Secretory Mechanism of the Digestive Glands

BY

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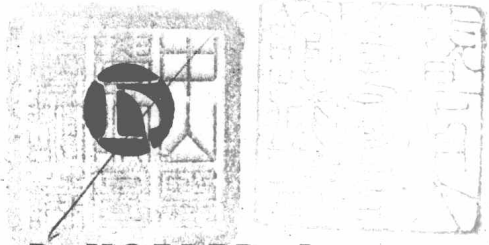

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SECRETORY MECHANISM OF THE DIGESTIVE GLANDS

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PREFACE TO THE SECOND EDITION

The general arrangement of the material in this second edition remains the same as in the first. However, it has been thoroughly checked and brought up to date throughout.

Attention might also be called to the fact that we have discussed the results of the investigation of the electrophoretic fractioning of the pancreatic juice for the first time; have added new facts concerning the possible role of carbonic anhydrase in the process of formation of the hydrochloric acid by the parietal cells; have incorporated data obtained by S. Wolf and H. G. Wolff on a patient with a gastric fistula which appeared after the publication of the first edition of this book; and have included further proofs found by Swedish investigators of the specific action of histamine on the parietal cells. Many other new findings have been incorporated in the text. On the whole more than 260 new experimental investigations, which have appeared since the publication of the first edition of this work, are reviewed and discussed.

Progress in our understanding of the secretory functions of the digestive tract is reflected in this edition by the presence of many completely new sections such as those on the effect on the secretory activity of the gastric glands of pilocarpine, acetylcholine, and caffeine; on the inhibition of gastric secretory activity by different methods; on pancreozymine; on antagonistic and synergistic phenomena in the autonomic nervous system; on secretory-inhibitory nerves; and on nervous and hormonal regulation of the pancreatic secretion.

My thanks are due to Miss J. F. Oswald (M.A. Edin.), T. J. Speakman, M.Sc., M.D., and W. C. Kite, M.Sc., M.D. for their help in preparation of the second edition.

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PREFACE TO THE FIRST EDITION

This book is based on several courses of lectures given during the last ten years to postgraduate students at McGill University and on some lecture-reviews presented at University College, London, and at the Universities of Edinburgh and Birmingham, in the summer of 1938. It is not a monograph and I have not attempted to review the whole of the literature concerned with the secretory function of all the digestive glands. The material for this book is chiefly derived from the work performed by my co-workers and myself, especially during the last fourteen years in the Department of Physiology of McGill University. The book deals mainly with the mechanisms regulating the secretory activity of the digestive glands as exemplified in particular by the functions of the gastric, salivary, and pancreatic glands, while other digestive glands are also to some extent taken into consideration. In a lesser degree it deals with the intimate processes of secretion taking place in the glandular cells during their activity. Although in the discussion of various problems I have proceeded along the lines of investigation followed in our laboratory, the more important facts known in regard to the secretory function of the digestive tract up to the present date have as far as possible been included. This ensured a maximum of objectivity in the discussion of various facts and also made it possible to trace the origin and development of different problems, aspects which are so often overlooked by younger investigators.

Not pretending to be a monograph, this volume has the more modest aim of describing the mechanisms involved in the regulation of the secretory activity of the principal digestive glands under normal conditions. It may also serve as a physiological introduction to the pathology and the clinical investigation of the diseases of the secretory apparatus of the alimentary canal. I have therefore considered it worth while to discuss in some detail the secretory processes

of certain of the digestive glands, especially those of the stomach, because not infrequently a physician is unable to explain a morbid phenomenon through being unfamiliar with the intricacies of the physiological function of some organ.

Although we possess a fair amount of knowledge concerning the normal functioning of the digestive glands in man and such laboratory animals as the dog and cat, we still do not clearly understand the various mechanisms which regulate their secretory activity, far less the secretory process itself. I am firmly convinced that the further advance of our knowledge in this field will largely depend on the extent of which experimental physiological investigation of the secretory function of the digestive glands will in the future be combined with histophysiological study, for the following reasons. (1) Most of the digestive glands are organs of complicated structure, each gland being composed of different groups of secretory cells whose respective roles in the formation of the secretion have to be investigated; (2) the glandular cells, owing to the relative slowness of some phases of the secretory process, provide a rare opportunity for the study of histophysiological and histochemical phenomena, since by the morphological changes which they undergo they testify, as it were, to the character and extent of the physiological phenomena occurring in them under the conditions of activity or rest; (3) the much-needed physicochemical study of the secretory processes in the digestive glands can be successful only when a proper knowledge of the physiology and histophysiology of the glands has been acquired. Unfortunately all too little has been done up to the present time in the field of combined physiological and histological investigation of the secretory function of the digestive glands. In our laboratory some attempt has been made to remedy this situation.

Another important field of research that is waiting for workers is the relationship between the endocrine and the digestive glands. There has been no lack of investigations on this subject, but the great majority of them were performed before our knowledge of the physiology of the alimentary canal had reached its present stage. Instead of dealing with the direct or indirect effect of hyperfunction or hypofunction of a ductless gland on the complicated mechanisms regulating the secretory processes of different digestive glands, previous studies have mostly consisted of crude observations of the unfavorable or damaging influence of the lack or the excess of a

hormone in the body. The proper type of investigation is only now beginning to be performed, and it is for this reason that no data on the relationship between the endocrine glands and the glands of the alimentary canal have been included in this volume.

The ingenious observations made by William Beaumont (1833) on a patient with a gastric fistula culminated half a century later in the introduction by my late teacher, I. P. Pavlov, of the method of physiological surgery. Owing to causes the discussion of which is out of place here, the once keen interest in the physiology of the secretory function of the gastro-intestinal tract subsequently declined. The great possibilities of the method developed by Pavlov were never fully utilized in gastro-enterology by physiologists, pharmacologists, or experimental pathologists, and the number of physiological laboratories engaged in these studies was ridiculously small. However, during the last few years a marked revival of interest in both theoretical and clinical gastro-enterology has been definitely noticeable. This gives me reason to hope that the present volume will find readers, and that, in spite of the many shortcomings of the work, it may prove useful to them.

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This book is gratefully dedicated to Dr. Charles F. Martin, Emeritus Dean of the Medical Faculty of McGill University, whose generous support and understanding made possible the performance by my co-workers and myself of the greater part of our investigations mentioned in this volume. It would also have been difficult for me to achieve my scientific aims had I not enjoyed during the last fourteen years the constant friendly help and valuable advice of the former Secretary and later Dean of the Medical Faculty of McGill University, Dr. J. C. Simpson, Professor of Histology and Embryology.

My sincere thanks are due to the research workers who have at various times been attached to my laboratory at McGill University and also at Dalhousie University, Halifax: Armine Alley, L. A. Andreyev, J. C. Armour, E. J. W. Barrington, Hamilton Baxter, S. G. Baxter, D. J. Bowie, J. S. L. Browne, James Campbell, A. F. Chaisson, J. J. Day, A. J. Fleming, M. H. F. Friedman, Rhoda Grant, N. M. Gray, Catherine O. Hebb, Olga Komarov, S. A. Komarov, Luise Krueger, G. H. Lathe, Margaret E. MacKay-Sawyer, F. C. MacIntosh, D. W. Mackenzie, Jr., the late P. D. McLarren, H. E. Morton, J. V. V. Nicholls, L. J. Notkin, L. I. Pugsley, H. E. Rawlinson, M. J. Schiffrin, Maria A. Sergeyeva, G. W. Stavraky, C. J. Tidmarsh, C. Gwendoline Toby, A. M. Vineberg, Althea A. Warren, and D. R. Webster. Without their help and their interest in the study of the physiology of the gastro-intestinal tract it would have been impossible to collect the experimental material presented in this book.

I shall always remember with pleasure the effective co-operation between my laboratory and the Department of Physics of McGill University, when certain problems of glandular physiology were worked out with Professor J. S. Foster, Dr. G. O. Langstroth, and the late Dr. D. R. McRae.

I wish also to thank Dr. A. G. Huntsman, former Director of the

Atlantic Biological Station, St. Andrews, N.B., for the facilities which he afforded on the station to me and my co-workers, and for his interest in our work, during many summers.

I am greatly obliged to Miss Janet F. Oswald, M.A. (Edin.), former secretary in the Department of Physiology of McGill University, for most active help in the preparation of the manuscript for publication. Without her participation in this work and devotion to it, it would have been difficult for me to present the material in the form in which it now is. Dr. D. A. Ross of the same department kindly read over all the chapters and offered many valuable suggestions, which helped to put them into final shape. Here also I wish to acknowledge the very helpful co-operation given me by the staff of the Medical Library at McGill University.

My thanks are due to a number of colleagues who have taken the trouble to read certain chapters of the book in manuscript and for whose advice and criticisms I am very grateful. Professor C. C. Macklin read Chapters I, II, and IV; Professor D. L. Thomson, Chapters III and XX; Professor C. P. Martin, Chapter V; Professor E. S. Nasset, Chapter XXII; Dr. J. S. L. Browne, Chapter XIV; Dr. F. Hollander, Chapters XV and XVI. I wish also to thank Professor R. L. Stehle for much valuable help and advice.

I have received great encouragement in my work from several friends in Europe and America: Professor A. V. Hill, Sec.R.S., through whose kind offices I obtained the opportunity of continuing my scientific work in Canada; the late Professor B. A. McSwiney of St. Thomas's Hospital Medical School, London, whose active interest in the work of my laboratory sustained me through all these years; Professor I. de Burgh Daly of Edinburgh University, who not only was interested in our scientific achievements but never refused the hospitality of the *Quarterly Journal of Experimental Physiology*, of which he is editor, to any of our papers; Professor J. E. Thomas of Jefferson Medical College, Philadelphia, who on many occasions supported the scientific views of our laboratory. Dr. W. C. Alvarez of the Mayo Clinic, Rochester, Minnesota, and Dr. G. Schwartzman of Mount Sinai Hospital, New York, urged me to write this book and moreover found a publisher for it. A constant interest in the studies on gastro-intestinal physiology coming from our laboratory has been shown by a group of outstanding physicians and investigators of the Mount Sinai Hospital in New York: Drs. A. Berg, B. B. Crohn, E. Libman, F. Hollander, G. Schwartzman, A. Winkelstein, and others. Every spring for many years I have had the pleasure and

privilege of being invited to give them an account of the work that had been done in my laboratory during the preceding year.

The study of the secretory mechanism of the digestive glands on the scale described in these chapters was made possible not only by the support given to my laboratory in various forms by McGill University, but by a happy chance afforded to me by the then Dean of the Medical Faculty, Dr. C. F. Martin, to participate in a special scheme of "Experimental Surgery," supported by the Rockefeller Foundation. According to the plan formulated by me, part of the sum allotted for this purpose was to be used for the training of young surgeons for a year or two in one of the laboratories of the theoretical medical sciences before they entered hospital service, in order to familiarize them with the all-important experimental method, which is the foundation of all scientific experimental investigation and which they might subsequently apply in their clinical work. The plan was approved by a special committee of McGill University and by the Rockefeller Foundation, and for a period of several years a number of young surgeons were engaged in research work in my laboratory. [The theoretical grounds for this scheme were set forth by me in two papers: "The Experimental Method in Modern Medicine" (*Canadian Medical Association Journal*, vol. 22, p. 95, 1930) and "The Methods of Scientific Medicine" (*McGill Medical Undergraduate Journal*, vol. 2, p. 133, 1933). The former article was reprinted in the *Journal of the Association of American Medical Colleges* (vol. 5, p. 271, 1930).] The depression of the nineteen-thirties unfortunately forced the University to discontinue this project; nevertheless our grateful thanks are due to the Rockefeller Foundation for its support of a new scheme for the improvement of medical education on the North American continent.

In addition to the Rockefeller Foundation a few other foundations have given financial assistance to my laboratory. My sincere thanks are due to the Banting Research Foundation, the Ella Sachs Plotz Foundation, and the Emanuel Libman Foundation for their support. Some of my co-workers have received grants from the National Research Council of Canada, for which I am also very grateful.

It is my very pleasant duty to thank the publishing firm of Paul B. Hoeber, Inc., for their generous co-operation and for the care they have taken in the execution of this work. My thanks are also due to Miss Margaret G. Fiske of that Company, whose valuable assistance has helped greatly in the proper presentation of this book.

B. P. B.

CONTENTS

CHAPTER I

CORRELATION OF STRUCTURE AND FUNCTION IN THE DIGESTIVE GLANDS

This volume deals with the experimental analysis of the secretory function of the digestive glands in carnivorous animals and man. This work is still only in the initial stages and far from complete. Consequently any attempts at this time to explain the mechanism by which the digestive glands are set into activity, and by which their activity is regulated, will of necessity be imperfect. Nevertheless I considered that it might be useful to sum up our present knowledge in this province of physiology in order to facilitate further study of physiological and pathological problems related to the function of the alimentary canal.

GLANDS OF EXTERNAL AND INTERNAL SECRETION

The digestive glands constitute a large group of organs which are embedded in the walls of the alimentary canal, or which lie outside it and are connected with it by special ducts. The surface epithelium, which forms a lining for the digestive tube and contains mucous, goblet, and other cells, must also be included in this group of secreting organs. The secretory product of the digestive glands has been called an *external* secretion, because the alimentary canal may with some justification be considered an extension of the external surface of the body (Babkin, 1928[a], p. 2). It is customary to classify the *ductless glands* or *glands of internal secretion* as a separate group, distinct from the *glands of external secretion.* This distinction is based on the fact that the ductless glands discharge their secretions directly into the blood (the Germans call them *Blutdrüsen*), while the glands of external secretion discharge their secretory products on to one of the (physiologically) external sur-

faces of the body, such as the gastro-intestinal tract, air passages, urinary passages, or skin. In certain respects, however, such a distinction is not altogether justifiable. It is probable that some glands produce both a "hormone" and a "digestive juice." Thus, for example, the mucous membrane of the duodenum and jejunum secretes the succus entericus, containing, in addition to secretin, at least seven different enzymes (Volborth, 1925). The secretin molecule, according to La Barre (1933, 1936), is a complex one and is composed of two parts, namely, *excretin*, a hormone which stimulates the secretion of pancreatic juice, and *increti*n, a hormone which produces hypoglycemia. Similarly there is present in human gastric juice a substance which stimulates the hematopoietic organs (Castle, 1929; Castle *et al.*, 1929, 1930). Goodfriend, Chain, and Florey (1938) found a reticulocytogenic agent for reactive guinea pigs in the pyloric, duodenal, and ileal secretions of the pig, in the pyloric and duodenal secretions of the cat, and in the duodenal secretions of the rabbit and the goat. This substance was absent from the fundic secretions of the pig and the cat. Thus a "hormone" formed in an organ belonging to the gastro-intestinal system may influence the activity of organs belonging to other systems. It is not known whether a "digestive juice" and a "hormone" are produced in one gland by cells of the same type or by two distinct sets of cells.

The controversies over the definition and nomenclature of the "external" and "internal" secretions, and concerning the word "gland" itself, have been thoroughly discussed by Swale Vincent (1927). In the present volume we shall deal with the secretory processes of those glands and epithelia which discharge their secretions into the alimentary canal, and which from time immemorial have rightly been called the *digestive glands*. This will not preclude some consideration of the functional relationship between the glands of "external" and "internal" secretion.

STRUCTURE OF THE DIGESTIVE GLANDS

Before discussing the mechanism of glandular activity I shall mention a few histological and cytological facts that are helpful in the study of this mechanism. With the outstanding exception of R. Heidenhaim, students of the physiology of the gastro-intestinal tract have rarely paid due attention to the morphology of the