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Foreword

Updating the vast and rapidly moving domain of 'Endocrine tumors of the pancreas' is an ambitious project. Close interconnections between scientific advances, bioclinical techniques, morphological explorations and genetic investigations make, for non-top-level specialists, this topic particularly difficult to follow. Internists and gastroenterologists or endocrinologists very often feel puzzled when reading the most recent papers published in this field. As in several other specialities, clinical science is largely influenced by highly specific basic information; however, in many respects, clinical observation remains essential as a starting point and its importance in the development of basic research should not be underestimated. Numerous examples might be presented in this line, such as autoimmune diseases which led, on the basis of the accompanying vascular lesions, to evidence for the role of T lymphocytes in capillary integrity, or rheumatoid arthritis improvement by glucocorticoids, allowing the demonstration that a variety of target cells are sensitive to hormonal physiological and pharmacological actions. Zollinger-Ellison syndrome is another paradigm of this assertion. From the time of its initial description (1955), interest for this syndrome has grown, extending to more and more fields, such as ulcer disease, endocrine tumors, genetics, digestive physiology, and hormone structure and processing. Science is not evolving in a harmonious progression towards well-defined aims: besides spectacular jumps, steps for progress are sometimes difficult to climb, more numerous and stiffer than forecast; hidden errors should be disclosed and too ambitious conclusions should be revised. However, as regards clinical research, any durable effort might be beneficial for the patient and this was the case concerning the Zollinger-Ellison syndrome. Over 40 years, medical benefits obtained for better diagnosis and treatment of gastrinomas have rewarded the efforts of the medical community mainly working in the traditional way of case collection, accurate follow-up, anatomical observations and attempts at obtaining specific and sensitive tests for early recognition. If 'gastrin' remains the key word for a pathophysiological approach, its major clinical importance results from the observation of high plasma levels of hormones, which in itself is not representative either by being the most valuable or the most specific test for diagnosis. Overlapping of the observed values with those obtained under nontumoral conditions might often be clarified by pharmacological tests (secretin, calcium, etc.): unfortunately,
these were defined empirically and, in a large range of responses, poorly specific. Thus, gastric secretion studies on the one hand, and morphological explorations (endoscopy, MNR and CT scan, radioisotopic tests), on the other hand, remain of fundamental importance in a large portion of the patient population. The relevance of this 'extragastrin' approach is undisputable for prognostic assessment (tumoral extension, metastases) and therapeutic follow-up.

Back to science, interferences between the progressive elaboration of the Zollinger-Ellison syndrome as a clinical entity and the development of fundamental research on gastrin (and regulatory peptides to a larger extent) have often been underlined and these could be presented as a model. From the time of first extraction from a surgically excised gastrinoma, by Gregory and Tracy (1960) until studies on gastrin processing in isolated gastrinoma cells, the human disease has been the source of numerous lines for leading scientific works, sometimes limited to basic problems, sometimes yielding new tools for solving clinical problems. A remarkable example of this type of feedback lies in the observation of somatostatin cells (initially recognized as D cells) in the gastrinoma tissue which, 25 years later, fully justified the characterization of somatostatin receptors on endocrine cells in the same tissue after injection of labelled somatostatin analogs. Likewise, the trophic activity of gastrin, suspected for parietal cells on the basis of their very large increase in number in the Zollinger-Ellison syndrome, was more recently characterized in endocrine cells: ECL cells are the most sensitive to this trophic action and this is especially apparent in gastrinoma patients receiving a prolonged and efficacious antisecretory treatment. A further extension of this topic would involve the occurrence of cancer of the digestive tract, both gastric and colonic. Besides their highly scientific interest, these observations lead to various practical improvements in patients' follow-up, particularly in the assessment of tumoral extension and in the prevention of damaging therapeutic side effects.

The above considerations might be extended to other endocrine tumors of the pancreas, although Zollinger-Ellison syndrome is the most frequent of these conditions, with two fundamental presentations, sporadic and part of a MEN1 syndrome. Besides specifically adapted approaches in each of them, gastrinoma on the whole shares numerous scientific and clinical problems with the other aspects of the pancreatic endocrine tumors.

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In the first part of this book, the reader will be educated (if necessary) in MEN1 genetics which covers the whole of these pancreatic tumors, whatever the diversity of their endocrine secretions; additional sections deal with their embryology, hormone processing, histopathology including immunopathology, and secretory activity markers. The second part discusses the clinical and therapeutic aspects according to the predominant hormone secretion responsible for specific
and nonspecific symptomatology World-rekknowned experts, supported by active and creative teams, present analytic as well as synthetic contributions based largely on original material This will likely avoid, at least for a significant period of time, obsolescence of this remarkable and extensive updating A few chapters of this part are, however, not tumor-specific such as those dealing with hormone secretion that allows an approach to functional localization, surgical problems and nonspecific therapeutics. In the third part, this last topic is added to recent information on the modern aspects of the treatment of advanced disease such as excision and transplantation surgery, local and systemic chemotherapies and interferon

Michel Mignon and Robert T. Jensen, acting as co-editors, took the heavy responsibility of undertaking this updating Their experience in the topic is outstanding, not only in the number of followed cases, but also by the broad spectrum of steps forward resulting from their suggestions, their results and the dynamics of their research So, if their personal participation in several chapters is highly significant, their expertise is also extended to the relevant selection of the numerous authors who participated, making this book an indispensable instrument for education, reflection and projection to the future No doubt, for gastroenterologists, endocrinologists and internists this updating will become a ‘classic’

Prof Serge Bonfils
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Foreword X

Preface

Gastrointestinal pancreatic endocrine tumors have many special features that distinguish them from other gastrointestinal tumors. They present unique aspects of pathogenesis, histology, diagnosis, localization, and treatment in that they often arise ectopically, are in most cases relatively slow-growing but nevertheless malignant, often present clinically at a stage when the tumor is difficult to detect, and in that both the hormonal excess state and tumor must be dealt with. Over the last few years, there have been numerous advances in areas related to these tumor syndromes, ranging from an increased understanding of the pathogenetic and developmental aspects to new, unique methods for localizing these tumors and controlling the hormonal excess state. With the increased ability to control the hormonal symptoms, either medically or surgically, has come an increased need to understand the natural history of the tumors themselves. An increased need has also arisen to develop effective therapies directed at the tumor itself, both in patients with early small but hormonally active tumors and in those with advanced metastatic disease.
In this volume, we have attempted to deal with the advances in each of these areas, and have been fortunate in obtaining, in all cases, outstanding authorities to cover their particular areas. It was our specific intention that the volume should deal with the advances of the last few years, rather than just give a review of the syndromes and tumors, which is available in a number of other volumes.

The editors would like to thank Prof. Carmelo Scarpignato for giving us the opportunity to edit this book and S. Karger AG, Medical and Scientific Publishers, Basel, for their support. In particular, we thank Ms. Denise Greder for her help in the planning of this volume and Ms. Anke Rogal and colleagues at Karger's Copy Editing Department for their mastery in revising the text and proofs.

We would like to dedicate this volume to Prof. Robert M. Zollinger and Prof. Serge Bonfils, each of whom has been, for many years, a pioneer in the field of gastrointestinal hormonal syndromes. Both Prof. Zollinger, with his original description of the Zollinger-Ellison syndrome in 1955 and his subsequent detailed studies on the surgical approach, and Prof. Bonfils, with his group's extensive studies on Zollinger-Ellison syndrome and other endocrine tumors, have contributed greatly towards the increased awareness of these syndromes and the development of effective treatments. Each has played a very large role in setting the foundations for many of the advances being reviewed in this volume.

Prof. Michel Mignon
Dr. Robert T. Jensen

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