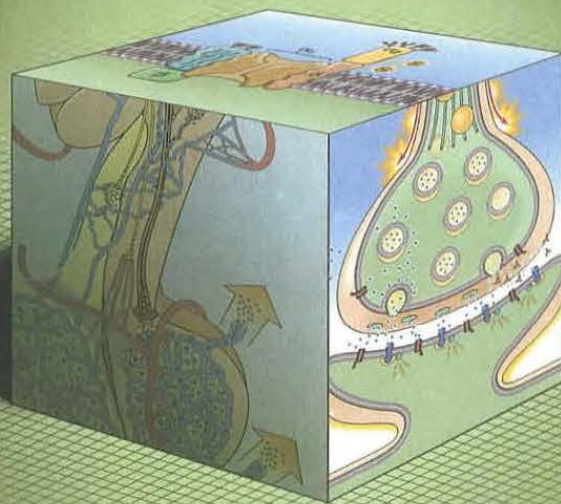


Walter F. Boron ■ Emile L. Boulpaep

# MEDICAL PHYSIOLOGY



SAUNDERS

Boehringer Ex. 2005

**DOCKET**  
**ALARM**

Find authenticated court documents without watermarks at [docketalarm.com](http://docketalarm.com).

# MEDICAL PHYSIOLOGY

A Cellular and Molecular  
Approach

*Walter F. Boron, MD, PhD*

Professor

Department of Cellular and Molecular Physiology

Yale University School of Medicine

New Haven, Connecticut



*Emile L. Boulpaep, MD*

Professor

Department of Cellular and Molecular Physiology

Yale University School of Medicine

New Haven, Connecticut

**SAUNDERS**

An Imprint of Elsevier

Boehringer Ex. 2005

SAUNDERS

An Imprint of Elsevier

The Curtis Center  
Independence Square West  
Philadelphia, Pennsylvania 19106

MEDICAL PHYSIOLOGY

ISBN 0-7216-3256-4

Copyright © 2003, Elsevier Science (USA). All rights reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without permission in writing from the publisher.

Permissions may be sought directly from Elsevier's Health Sciences Rights Department in Philadelphia, USA: phone: (+1)215-238-7869, fax: (+1)215-238-2239, email: [healthpermissions@elsevier.com](mailto:healthpermissions@elsevier.com). You may also complete your request on-line via the Elsevier Science homepage (<http://www.elsevier.com>), by selecting 'Customer Support' and then 'Obtaining Permissions'.

Notice

Medicine is an ever-changing field. Standard safety precautions must be followed, but as new research and clinical experience broaden our knowledge, changes in treatment and drug therapy become necessary or appropriate. Readers are advised to check the most current product information provided by the manufacturer of each drug to be administered to verify the recommended dose, the method and duration of administration, and contraindications. It is the responsibility of the treating physician, relying on experience and knowledge of the patient, to determine dosages and the best treatment for each individual patient. Neither the Publisher nor the editor assumes any liability for any injury and/or damage to persons or property arising from this publication.

The Publisher

Library of Congress Cataloging-in-Publication Data

Boron, Walter F.

Medical physiology / Walter F. Boron, Emile L. Boulpaep—1st ed.

p. cm.

ISBN 0-7216-3256-4

I. Human physiology. I. Boulpaep, Emile L. II. Title

[DNLM: 1. Physiology. QT 104 B7356M 2003]

QP34.5 .B65 2003

612—dc21

00-051597

Acquisitions Editor: William R. Schmitt

Developmental Editor: Melissa Dudlick

Publishing Services Manager: Frank Polizzano

PI/DNP

Printed in China

Last digit is the print number: 9 8 7 6 5 4

Boehringer Ex. 2005

**DOCKET**  
**ALARM**

Find authenticated court documents without watermarks at [docketalarm.com](http://docketalarm.com).



# The Endocrine Pancreas

Eugene J. Barrett

## The Islets of Langerhans Are Endocrine and Paracrine Tissues

The pancreas contains two types of glands: (1) exocrine glands, which secrete digestive enzymes and  $\text{HCO}_3^-$  into the intestinal lumen (see Chapter 42), and (2) endocrine glands, called the "islets of Langerhans."

The normal human pancreas contains between 500,000 and several million islets. Islets can be oval or spherical and measure between 50 and 300  $\mu\text{m}$ . Islets contain at least four types of secretory cells— $\alpha$  cells,  $\beta$  cells,  $\delta$  cells, and F cells—plus various vascular and neural elements (Fig. 50-1 and Table 50-1).  $\beta$  cells secrete insulin, proinsulin, C peptide, and a newly described protein, amylin.  $\beta$  cells are the most numerous type of secretory cell within the islets; they are located throughout the islet but are particularly numerous in the center.  $\alpha$  cells principally secrete glucagon,  $\delta$  cells secrete somatostatin, and F cells (also called pancreatic polypeptide cells) secrete pancreatic polypeptide.

The cells within an islet receive information from the world outside the islet. These cells also can communicate with each other and influence each other's secretion. We can group these communication links into three categories:

1. **Humoral communication.** The blood supply of the islet courses outward from the center of the islet toward the periphery, carrying glucose and other secretagogues. In the rat—and less strikingly in humans— $\beta$  cells are more abundant in the center of the islet, whereas  $\alpha$  and  $\delta$  cells are more abundant in the periphery. Cells within a given islet can influence the secretion of other cells as the blood supply courses outward through the islet carrying the secreted hormonal product of each cell type with it. For example, glucagon is a potent insulin secretagogue, insulin modestly inhibits glucagon release, and somatostatin potently inhibits the secretion of both insulin and glucagon (as well as the secretion of growth hormone and other nonislet hormones).
2. **Cell-cell communication.** Both gap and tight junctional structures connect islet cells with one another. Cells within an islet can communicate via gap junctions, which may be important for the regulation of both insulin and glucagon secretion.
3. **Neural communication.** Another level of regulation of islet secretion occurs via innervation from both the sympathetic and the parasympathetic divisions of the autonomic nervous system (ANS). Cholinergic

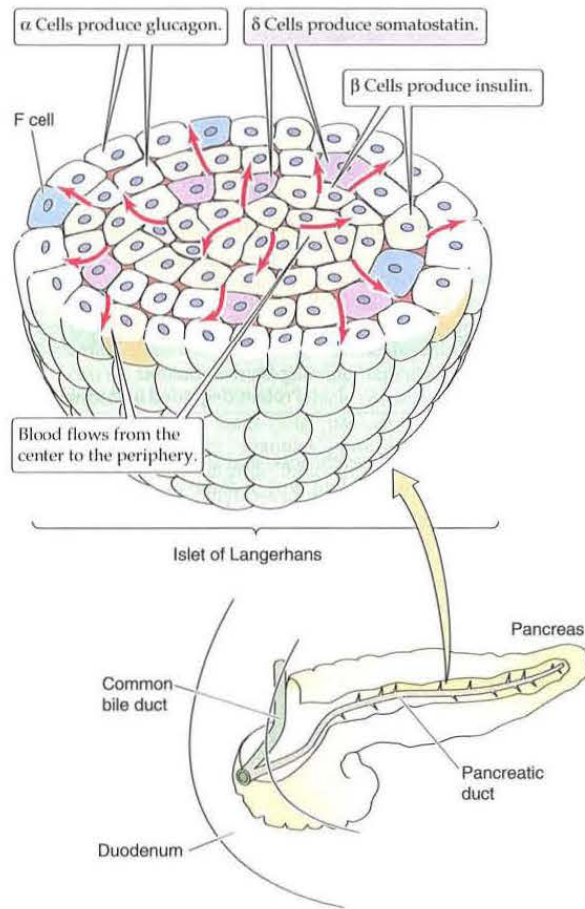


FIGURE 50-1. Islet of Langerhans.

stimulation augments insulin secretion. Adrenergic stimulation can have either a stimulatory or inhibitory effect, depending on whether  $\beta$ -adrenergic or  $\alpha$ -adrenergic stimulation dominates (p. 1065).

These three communication mechanisms allow for a tight control over the synthesis and secretion of islet hormones.

whelming acidosis. No effective therapy was available, and few prospects were on the horizon. It was known that the blood sugar was elevated in this disease, but beyond that, there was little understanding of its pathogenesis.

In 1889, Minkowski and von Mering demonstrated that removing the pancreas from dogs caused hyperglycemia,

**INSULIN**

The discovery of insulin was among the most exciting and dramatic events in the history of endocrine physiology and therapy. In the United States and Europe, insulin-dependent diabetes mellitus (IDDM), or type 1 diabetes, develops in about 1 in every 600 children in their lifetime. However, the prevalence is only about 1 in 10,000 in eastern Asia. Before 1922, all children with diabetes died within 1 or 2 years of diagnosis. It was an agonizing illness; the children lost weight despite eating well, became progressively weaker and cachectic, were soon plagued by infections, and eventually died of over-

TABLE 50-1

**PRODUCTS OF PANCREATIC ISLET CELLS**

CELL TYPE	PRODUCT
$\alpha$	Glucagon
$\beta$	Insulin Proinsulin C peptide Amylin
$\delta$	Somatostatin
F	Pancreatic polypeptide

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.