright, 1949, by
INTERSCIENCE PUBLISHERS, INC.

All Rights Reserved

This book or any part thereof must
not be reproduced without permission
of the publishers in writing. This
applies specifically to photostatic and
microfilm reproductions.

INTERSCIENCE PUBLISHERS, INC.
215 Fourth Avenue, New York 3, N. Y.

For Great Britain and Northern Ireland:
INTERSCIENCE PUBLISHERS LTD.
2a Southampton Row, London

Printed in the United States of America by
Business Press, Inc., Lancaster, Pa.

Monographs in the Physiological Sciences

**NERVOUS AND NEURO HUMORAL
REGULATION OF
INTESTINAL MOTILITY**



MONOGRAPHS IN THE
PHYSIOLOGICAL SCIENCES

Editorial Board

MAURICE B. VISSCHER
UNIVERSITY OF MINNESOTA

DETLEV W. BRONK
JOHNS HOPKINS UNIVERSITY

EUGENE M. LANDIS
HARVARD MEDICAL SCHOOL

ANDREW C. IVY
UNIVERSITY OF ILLINOIS

INTERSCIENCE PUBLISHERS, INC., NEW YORK
INTERSCIENCE PUBLISHERS LTD., LONDON

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.

I am indebted to C. G. Peterson for reading the manuscript and making helpful suggestions, to Virginia Mount Rankin for assistance with the bibliography, to Eunice Goodrich and Margaret Wolff for their stenographic work, and to Dewey Campbell for technical assistance in many of the experiments. I wish to thank the following publications for their kind permission to reproduce some of the figures used in the book: *American Journal of Physiology*, *Journal of Pharmacology and Experimental Therapeutics*, *American Journal of Digestive Diseases*, *Journal of Physiology, Surgery*, and *Journal of Neuropathology and Experimental Neurology*.

W.B.Y.

Portland, Oregon
December, 1948

CONTENTS

Preface	v
I. Introduction	3
I. Terminology	3
II. Physiologic Types of Smooth Muscle	4
References	5
II. Recording of Intestinal Motility and the Interpretation of Records	6
I. Direct Visualization	7
II. Radiologic Methods	8
III. Recording of Propulsive Motility	8
IV. Recording of Intraluminal Changes in Pressure or Volume	9
Isobaric Method	9
Isometric Method	14
Methods Involving Changes in Both Pressure and Volume	15
Summary	16
References	16
III. Extrinsic Innervation of the Intestine and Methods of Dener- vation	18
I. Vagal Innervation	18
II. Sympathetic Innervation	19
III. Two-Fistula Method	22
References	24
IV. Sensitization of the Intestinal Musculature to Adrenaline by Denervation	25
I. Effect of Vagotomy	26
II. Effect of Sympathetic Decentralization of the Preaortic Ganglia	26
III. Effect of Complete Decentralization of the Preaortic Ganglia	27
IV. Effect of Mesenteric Denervation	27
V. Development and Duration of the Hypersensitivity	29
VI. Possible Effects of Denervation on Intestinal Blood Vessels	29
Summary	29
References	30
V. Denervated Intestinal Segment as an Indicator for Adrenine and Sympathin	31
I. Relative and Absolute Sensitivity to Adrenaline	31
II. Basal Rate of Adrenine Liberation	33
III. Reflex and Psychic Causes of Liberation of Adrenomimetic Substances	33
Reflex Mechanisms	33
Psychic Causes	35
Summary	36
References	36

VI. Mechanism of Gastro-intestinal Inhibition Elicited by Stimuli in the Anorectal Region	37
I. Reflex Gastro-intestinal Inhibition from Anorectal Stimuli	37
II. Humoral Transmission of the Effects of Anorectal Stimulation	39
Summary	40
References	40
VII. Extrinsic Intestino-gastric Reflexes Elicited by Mechanical Stimuli	42
Summary	44
References	44
VIII. Intestino-intestinal Inhibitory Reflex	46
I. Peripheral Nervous Pathways	46
Role of Extrinsic and Intrinsic Pathways	47
Role of Preaortic Ganglia	47
Role of Sympathetic and Vagal Pathways	49
II. Central Nervous Pathways	49
Localization within the Central Nervous System	49
Neuronal Connections within the Central Nervous System ..	50
III. Oscillographic Studies of Nervous Activity Elicited by Intestinal Distention	51
IV. Summation and Sensitization of the Intestino-intestinal Inhibitory Reflex	53
Summation	53
Sensitization	55
V. Utility of the Intestino-intestinal Inhibitory Reflex	56
Summary	57
References	58
IX. Afferent Innervation of the Intestine as Determined by Intestinal Distention	60
I. Afferent Pathways for the Intestino-intestinal Inhibitory Reflex	60
II. Afferent Pathways for the Intestinopannicular Reflex	61
III. Afferent Fibers Concerned with Awareness of Distention	61
IV. Afferent Pathways Concerned with Production of Gastric Inhibition, Vomiting, and Anorexia by Intestinal Distention ..	62
Summary	62
References	63
X. Role of Adrenaline in Intestinal Motility	64
I. Production of an Adrenomimetic Substance in the Intestine	64
II. Inactivation of Adrenaline in the Intestinal Wall and Liver ..	67
III. Mechanism of Inhibition of Intestinal Smooth Muscle by Adrenaline	67
Relation of Effects of Adrenaline on Intestinal Circulation ..	67
Relation of Extrinsic and Intrinsic Nerves	69
IV. Physiologic Role of Adrenaline	69
Summary	72
References	73
XI. Comparison of Inhibitory Adrenergic and Excitatory Adrenergic Neuro-effector Transmission. Nature of Sympathin	74
I. Relative Importance of the Various Groups of the Adrenaline Molecule	75
II. Mediator(s) and Sympathin(s) Produced at Adrenergic Neuro-effector Junctions	76
Two-Sympathins Theory	77
Two-Mediators Theory	79
Adrenaline Metabolite Theories	80
Summary	81
References	82

XII. Role of Acetylcholine in Intestinal Motility	84
I. Production of Acetylcholine by the Intestine	84
II. Inactivation of Acetylcholine by Intestinal Tissues	88
III. Evidence for Cholinergic and Adrenergic Intrinsic Neurones ..	89
IV. Inferences from the Action of Atropine on Intestinal Motility	92
V. Inferences from the Action of Anticholinesterases on Intestinal Motility	94
VI. Role of Acetylcholine in the Various Types of Intestinal Motility	96
Summary	98
References	99
XIII. Reflex Effects of Peritoneal Irritation on Intestinal Motility ..	102
I. Peritoneo-intestinal Inhibitory Reflex	102
II. Reflex Vomiting from Peritoneal Irritation	103
References	104
XIV. Reflex Effects on Gastric and Intestinal Motility Elicited by Distention of the Biliary System	105
Summary	107
References	108
XV. Reflex Effects on Gastro-intestinal Motility Elicited by Stimuli in the Urinary Tract	109
I. Effects on Motility of the Small Intestine	109
II. Effects on Motility of the Stomach	112
Summary	113
References	113
XVI. Nervous Mechanisms Concerned with the Effects of Feeding on Intestinal Motility	114
I. Earlier Observations	114
II. Nervous Mechanisms for the Effects on Intestinal Motility	115
Summary	118
References	119
XVII. Hypothalamic and Corticocerebral Influences on Gastro-intes- tinal Motility	120
I. Hypothalamic Influences	120
Stimulation Studies	120
Effects of Lesions	124
II. Corticocerebral Influences	125
Stimulation	125
Ablation	127
Summary	127
References	128

***NERVOUS AND NEURO HUMORAL
REGULATION OF
INTESTINAL MOTILITY***

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.

References

1. Bozler, E. Action potentials and conduction of excitation in muscle. Biol. Symposia 3: 95-110, 1941.
2. Cannon, W. B., and Rosenblueth, A. *Autonomic Neuro-effector Systems*. New York, Macmillan, 1939.
3. Dale, H. H. Nomenclature of fibres in the autonomic system and their effects. J. Physiol. 80: 10-11P, 1933.
4. Fischer, E. Vertebrate smooth muscle. Physiol. Rev. 24: 481, 1944.

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 laparotomy 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

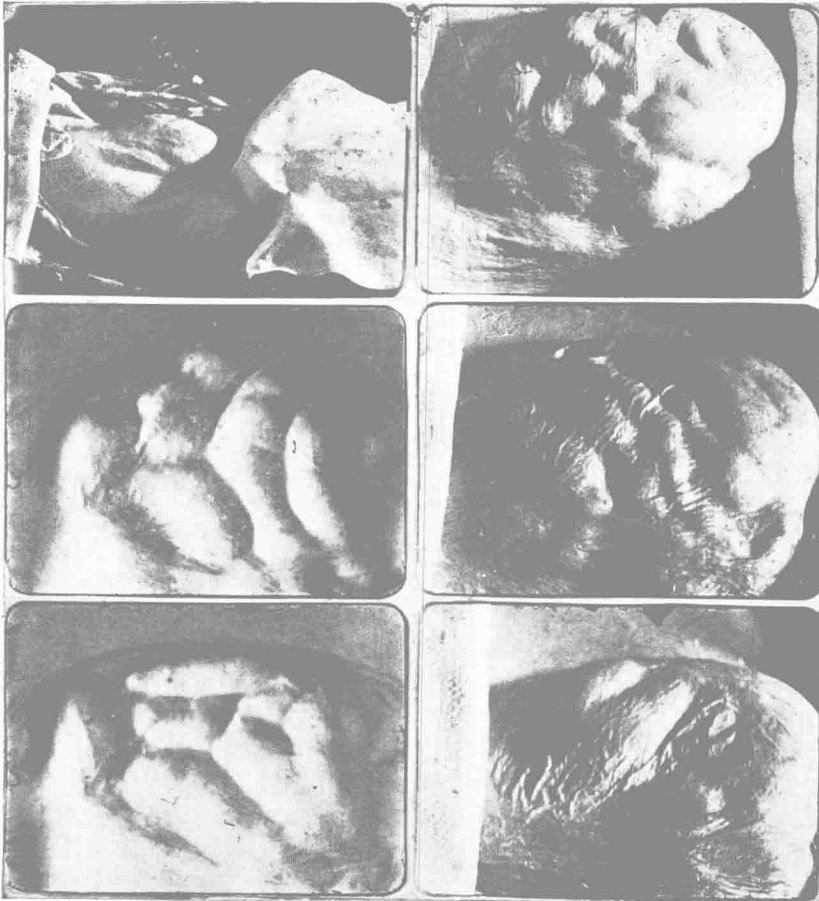


Fig. 1. Loops of small bowel clearly visible under atrophic skin in a patient with a large ventral hernia (12).

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