Diseases of the Small Intestine in Childhood

J Walker-Smith

Second Edition

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John Walker-Smith MD (Syd), FRCP (Ed), FRCP (Lond), FRACP.

Consultant Paediatrician, St Bartholomew's Hospital, London;
Senior Lecturer in Child Health,
The Medical College of St Bartholomew's Hospital
and The London Hospital Medical College at
the Queen Elizabeth Hospital for Children, London;
Honorary Consultant Physician, Hospitals for Sick Children, London.
Formerly Staff Physician in Gastroenterology,
Royal Alexandra Hospital for Children, Sydney, Australia.

With a Foreword by

A. M. Dawson MD, FRCP (Lond)

Consultant Physician, St Bartholomew's Hospital, London

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Foreword

It is a great pleasure to write a foreword to the second edition of this book. Its early appearance and the translation of the previous edition into other languages is undeniable proof of the success and value of the first edition.

Dr Walker-Smith is to be congratulated on bringing his text up to date in the simple clear style that has been the hallmark of his monograph. There is a nice blend of basic physiology, pathology and the practical aspects of the diagnosis and management of children with disorders of the small gut, which so obviously represents his personal experience. What a refreshing change from the over-documented annotated bibliography that often passes for a textbook.

It is a fascinating read for the adult physician and fast becoming a must on the shelves of paediatricians.

A. M. DAWSON
Royal Hospital of St Bartholomew
London

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I should also like to express my thanks to Professor C. C. Booth, who first inspired me to take an interest in small intestinal disease, and then to Professor T. Stapleton and the staff of the Institute of Child Health in Sydney where my studies in small intestinal disease in children first began. I am also indebted to Professor R. Walsh and Dr Helen Walsh who did so much to encourage me at that time. I also would like to acknowledge the especial debt I owe to Dr A. M. Dawson and his team at St Bartholomew's Hospital who have done so much to foster paediatric gastroenterology. I must also record my continuing debt to the European Society for Paediatric Gastroenterology and Nutrition who have done much to stimulate interest in small intestinal disease in childhood, and would especially like to record my thanks to Professor Jean Rey, Dr J. Visakorpi and Dr D. H. Shmerling who have been a great source of help and inspiration.

I am also greatly indebted to my secretary Mrs E. Lister who has worked so hard on the manuscript of the second edition.

Finally, I would like to record my thanks to my wife and family who have been so understanding in the time given up to write this book.

Preface

During the four years that have elapsed since the first edition of *Diseases of the Small Intestine in Childhood* was written there has been a remarkable expansion of knowledge in this area. This is in large measure due to the increasing awareness of the importance of small intestinal disease among children, particularly in the developing world where diarrhoeal disease continues to have such a high prevalence and, indeed, continuing mortality. As a consequence increasing research is being undertaken in this field, and in view of the rapid increase in knowledge a new edition was felt to be necessary to take into account these recent developments.

In the first edition, the preliminary exciting work on the identification of stool virus particles by electron microscopy in children with acute gastroenteritis was referred to briefly. In this edition, a completely new section is devoted to rotavirus gastroenteritis and also to the other viruses, now identifiable in the stools of children with acute gastroenteritis. It is remarkable how much information, quite unknown until 1973, is now available in this area. Yet it is obvious that a great deal more research requires to be done; for example, the relative importance of rotavirus infection in the genesis of diarrhoea in the developing world is still far from clear.

Throughout this new edition increasing attention is given to immunological studies, and in the introductory chapter a new account is given of the immunological function of the small intestine. This reflects the increasing importance attributed to immunological factors in genesis of small intestinal disease.

The importance of cow's milk protein intolerance in paediatric gastroenterology is reflected by the new work in this field, especially the diagnostic role of serial small intestinal biopsies in relation to milk withdrawal and challenge. The chapter on this malady has been considerably expanded.

The increasing problem of Crohn's disease in childhood, during the past five years, has led to more space being devoted to this subject including a discussion of improved diagnostic techniques and a review of current management.

The close relationship between nutrition and small intestinal disease is emphasised throughout the book and has been given more emphasis in this edition.

The author hopes these additions will greatly increase the value of the book to those for whom the first edition was primarily designed, and that readers will continue to find it easy to read and a useful source of up-to-date references.

Finally, the author once again, would like to express his sincere thanks to his colleagues at St Bartholomew's Hospital and the Queen Elizabeth Hospital for Children, especially to the junior staff of the gastroenterology department at the Queen Elizabeth Hospital for Children who have done so much to help and advise in the writing of this edition.

J. A. Walker-Smith,
Royal Hospital of St Bartholomew, London, July, 1978.

Preface to the First Edition

The development of specialities within paediatric medicine such as paediatric gastroenterology has been slower than in adult medicine but with the development in recent years of new diagnostic techniques which are safe and readily available for use in children, this specialisation is now rapidly occurring. The number of published texts which deal specifically with these developments so far, has been very limited and this book aims to go some way towards meeting this deficiency in the field of paediatric gastroenterology.

The small intestine is the principal organ of absorption in the body and so abnormality of this organ may have far-reaching consequences for the child's physical well-being and general development by virtue of malabsorption of vital nutrients. Thus knowledge of diseases of this organ and their consequences plays a most important part in paediatric practice.

Diseases of the small intestine have been selected for this publication as there has been a considerable amount of new work in this field in recent years. Much of this has not yet appeared in standard paediatric texts and is at present only available in medical journals, yet this group of disorders is a most important one and accounts for a large proportion of gastroenterological disease seen in childhood. As an example of this, during one twelve month period from 1 July 1967 to 1 July 1968 over 1,100 children were admitted to the Royal Alexandra Hospital for Children, Sydney, with a major disorder of the small intestine. While the great majority of these children suffered from gastroenteritis, there were also many suffering from conditions such as giardiasis, coeliac disease, meconium ileus, malrotation, congenital atresia, strongyloidiasis and intestinal lymphangiectasia. This illustrates that disease of the small intestine occurring in childhood should be regarded as a major part of the whole field of paediatrics.

Many of the clinical observations made in this book are based on the author's experience of gastroenterology at the Royal Alexandra Hospital for Children, Sydney, Australia, and St. Bartholomew's Hospital and the Queen Elizabeth Hospital for Children, London, England. For convenience in the text, these hospitals are referred to with slightly abbreviated titles without mentioning their city of origin, I have attempted however, also to summarise current opinion and the results of research from many centres throughout the world.

The purpose of this book is thus to provide a review of diseases of the small intestine in children with emphasis upon a discussion of their causes, clinical manifestations and the newer techniques which are used in diagnosis as well as modern methods of management, particularly those which are dietetic.

Attention has been focused on the commoner and more important diseases of the small intestine in children as seen in Britain and Australia and less attention has been devoted to the less common diseases. However, a bibliography is attached to each chapter for further reading. Each bibliography is not intended to be comprehensive, but rather aims to indicate those articles which the author has found to be a useful source of reference and which he commends to the reader for further study.

It is hoped that this book will be of value to the consultant paediatrician and paediatric surgeon as well as to the paediatric registrar and house officer as a practical guide to their understanding of these diseases. It is also intended for those adult physicians, gastroenterologists and surgeons who wish to survey the clinical spectrum of disease of the small intestine in childhood; a spectrum of disease different from that seen in adult life. When the same disease occurs in both children and adults, the different manifestations in the two age groups is emphasised. It is hoped that general practitioners, medical students, dietitians, and members of the nursing profession may find this book a useful source of reference.

Finally the author would like to express his appreciation to his colleagues at the three hospitals mentioned above for their help and encouragement which has led to the production of this book.

J. A. WALKER-SMITH
Royal Hospital of St Bartholomew
London July 1974

Contents

I

General Introduction

DEVELOPMENT OF PAEDIATRIC GASTROENTEROLOGY

Diseases of the small intestine have long afflicted children. Gastroenteritis and cholera, disorders which have their principal effect on the small intestine, have through the ages had a high prevalence and mortality among infants and children. They continue to do so today in the less fortunate parts of the world, but small intestinal disease is also an important health problem among children of all countries.

Many individuals over the past century have added to the knowledge of these diseases, but only in the last 25 years have certain centres become especially associated with the development of paediatric gastroenterology. Reviews of paediatric gastroenterology in the journal *Gastroenterology*, in 1967 and 1970, and the formation of the European Society for Paediatric Gastroenterology in 1968, have drawn attention to these developments and have led to a wider recognition of the diversity and importance of paediatric gastroenterology and, in particular, small intestinal disease in children.

In recent years there has been a much wider understanding of the physiology and pathology of the small intestine in man. This has been due: firstly, to new laboratory techniques, notably those using preparations of animal small intestine, and secondly, to the development of sophisticated methods of investigating small intestinal structure and function in man, such as small intestinal biopsy and small intestinal perfusion.

A great deal of this new investigative work has been done in adults, but increasingly more and more observations are being made in children. As a result, the body of knowledge available concerning the small intestine, its structure and function both in health and in disease in childhood has enormously increased.

Of particular importance in the development of paediatric gastroen-

terology was the demonstration by Sakula and Shiner in 1957 of a flat, small intestinal mucosa on biopsy of the small bowel of a child with coeliac disease. The subsequent confirmation of this observation in large numbers of children with coeliac disease by many other investigators, and the development of a safe intestinal biopsy capsule as a diagnostic tool in paediatric practice, led to a great surge of interest in small intestinal disease in children and played a major part in the development of paediatric gastroenterology as a legitimate specialty within paediatrics.

There is still a real danger that when specialists concentrate on one organ or on one restricted branch of medicine that they may neglect the whole individual. As the function of the small intestine impinges so much on the function of so many other organs, those clinicians who interest themselves in this organ and its diseases should be particularly aware of the principles and practice of general paediatrics. It is equally true that the general paediatrician should have a real understanding of diseases of the small intestine and their management.

FUNCTION OF THE SMALL INTESTINE

The small intestine is the principal organ of absorption in the human body and complete resection of the small intestine is not compatible with life. It is thus a vital organ whose continuing healthy function is a major determinant for the continuing good health and normal development of the growing infant and child.

The small intestine has a number of important functions. These include:

1. The onward passage of the ingested food bolus
2. Continued digestion of this bolus
3. Absorption of the digested nutrients into the blood and lymph vessels
4. An important immunological function including the production of secretory immunoglobulins
5. A regulatory role in protein metabolism
6. Secretion of hormones

Disease of the small intestine may manifest as a disruption of one or more of these functions. Interference with the first of these produces the various syndromes of complete or incomplete small intestinal obstruction. Interference with the remaining functions characteristically produces diarrhoea, usually with failure to thrive, but there may

also be systemic abnormalities, i.e. there are associated disturbances of organs outside the alimentary tract secondarily affected by disease of the small intestine. Indeed, a child with primary small intestinal disease may present with systemic symptoms alone and with no symptoms of gastrointestinal disturbance, e.g. a child with coeliac disease may present only with shortness of stature.

There is inadequate space to review all these functions here, but it is appropriate to mention some aspects of particular clinical importance and discuss them briefly.

Site of Absorption

Knowledge of the site of absorption of various nutrients from the small intestine (Fig. 1.1) is of importance in understanding the various disturbances of absorption that may occur when lesions of the small intestinal mucosa chiefly affect the proximal small intestine (e.g. coeliac disease), the distal small intestine (e.g. Crohn's disease), or the whole length of the small intestine (e.g. tropical sprue).

Important differences in function between proximal and distal small intestinal function are listed in Table 1.1.

Table 1.1
Functional differences between jejunum and ileum

	Jejunum	*Ileum*
Absorption of sugar	++	+
protein	++	+
fat	++	+
Bicarbonate	absorb	secrete
Vitamin B_{12}	−	+
Bile salts	−	+
Water and electrolyte absorption	'glucose-dependent'	'glucose-independent'

Courtesy Dawson, 1974.

Mechanisms of Absorption

Knowledge of the mechanisms of absorption of nutrients may have important clinical relevance to the understanding of small intestinal disease, and to illustrate this point the mechanisms of fat and protein absorption will be briefly discussed here. Absorption of other nutrients is discussed in appropriate chapters.

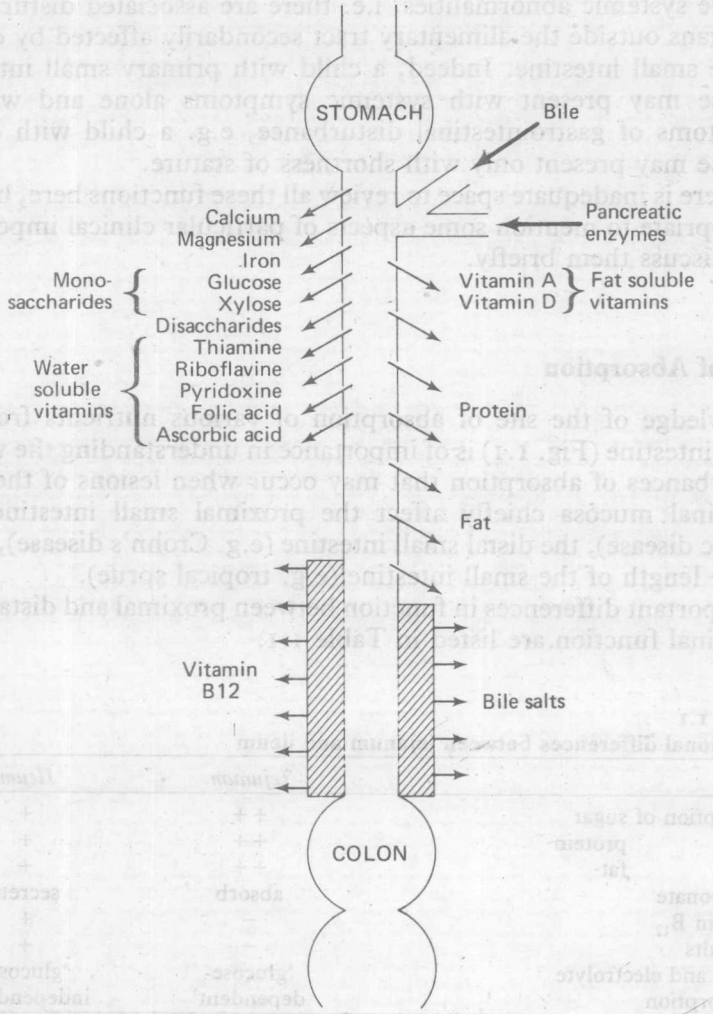

Fig. 1.1 Sites of absorption from the small intestine. (Permission of Booth, 1968.)

Fat Absorption

The fat in the diet of man includes triglycerides, cholesterol, and fat-soluble vitamins. Triglycerides, the major source of dietary lipid, are tri-esters of glycerol, i.e. they consist of three molecules of fatty acid esterified to glycerol. Fatty acids are described as long, medium

or short, depending upon their chain length, and they may be saturated or unsaturated, depending upon the presence or absence of a double bond.

In man, most dietary triglycerides contain long-chain fatty acids (LCT), the most important of which are the mono-unsaturated fatty acid, known as oleic acid, containing 18 carbon atoms, and the saturated palmitic acid containing 16 carbon atoms. Medium-chain triglycerides (MCT) contain fatty acids of 6 to 12 carbon atoms in length and do not constitute more than a minor proportion of normal dietary lipids.

Three of the fatty acids are generally known as essential fatty acids (EFA). These are linoleic acid, linolenic acid, and arachidonic acid. Linoleic acid usually accounts for most of the essential fatty acids in a normal diet. In fact, most foods contain small quantities of linoleic acid in the cell walls, e.g. cereals 0·5 per cent. When an artificial diet is introduced consideration of dietary deficiency of essential fatty acids must be given, especially in babies where it has been suggested that 2 to 4 per cent of dietary energy should be provided as linoleic acid. In breast milk, 7 per cent of the fatty acids are linoleic acid.

Medium chain triglyceride preparations do not contain EFA unless specifically added.

Dietary triglycerides are hydrolysed within the lumen of the small intestine by the pancreatic enzyme lipase in the presence of bile salts. Fatty acids and monoglycerides so produced form, with the aid of bile salts, mixed micelles chiefly. Micelles are water soluble polymolecular aggregates which have detergent properties. Mixed micelles are essential for the absorption of fat soluble nutrients. Bile acids form micelles when their concentration reaches a certain critical value. In man this is of the order of 1–2 mM.

Thus, the products of pancreatic lipolysis, bile salts and lecithin form mixed micelles. It is probable that absorption of the bulk of lipids takes place from this micellar phase. The exact mode of mucosal uptake was controversial until Strauss, in 1966, provided unequivocal evidence that the major products of intraluminal hydrolysis are absorbed into the enterocytes by passive diffusion from bile salt micelles.

Once long chain fatty acids (chain length of C 16 to 18) and monoglycerides are absorbed into the cell, re-esterification to triglycerides occurs. These triglycerides are then surrounded by a coating of protein, cholesterol ester, and phospholipid to form chylomicrons which appear in the lymph and then are transported to the blood via the thoracic duct.

Most triglycerides in the diet are long chain, but medium chain triglycerides (chain length C 6 to 12), which are present in special infant milks such as Pregestimil, are absorbed by a different process. These acids have a greater water solubility than the long chain fatty acids. They are hydrolysed more rapidly and are not as dependent on pancreatic lipolysis. Once absorbed into the epithelial cell they are not re-esterified but go straight to the liver via the portal vein. Thus, medium chain triglycerides are absorbed more rapidly and efficiently. Beta-lipoprotein is necessary for chylomicron formation.

In certain conditions this sharp division between the mode of fatty acid transport related to chain length may not always apply; for example, in biliary obstruction some long chain fatty acids are transported via the portal vein.

Disease of the small intestine may disrupt the normal process of fat absorption in a number of ways and knowledge of these simple physiological principles helps in understanding these disturbances.

Diseases of the small intestine that interfere with fat absorption include the following:

1. Deficiency of conjugated bile salts as occurs in the stagnant loop syndrome (*see* Chapter 10).
2. Decreased uptake of fat as occurs with reduction in absorptive area, e.g. in massive resection of the small intestine (*see* Chapter 11) and in association with mucosal damage, e.g. coeliac disease (*see* Chapter 4).
3. Deficiency of chylomicron formation, e.g. abetalipoproteinaemia (*see* Chapter 12)
4. Deficiency of transport of chylomicrons via the thoracic duct, e.g. intestinal lymphangiectasia (*see* Chapter 12).

The management of fat malabsorption in such disorders is to correct the primary disorder, when possible, by appropriate treatment, e.g. coeliac disease with a gluten-free diet, but when this is not possible (e.g. massive intestinal resection) by the substitution of medium chain triglycerides (MCT) for long chain triglycerides in the diet. This may considerably reduce the severity of the steatorrhoea. Proprietary milk feedings that contain MCT include Portagen and Pregestimil (*see* Appendix).

Protein Absorption

Normally, in childhood, the digestion and absorption of dietary and endogenous protein is very efficient. Protein is hydrolysed within the

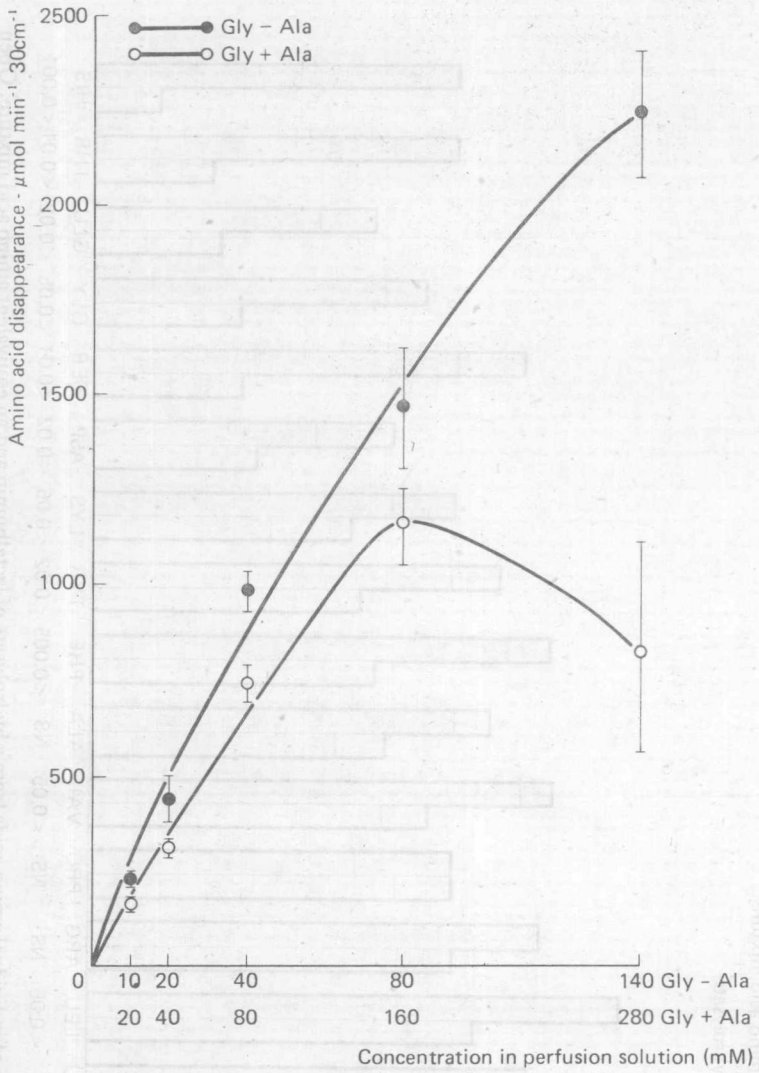

Fig. 1.2. Comparisons of intraluminal disappearance rates of amino acids during perfusion of 30 cm segments of human jejunum with test solutions containing glycyl-L-alanine (Gly-Ala, closed circles) or equivalent equimolar concentrations of glycine + L-alanine (Gly + Ala, open circles). Values are mean ± SEM, $n = 4$ or more.