Scientific Foundations of Gastroenterology

Edited by

WILFRED SIRCUS
and
ADAM N. SMITH

Scientific Foundations of Gastroenterology

Edited by

WILFRED SIRCUS

MD PhD FRCP FRCPE

Reader in Medicine, University of Edinburgh
Senior Consultant Physician,
The Gastrointestinal Unit of the University of Edinburgh
and Western General Hospital, Edinburgh

and

ADAM N. SMITH

MD FRCSE

Reader in Clinical Surgery, University of Edinburgh
Consultant Surgeon,
The Gastrointestinal Unit of the University of Edinburgh
and Western General Hospital, Edinburgh

LONDON
WILLIAM HEINEMANN MEDICAL BOOKS LTD.

First published 1980

ISBN 0 433 30410 3

Text set in 10/11 pt VIP Times, printed and bound
in Great Britain at The Pitman Press, Bath

LIST OF CONTRIBUTORS

E. AMDRUP, MD PhD
Professor in Surgery; Chief Surgeon, Surgical Gastroenterological Department, Kommunehospitalet, University of Aarhus, Denmark.

S. R. BLOOM, MB FRCP
Reader in Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London.

J. H. BOND, Jr, MD
Chief of Gastroenterology Section, Veterans Administration Medical Center, Minneapolis, Minnesota; Associate Professor of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota, USA.

J. BONÉ, MD
Senior Lecturer; Chief Surgeon, Surgical Gastroenterological Department, Kommunehospitalet, University of Aarhus, Denmark.

I. A. D. BOUCHIER, MD FRCP FRCPE
Professor of Medicine, University of Dundee; Hon Consultant Physician, Ninewells Hospital and Medical School, Dundee.

F. P. BROOKS, MD ScD
Professor of Medicine and Physiology, School of Medicine, University of Pennsylvannia, USA.

KATHARINE E. CARR, PhD
Lecturer in Anatomy, University of Glasgow.

D. C. CARTER, MD FRCS (Ed)
St Mungo Professor of Surgery, Glasgow University; Hon Consultant Surgeon, Glasgow Royal Infirmary.

P. B. COTTON, MD FRCP
Consultant Physician, The Middlesex Hospital, London.

A. CUSCHIERI, MD ChM FRCS FRCSE
Professor of Surgery; Head of Department of Surgery, Ninewells Hospital and Medical School, Dundee.

I. M. P. DAWSON, MA MD FRCP FRCPath
Professor of Pathology, Nottingham University Medical School; Hon Consultant Pathologist, Nottingham Area Health Authority.

ELEANOR E. DESCHNER, MD
Associate Professor of Medicine and Radiology, Cornell University Medical College; Associate Member, Memorial Sloan-Kettering Cancer Center; New York, USA.

B. S. DRASAR, PhD DSc MRCPath
Senior Lecturer in Medical Microbiology, Departments of Medical Microbiology, Nutrition and Ross Institute of Tropical Hygiene, London School of Hygiene and Tropical Medicine.

D. A. DREILING, MD
Alfred and Florence Gross Professor of Surgery; Vice-Chairman and Deputy Director of Surgery, Mount Sinai Hospital; Director, Center for Laboratory Animal Science; Editor, Mount Sinai Journal of Medicine, New York, USA.

R. EARLAM, MA MChir FRCS
Consultant Surgeon, The London Hospital.

M. A. EASTWOOD, MB MSc FRCPE
Consultant Physician, Gastrointestinal Unit, Western General Hospital, Edinburgh and Part-time Senior Lecturer, University of Edinburgh.

N. EMMELIN, MD
Professor of Physiology, Faculty of Medicine, University of Lund, Sweden.

J. T. FARRAR, MD
Professor of Medicine, Medical College of Virginia; Chief of Staff, McGuire Veterans Administration Medical Center, Richmond, Virginia, USA.

ANNE FERGUSON, PhD FRCP MRCPath
Senior Lecturer and Consultant Physician, Gastrointestinal Unit, Western General Hospital and University of Edinburgh.

H. M. GILMOUR, MB ChB MRCPath
Senior Lecturer, Department of Pathology, University of Edinburgh.

R. C. HEADING, BSc MB ChB FRCPE
Senior Lecturer, University of Edinburgh; Consultant Physician, Royal Infirmary of Edinburgh.

J. HELLEMANS, MD Agg HO
Professor of Geriatrics, Head of Department of Geriatrics, University Hospital St Pieter, Leuven, Belgium.

R. A. HINDER, MB BCh PhD FRCS FRCSE
Principal Surgeon and Senior Lecturer, Johannesburg Hospital and University of the Witwatersrand, Johannesburg, South Africa.

M. HOBSLEY, *TD* MChir PhD FRCS
Professor of Surgical Science, The Middlesex Hospital Medical School; Hon Consultant Surgeon, The Middlesex Hospital, London.

HELENA E. HUGHES, FRCPath FRCOG FIAC
Consultant in Exfoliative Cytologt, Glasgow Royal Infirmary; Hon Lecturer in Diagnostic Cytology, University of Glasgow.

C. W. IMRIE, BSc MB ChB FRCS
Consultant Surgeon, Royal Infirmary, Glasgow.

K. A. KELLY, MD MS(Surg) FACS
Professor of Surgery, Mayo Medical School, Rochester, Minnesota; Consultant in Surgery and Surgical Research, Mayo Clinic, Rochester, Minnesota, USA.

S. J. KONTUREK, MD PhD
Professor of Physiology and Medicine; Department Chairman and Director of the Institute of Physiology, Medical Academy, Krakow, Poland.

M. J. S. LANGMAN, MD FRCP
Professor of Therapeutics, University of Nottingham Medical School.

M. D. LEVITT, MD
Associate Chief of Staff for Research, Veterans Administration Medical Center, Minneapolis, Minnesota; Professor of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota, USA.

M. LIPKIN, MD
Professor of Medicine, Cornell University Medical College; Professor, Graduate School of Medical Sciences, Cornell University; Head of Laboratory of Gastrointestinal Research, Memorial Sloan-Kettering Cancer Center, New York, USA.

R. N. M. MACSWEEN, BSc MD FRCP FRCPath
Professor in Pathology, University of Glasgow; Hon Consultant Pathologist, Western Infirmary, Glasgow.

P. D. MARSDEN, MD FRCPE MRCP DTM&H DAP&E
Professor of Medicine, University of Brasilia, Brazil; Adjunct Professor of Medicine, Cornell Medical Center, New York, USA; Hon Senior Lecturer, London School of Hygiene and Tropical Medicine.

ADRIAN MARSTON, MA DM McH FRCS
Consultant Surgeon, The Middlesex and Royal Northern Hospitals, London; Senior Lecturer in Surgery, University of London.

R. B. MCCONNELL, MD FRCP
Research Fellow, Nuffield Unit of Medical Genetics, Department of Medicine, University of Liverpool; Consultant Physician, Royal Liverpool Hospital and Gastroenterology Unit, Broadgreen Hospital, Liverpool.

M. V. MERRICK, MA BM BCh MSc FRCP
Consultant in Nuclear Medicine; Part-time Senior Lecturer, University of Edinburgh, Departments of Medicine, Radiology and Medical Physics.

J. J. MISIEWICZ, BSc MB BS FRCP
Consultant Physician, Department of Gastroenterology, Central Middlesex Hospital, London; Member of External Scientific Staff, Medical Research Council; Hon Consultant Gastroenterologist, St Mark's Hospital, London.

J. NIMMO, BSc MB ChB FRCP
Consultant Physician, Eastern General Hospital, Edinburgh; Part-time Senior Lecturer, University of Edinburgh.

A. S. PAINTAL, MD PhD DSc FRSE FNA
Professor of Physiology, Director, Vallabhbhai Patel Chest Institute, University of Delhi, India.

T. G. PARKS, MCh FRCS
Reader in Surgery, The Queen's University, Belfast; Consultant Surgeon, Royal Victoria Hospital and Belfast City Hospital, Northern Ireland.

D. W. PIPER, MD FRCP FRACP
Professor of Medicine, University of Sydney; Physician, The Royal North Shore Hospital of Sydney, New South Wales, Australia.

R. M. PRESHAW, MD FRCSE FRCS(C)
Associate Professor, Division of Surgery, University of Calgary, Alberta, Canada.

JULIA M. POLAK, MD MRCPath
Lecturer in Histochemistry, Royal Postgraduate Medical School, Hammersmith Hospital, London.

A. B. PRICE, MA BM BCh MRCPath
Consultant Histopathologist, Northwick Park Hospital and Clinical Research Centre, Harrow.

R. I. RUSSELL, MD PhD FRCP(Ed) FRCP(Glas)
Consultant-in-charge, Gastroenterology Unit, Royal Infirmary, Glasgow; Hon Lecturer, University of Glasgow.

G. W. SCOTT, MB MS FRCS(C)
Director, Surgical-Medical Research Institute; Professor of Surgery, University of Alberta.

T. SCRATCHERD, MD FRCP(Ed)
Professor of Physiology, Department of Physiology, University of Sheffield.

J. W. T. SEAKINS, MA PhD
Senior Lecturer, Department of Chemical Pathology, Institute of Child Health and Hospital for Sick Children, London.

J. J. SHEPHERD MD FRCSE FRACS
Professor of Surgery, University of Tasmania; Visiting Surgeon, Royal Hobart Hospital; Senior Visiting Specialist in Surgery, Repatriation General Hospital, Hobart, Tasmania.

D. B. A. SILK, MD MRCP
Consultant Physician, Department of Gastroenterology, Central Middlesex Hospital, London.

M. SIURALA, MD
Formerly Professor of Medicine, Mejlans Hospital, Helsinki, Finland.

H. THOMPSON, MD FRCPath
Reader in Pathology, University of Birmingham; Hon Consultant in Pathology, Central Area Health District, Birmingham.

O. M. TISCORNIA MD
Assistant Professor of Anatomy, School of Medicine, Buenos Aires; Chief of Gastroenterological Unit, Hospital de Clinicas, Buenos Aires, Argentina.

P. G. TONER, DSc MRCPath
Reader in Pathology, University of Glasgow; Hon Consultant Pathologist, Glasgow Royal Infirmary.

L. A. TURNBERG, MD FRCP
Professor of Medicine, University of Manchester; Consultant Physician, Hope Hospital, Salford.

G. R. VANTRAPPEN, MD Agg HO
Professor of Medicine, Head of Department of Medical Research, University of Leuven; Head of Division of Gastroenterology, University Hospital of St Rafael, Leuven, Belgium.

K. V. VARIS, MD
Senior Lecturer in Gastroenterology; Assistant Physician-in-Chief, Second Department of Medicine, University of Helsinki, Finland.

C. W. VENABLES, MS FRCS
Senior Lecturer in Surgery, Hon Consultant in Surgical Gastroenterology, Royal Victoria Infirmary, Newcastle upon Tyne.

M. WARD, MB MRCP FRACP
Gastroenterologist, Royal Brisbane Hospital, Queensland, Australia.

PREFACE

This book has arisen out of the extremely rapid growth in recent years of the clinical speciality of Gastroenterology. This is reflected in technological advances in basic science, in investigative methodology and in scientifically-based modes of management.

A knowledge of these aspects is clearly essential for all clinicians and medical scientists whose work relates to the alimentary tract. A high standard of gastroenterological practice requires both physicians and surgeons to be familiar with the basic science of the discipline. The introduction in this book of critical appraisals of surgical care emphasizes the combined approach to investigation and management.

Basic scientific information having wide scope and diverse origins tends to be excluded from conventional text books and monographs. This book has been designed to fill this gap. Each of the fifty chapters presents a critical review of the state of contemporary knowledge. The size of individual chapters and the amount of information (or the scope of detail) to an extent reflects the ease of obtaining this from conventional sources.

An introductory section covers what we believe to be the most important of general gastrointestinal topics at the present time. The subsequent chapters have a regional application. The liver has been excluded as it will be the subject of another book in the *Foundation* series.

The authors have been chosen for their special experience so that the contributions are truly intercontinental. We have deliberately chosen not to standardize spelling so that both the American and the traditional forms of the English language are used, and have permitted flexibility in the use of synonyms such as 'gastrointestinal' and 'alimentary', thus following the pattern set by journals of Gastroenterology now emanating from several countries. We have even accepted abbreviations hallowed by tradition e.g. GI for gastrointestinal tract. Illustrations have been limited to those facilitating presentation or comprehension of the text; we did, however, feel it appropriate to have a more lavishly illustrated ultrastructure section. A small amount of overlap between chapters has been allowed where of advantage to the treatment of the subject.

We would like to express our gratitude to those authors who skilfully and speedily fulfilled their task and trust that the others will have forgiven us for our fervour and doggedness in pursuit of their manuscripts. We would like to pay special tribute to Miss Mary Wilson whose indefatigable regard for order and detail greatly helped our endeavour. It has been a pleasure to work with Richard Emery and Ann Kirk of Heinemann Medical Books Ltd. and we are particularly indebted to the latter for her patience and skill.

W. Sircus
A. N. Smith

September, 1979

CONTENTS

SECTION I

GENERAL ASPECTS

		PAGE
1.	MICROANATOMY OF THE GASTROINTESTINAL TRACT P. G. Toner and Katharine E. Carr	1
2.	GASTROINTESTINAL CELLS: PROLIFERATION AND DIFFERENTIATION M. Lipkin and Eleanor E. Deschner	25
3.	GENETICS AND GASTROINTESTINAL DISEASE R. B. McConnell	31
4.	INBORN ERRORS OF METABOLISM J. W. T. Seakins	44
5.	GASTROINTESTINAL IMMUNOLOGY Anne Ferguson	51
6.	MICROBIOLOGY OF THE GASTROINTESTINAL TRACT B. S. Drasar	67
7.	PARASITIC ECOLOGY OF THE GASTROINTESTINAL TRACT P. D. Marsden	82
8.	EPIDEMIOLOGY OF GASTROINTESTINAL DISEASE M. J. S. Langman	88
9.	ALIMENTARY ENDOCRINE SYSTEM S. R. Bloom and Julia M. Polak	101
10.	REGULATION OF FOOD INTAKE A. S. Paintal	123
11.	INTRAVENOUS NUTRITION AND ELEMENTAL DIETS R. I. Russell	130
12.	DRUGS: ABSORPTION AND ACTION J. Nimmo	141
13.	METAPLASIA AND NEOPLASIA OF THE GASTROINTESTINAL TRACT A. B. Price	148
14.	ALIMENTARY TRACT ISCHAEMIA Adrian Marston	159
15.	ALIMENTARY TRACT HAEMORRHAGE C. W. Venables	171
16.	CYTOLOGY IN GASTROINTESTINAL DISEASE Helena E. Hughes	180
17.	FIBREOPTIC ENDOSCOPY P. B. Cotton	193
18.	NUCLEAR AND SONIC DIAGNOSTIC METHODS M. V. Merrick	204

SECTION II

SALIVARY GLANDS

PAGE

19. SECRETORY MECHANISMS 219
N. EMMELIN

SECTION III

OESOPHAGUS

20. MOTILITY 227
G. R. VANTRAPPEN and J. HELLEMANS

21. TISSUE REACTIONS IN DISEASE 253
H. THOMPSON

22. EVALUATION OF SURGICAL PROCEDURES 267
R. EARLAM

SECTION IV

STOMACH AND DUODENUM

23. ABDOMINAL VAGI 279
E. AMDRUP and J. BONÉ

24. GASTRIC MOTILITY AND EMPTYING 287
R. C. HEADING

25. SECRETORY MECHANISMS OF ACID AND PEPSIN 296
S. J. KONTUREK

26. TESTS OF GASTRIC SECRETORY FUNCTION 316
M. HOBSLEY

27. MUCUS: CHEMISTRY AND CHARACTERISTICS 333
D. W. PIPER

28. AETIOLOGY OF PEPTIC ULCER 344
D. C. CARTER

29. GASTRITIS 357
M. SIURALA and K. V. VARIS

30. EVALUATION OF SURGICAL PROCEDURES 370
K. A. KELLY and R. A. HINDER

SECTION V

SMALL INTESTINE

31. MECHANISMS OF DIGESTION AND ABSORPTION 389
F. P. BROOKS

32. WATER AND ELECTROLYTE METABOLISM 397
L. A. TURNBERG

33. DISORDERED PROTEIN METABOLISM 408
D. B. A. SILK

PAGE

34. ASSESSMENT OF FUNCTION 426
M. WARD

35. MOTILITY 445
J. T. FARRAR

36. TISSUE REACTIONS IN DISEASE 451
I. M. P. DAWSON

37. EVALUATION OF SURGICAL PROCEDURES 460
A. CUSCHIERI

SECTION VI

LARGE INTESTINE: COLON, RECTUM AND ANUS

38. COLON FUNCTION 473
M. A. EASTWOOD

39. MOTILITY 483
J. J. MISIEWICZ

40. INTESTINAL GAS 492
M. D. LEVITT and J. H. BOND

41. ANORECTAL FUNCTION 499
J. J. SHEPHERD

42. TISSUE REACTIONS IN DISEASE 511
H. M. GILMOUR

43. EVALUATION OF SURGICAL PROCEDURES 524
T. G. PARKS

SECTION VII

BILIARY TRACT AND PANCREAS

44. BILIARY TRACT: ANATOMY AND PATHOPHYSIOLOGY 547
G. W. SCOTT

45. BILE, BILE ACIDS AND GALLSTONES 565
I. A. D. BOUCHIER

46. PANCREATIC SECRETORY MECHANISMS 579
T. SCRATCHERD

47. TESTS OF PANCREATIC FUNCTION 591
D. A. DREILING and O. M. TISCORNIA

48. TISSUE REACTIONS IN DISEASE 602
R. N. M. MACSWEEN and C. W. IMRIE

49. EVALUATION OF SURGICAL PROCEDURES: BILIARY TRACT 612
R. M. PRESHAW

50. EVALUATION OF SURGICAL PROCEDURES: PANCREAS 622
C. W. IMRIE

SECTION I

GENERAL ASPECTS

1. MICROANATOMY OF THE GASTROINTESTINAL TRACT 1
2. GASTROINTESTINAL CELLS: PROLIFERATION AND DIFFERENTIATION 25
3. GENETICS AND GASTROINTESTINAL DISEASE 31
4. INBORN ERRORS OF METABOLISM 44
5. GASTROINTESTINAL IMMUNOLOGY 51
6. MICROBIOLOGY OF THE GASTROINTESTINAL TRACT 67
7. PARASITIC ECOLOGY OF THE GASTROINTESTINAL TRACT 82
8. EPIDEMIOLOGY OF GASTROINTESTINAL DISEASE 88
9. ALIMENTARY ENDOCRINE SYSTEM 101
10. REGULATION OF FOOD INTAKE 123
11. INTRAVENOUS NUTRITION AND ELEMENTAL DIETS 130
12. DRUGS: ABSORPTION AND ACTION 141
13. METAPLASIA AND NEOPLASIA OF THE GASRTOINTESTINAL TRACT 148
14. ALIMENTARY TRACT ISCHAEMIA 159
15. ALIMENTARY TRACT HAEMORRHAGE 171
16. CYTOLOGY IN GASTROINTESTINAL DISEASE 180
17. FIBREOPTIC ENDOSCOPY 193
18. NUCLEAR AND SONIC DIAGNOSTIC METHODS 204

1. MICROANATOMY OF THE GASTROINTESTINAL TRACT

P. G. TONER and KATHARINE E. CARR

Introduction

Mouth and oesophagus

Salivary glands

Stomach

Small intestine

Large intestine

Luminal environment

Connective tissues, muscle and serosa

INTRODUCTION

Electron microscopy has extended the horizons of gut morphology. Thin sectioning techniques and transmission microscopy have provided much new information on the organization of cytoplasmic fine structure while more recently, the scanning electron microscope has broken out from the traditional limitations of tissue sections to reawaken an awareness of surface morphology. In resolving power and depth of field, the scanning microscope surpasses the binocular light microscopes but in conceptual terms their images are equivalent although they use quite different image forming systems. The scanning microscope forms a high resolution image of the surface topography of suitable specimens, from the villous pattern of the gut to the microvilli of the single cell. The depth of field contributes to a uniquely detailed and clearly defined three dimensional representation of surface contours, allowing us an instant appreciation of surface detail which makes extensive verbal description redundant. The sensation of reality provided by the scanning micrograph promotes an intuitive grasp of surface structure which could otherwise be achieved only by laborious reconstruction from two-dimensional images.

Microanatomy in contrast has often been thought of as a rather static discipline. In the last few years, however, fresh insights have been gained and concepts born; new cell types have been discovered and the functions of old ones reassessed. The scope of this chapter is confined largely to the mucosal surfaces where most recent interest has been concentrated. The contribution of scanning electron microscopy has been highlighted, without dwelling upon the technicalities; information on this rapidly advancing new technique is available in a recent review (Toner and Carr, 1979). Further details of the ultrastructural organization of specific cell types may be found in a fuller text (Toner *et al.*, 1972).

MOUTH AND OESOPHAGUS

Surface Structure

The superficial cell layer of the oesophageal mucosa, when seen in the conventional vertical plane of section, has a row of rather unimpressive stubby surface projections usually described in the past as microvilli. In surface view, however, these profiles are integrated into

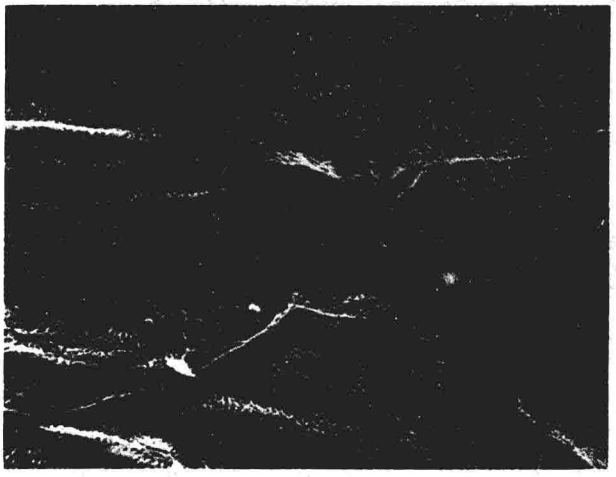

FIG. 1. Epithelial surface of the oesophagus of the American opossum, 6 cm above the lower oesophageal sphincter. Intercellular ridges are clearly seen and microridges can be made out. Approx. × 1500. (By courtesy of Dr. Larry D. Ackerman. Ackerman *et al.*, 1976.)

their true three-dimensional arrangement, which consists of an elaborate system of microridges of fingerprint complexity, with additional marginal ridges around the cell perimeter (Fig. 1). In some species it has been suggested that these ridges may hold a layer of protective mucus close to the cell surface, and facilitate its spread away from the mouths of mucous glands.

Squamous Cells

The non-keratinized squamous mucosa which lines the human buccal cavity (Squier and Meyer, 1971), and oesophagus is generally divided into a basal and a prickle cell layer, with overlying intermediate and superficial layers. In man there are regional variations in the extent of keratinization, according to functional demands (Squier *et al.*, 1976). Mitotic activity is confined to cells in the basal layer or immediately above, and mitoses have been found to occur in clusters rather than randomly. The renewal time in oral epithelium is usually recorded as from 4 to 14 days, although wider variations according to site do occur. As the basal layers renew themselves, there is a parallel shedding of the superficial strata.

The functional and morphological sequence of events during maturation is complex, involving various interrelated processes, the final outcome of which varies from site to site and from species to species. Thus the rodent oesophagus undergoes full orthokeratinization while in man the epithelium remains non-keratinized; however, in human gingival and palatal mucosa, parakeratinization and orthokeratinization are encountered.

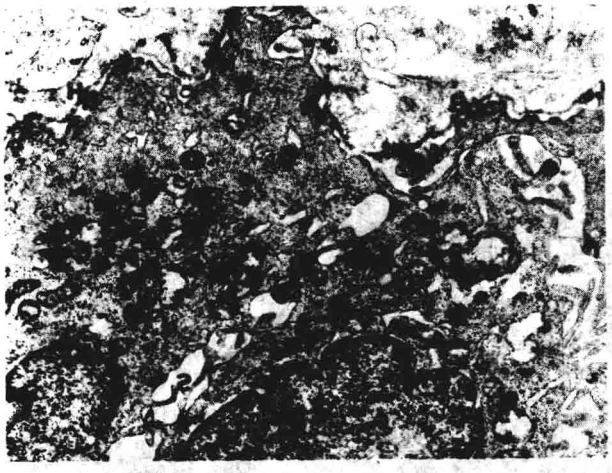

FIG. 2. Basal cell layer of normal human oesophagus, showing the continuous basal lamina (B) with intermittent hemidesmosomes (H). Cytoplasmic tongues project into the intercellular spaces (S), but the adjacent cells are in firm contact at points where desmosomes occur (D). Groups of mitochondria are seen. Approx. × 4250. (By courtesy of Dr. T. Al Yassin.)

The basal cells of the epithelium are cuboidal or oblong, with central nuclei. Their cytoplasm is relatively unspecialized, (Fig. 2) containing moderate numbers of mitochondria, a small Golgi apparatus and some free ribosomes, but little organized endoplasmic reticulum. Prominent desmosomes are a feature of squamous epithelium, reflecting the mechanical strength of the mucosa. Fine bundles of cytoplasmic tonofilaments, scattered throughout these cells, are finally inserted into the cytoplasmic plates of the desmosome. At the basal aspect of the epithelium (Fig. 2), where contact is made not with surrounding cells, but with the basal lamina, or

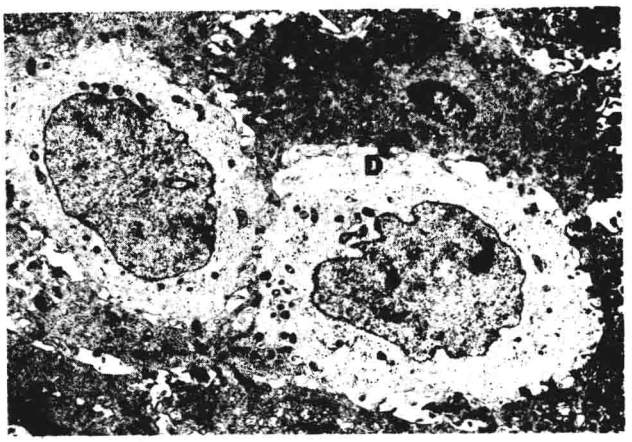

FIG. 3. Normal human oesophagus, basal layers. These two cells are the daughter cells of a mitosis. Note the pale cytoplasm, which contrasts with the more differentiated cells which surround the pair. These cells are still connected to each other and to their neighbours by desmosomes (D). Approx. × 2200. (By courtesy of Dr. T. Al Yassin.)

basement membrane, hemidesmosomes or half desmosomes are observed. Each consists of a single dark plate on the cell membrane into which the tonofilaments insert, along with the extracellular lamina which in a symmetrical 'full' desmosomes forms the intermediate median component between the adherent cells. The basal lamina itself, a continuous boundary 40 to 50 nm in thickness, with an underlying reinforcing layer of connective tissue fibres, is separated from the base of the epithelial cell by a pale interspace of about 50 to 65 nm. These rather undifferentiated basal cells have general structural features in line with those of progenitor cell populations elsewhere, particularly when seen shortly after mitotic division (Fig. 3).

As the cells pass from the basal to the intermediate zone of the oesophageal epithelium they become larger and flatter than the basal cells, while retaining similar general features. The tonofilament bundles in general adopt a more diffuse, random distribution. The desmosomes are more prominent than in the basal layer. Intercellular spaces of variable width occur, crossed at intervals by the interdigitating processes of adjacent cells at points where adhesion is maintained by the desmosomes (Fig. 4). This pattern is reflected in the 'prickle-cell' appearance faintly visible in this region under the high magnifications of the light microscope.

In the upper part of this intermediate or prickle cell layer of the epithelium, the 'membrane-coating granules' are first encountered (Fig. 5). These are small round or oval granules, from 60 to 350 nm in diameter, limited by a trilaminar membrane. There is a dense homogenous component in each granule, surrounded by a pale halo; a carbohydrate-rich component of the granule can be stained by special techniques (Fig. 6). Some may show a faint internal lamination (Fig. 7), but this is not as pronounced as in keratinized epithelium, where the distinctive periodicity of such granules is their most striking property. These granules may originate within

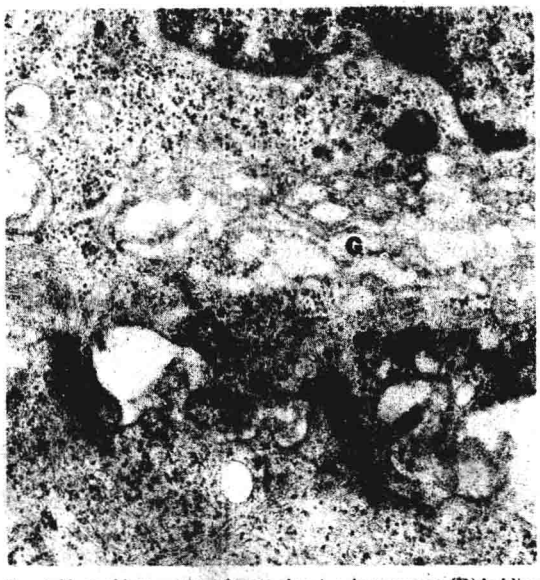

FIG. 4. Normal human oesophagus, showing desmosomes (D) holding together two cells of the intermediate cell layer. Notice the bridging of the intercellular space by the connecting processes of cytoplasm. The fine bundles of tonofilaments are seen to be inserted into the cytoplasmic surfaces of the demosome specializations. A nearby Golgi system (G) is seen, along with numerous free ribosomes. Approx. × 10 000. (By courtesy of Dr. T. Al Yassin.)

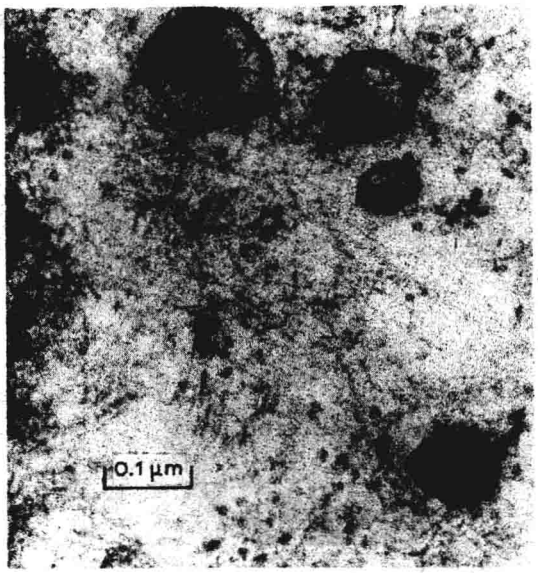

FIG. 5. Normal human oesophagus showing the typical membrane-coating granules of non-keratinised epithelium. Each granule consists of a dense core, a pale halo and a limiting membrane. Approx. × 120 000. (From Al Yassin and Toner, 1977.)

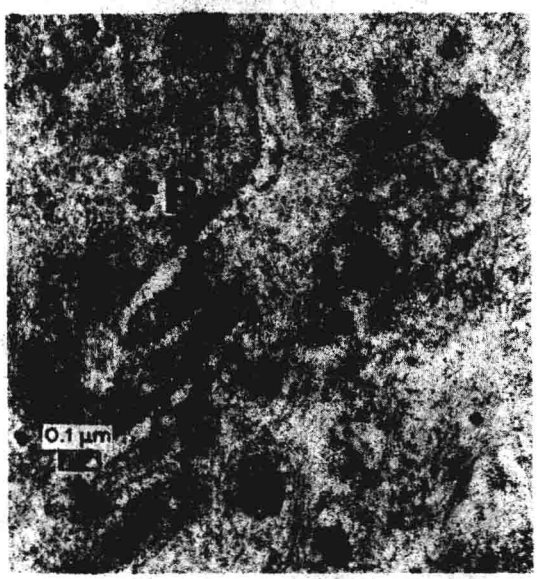

FIG. 6. Normal human oesophagus stained for carbohydrate moieties by the periodic acid silver proteinate procedure. Note the reactivity of the halo area of the membrane-coating granules. A few glycogen particles are densely stained (P). Approx. × 60 000. (From Al Yassin and Toner, 1977.)

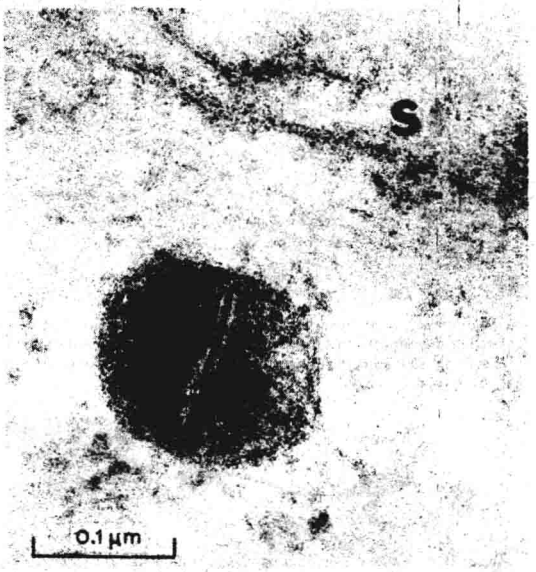

FIG. 7. Normal human oesophagus, showing a single, faintly laminated granule, close to the intercellular space (S). This lamination, reminiscent of the pattern seen in keratinising epithelium, is unusual in this site. Approx. × 200 000. (From Al Yassin and Toner, 1977.)

the Golgi apparatus but they then gather at the margins of the cell, where they are discharged into the intercellular space (Fig. 8). Acid phosphatase activity (Fig. 9) can be demonstrated there and within individual granules. This enzyme may promote epithelial desquamation. The coating membrane may contribute to the 'permeability barrier' at this level of the epithelium.

The superficial layer of the human oesophageal mucosa consists of flattened cells which have retained their nuclei, while losing most of the other formed cytoplasmic organelles. The tonofilaments now form a diffuse feltwork throughout the cell (Fig. 10) suspended in a rather pale cytoplasmic matrix. Vacuolation due to the presence of glycogen is often apparent. The cell

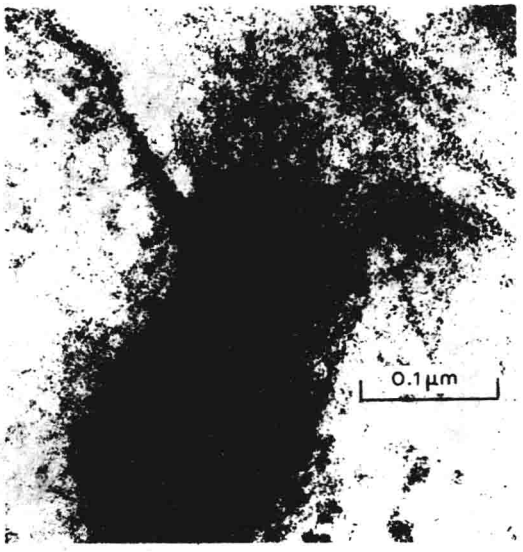

FIG. 8. Normal human oesophagus, showing a single membrane-coating granule being released into the intercellular space. It is thought that this phenomenon may contribute to the barrier function of squamous mucosa. Approx. × 190 000. (From Al Yassin and Toner, 1977.)

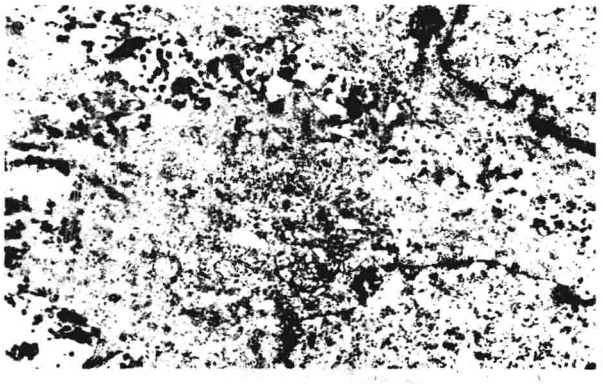

FIG. 9. Normal human oesophagus stained by the acid phosphatase procedure, showing the deposition of reaction product in the intercellular spaces, in the form of dense lead-containing granules. Approx. × 4000. (By courtesy of Dr. T. Al Yassin.)

FIG. 10. Normal human oesophagus, showing the superficial layer of the squamous mucosa, with the overlying lumen. Two residual desmosomes (D) are seen, but elsewhere the cells are not in close contact. The cytoplasm contains numerous irregularly disposed filaments with patches of denser matrix material. The cell membrane is noticeably thickened, even at this magnification. Approx. × 20 000. (From Al Yassin and Toner, 1977.)

surfaces have become altered in various ways. Desmosomes are reduced in numbers, although interdigitations between cells persist.

The trilaminar cell membrane of the surface layer undergoes a structural modification, its inner component becoming thicker and more heavily stained than in the basal and intermediate cell layers (Fig. 11). The presence of an external carbohydrate-rich cell coat can be demonstrated by appropriate staining procedures (Fig. 12). Thus the free surface of the human oesophageal

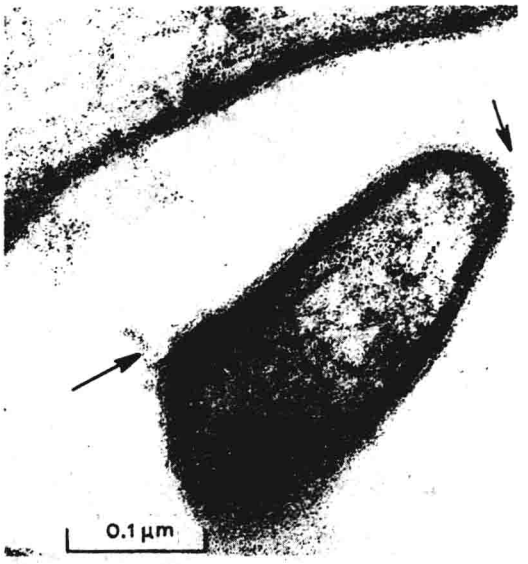

FIG. 11. Higher magnification view of superficial cells of normal human squamous oesophageal mucosa. Notice the density of the inner lamina of the cell membrane. The arrows indicate the tenuous filamens of the cell surface coat. Approx. × 200 000. (From Al Yassin and Toner, 1977.)

FIG. 12. Superficial cells of normal human squamous oesophageal mucosa, stained for carbohydrate moieties by the periodic acid silver proteinate technique. The carbohydrate-rich cell surface coat is well outlined, as well as the glycogen granules of the cytoplasm (arrows). Approx. × 70 000. (From Al Yassin and Toner, 1977.)

mucosa consists of flattened nucleated squames, each with an altered, thickened cell membrane, enveloping a loose feltwork of cytoplasmic tonofilaments. The principal barrier function of the mucosa may be constituted by the intercellular material secreted by the keratinocytes during the maturation process.

One small curiosity of epithelial structure may be mentioned in passing. Occasional intracytoplasmic desmosomes may be seen, particularly at points where adjacent cells seem to have pulled apart. These paradoxical structures have the morphology of typical desmosomes (Fig. 13), including a laminated structure and inserted tonofilaments, but they lie embedded within the cytoplasm instead of forming an attachment with another cell. They have no demonstrable link with the cell surface or with any cytoplasmic membrane system. These structures may arise by engulfment of 'torn-off' desmosomes at points where cells are temporarily separated by mechanical forces. Such separation may occur as a normal event during mitosis.

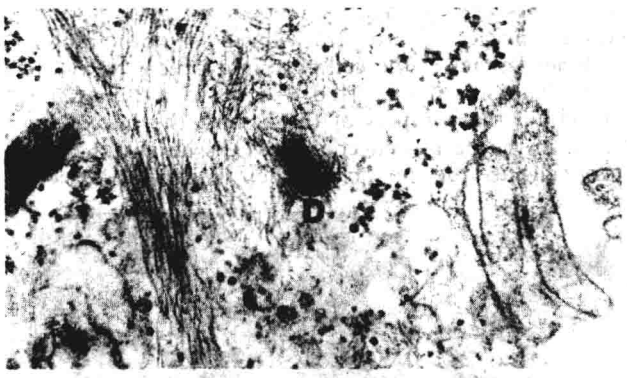

FIG. 13. Normal human oesophagus; cell from close to the basal layer, showing cytoplasmic filaments and ribosomes. One discrete intracytoplasmic desmosome (D) is seen, well separated from the cell surface. No connections to cytoplasmic membranes are seen. Approx. × 32 000. (By courtesy of Dr. T. Al Yassin.)

Langerhans Cells

The Langerhans cell is found in the upper layers of the epidermis, in buccal and oesophageal mucosa, and in other stratified squamous epithelia. On conventional histology, they appear as high level clear cells, their typical dendritic morphology being seen only after appropriate staining. These cells are strongly ATPase positive.

On electron microscopy (Al Yassin and Toner, 1976), the Langerhans cells are irregular in outline (Fig. 14), with cytoplasmic projections extending out from the perikaryon between surrounding squamous cells. They lack the desmosomal attachments and the cytoplasmic tonofilaments of the keratinocyte; they have a fairly well-developed Golgi system and scattered cisternae of granular endoplasmic reticulum. Dense pleomorphic lysosome-like bodies are relatively common. Owing to the irregular shape of the Langerhans cell, it may appear in one plane to have rather bulky cytoplasm (Fig. 14), while in another plane there may be only a thin cytoplasmic rim around the nucleus (Fig. 15).

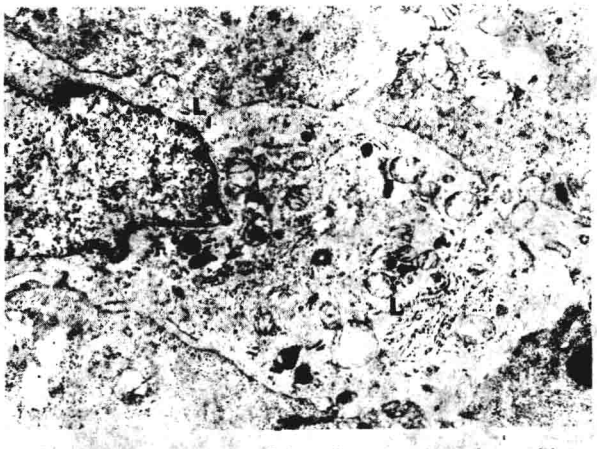

FIG. 14. Part of a Langerhans cell from the upper strata of normal human oesophagus. Notice the lack of desmosomal attachments and of cytoplasmic tonofilaments. The characteristic granules, situated at L, cannot be clearly seen at this magnification, but the well organised cytoplasmic organelles can be observed. Approx. × 5000. (By courtesy of Dr. T. Al Yassin.)

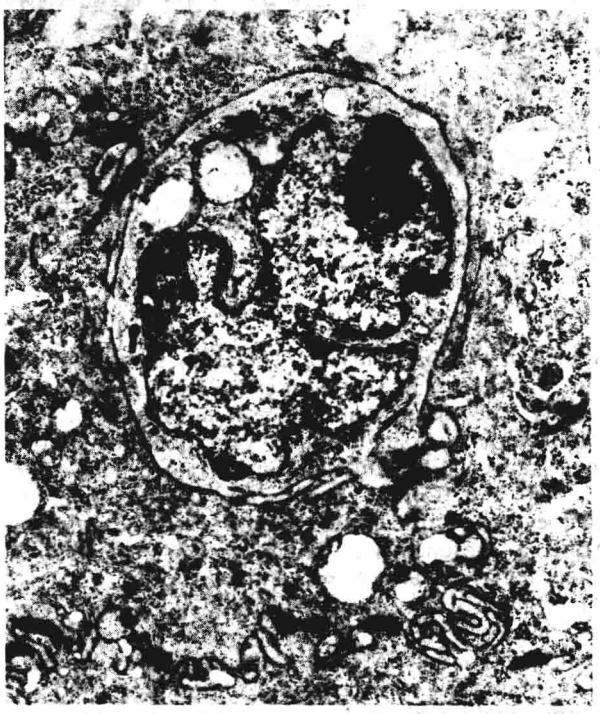

FIG. 15. Langerhans cell between keratinocytes of middle layers of normal human oesophagus. The plane of section passes through the narrow waist of the cell, showing little of the cytoplasm. Approx. × 6000. (By courtesy of Dr. T. Al Yassin.)

The most distinctive single ultrastructural feature is the presence of granules, which may occur in quite large numbers in a cell sectioned through its perikaryon. These are rod-shaped inclusions up to 460 nm in length, often with a rounded expansion up to 150 nm diameter at one end; the term 'tennis rackets' has been applied to

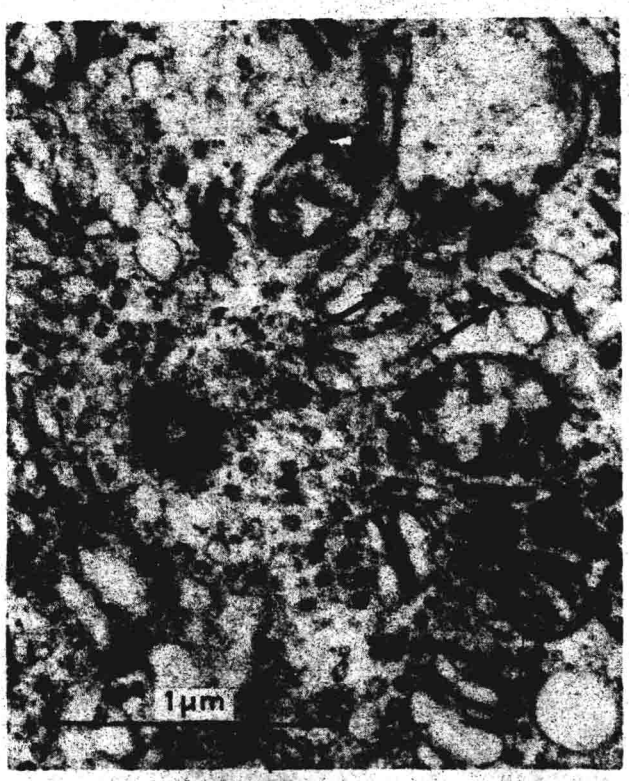

FIG. 16. Centriolar region of human Langerhans cell, showing Golgi membranes and several typical Langerhans granules (arrows) with characteristic 'tennis-racket' profiles. Dense lysosome-like granules are also present. Approx. × 35 000. (From Al Yassin and Toner, 1977.)

granules of this pattern (Fig. 16). The 'handle' of the tennis racket has a characteristic internal laminated structure. The presence of these granules is now taken as the most important single criterion for identification of a Langerhans cell. The function of the Langerhans cell is unknown and former hypotheses linking them to melanocytes are discounted. Evidence now exists supporting a mesenchymal origin with a role as an intraepithelial scavenger or in antigen capture.

The Langerhans cell is not the only non-keratinocyte of the mucosa. Melanocytes may occur, particularly in buccal mucosa, and Merkel cells, possibly related to sensory reception, can be found. As indicated above, intraepithelial lymphocytes are a common occurrence in squamous as in other mucosae.

Mucous Glands

The submucosal glands of human oesophagus lie in the submucous connective tissues, each connected to the mucosal surface by a straight duct. Each lobule contains acinar and ductal structures, the acini lined by predominantly mucus-secreting columnar cells, the ducts by cuboidal or stratified epithelium. These glands most closely resemble the minor salivary tissue of the buccal mucosa.

The mucous cells of the glands (Al Yassin and Toner, 1977) are closely packed, pyramidal in shape, and connected by junctional complexes. The nucleus is pushed to the periphery of the cell by the accumulated mass of pale foamy secretion granules, which often seem to coalesce (Fig. 17). There is a rim of well-organized granular endoplasmic reticulum at the basal and perinuclear areas, and an elaborate Golgi system is seen in favourable sections. There are occasional mitochondrial inclusions, consisting of bundles of parallel tubules; and finally there are scattered membrane-limited cytoplasmic inclusions, containing bundles of microfibrils associated with pale vacuoles. Several other types of acinar secretory cells are only occasionally encountered, but myoepithelial cells are plentiful, being found in every acinus (Fig. 17). These are flattened spindle-shaped cells, sandwiched between the acinar secretory cells, to which they are connected by occasional desmosomes, and the basal lamina of the acinus. Their cytoplasm contains sparse mitochondria and few membrane systems, but is rich in myofilaments, similar to those of smooth muscle. There are typical smooth muscle attachment zones at the cell base into which the cytoplasmic filaments are inserted. No nerve terminals are seen within the confines of the acinus; the nerves are located in the periacinar connective tissue and the secretory cells are presumably indirectly innervated.

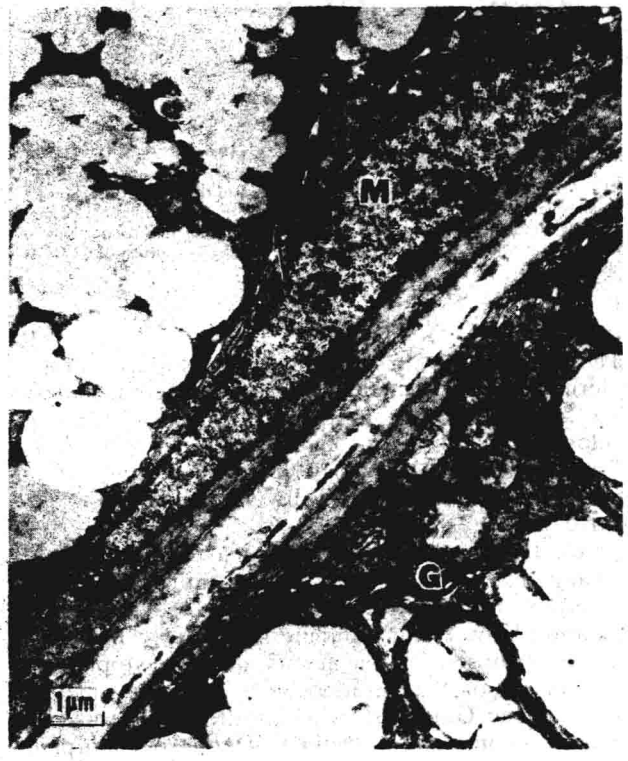

FIG. 17. Bases of two adjacent acini of human oesophageal submucosal glands. Within the upper acinus, part of a myoepithelial cell (M) is apparent. The arrow indicates the compressed rim of granular endoplasmic reticulum, and in another cell, part of the Golgi system (G) appears. The secretory granules are pale and foamy, appearing to coalesce, probably as an artefact of fixation. Approx. × 6000. (From Al Yassin and Toner, 1977.)