A Clinical Companion to Biochemical Studies

SECOND EDITION

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UNIVERSITY OF MANCHESTER

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Cover photo: Scanning electron micrographs of normal and sickled red blood cells, courtesy of James G. White, M.D., University of Minnesota.

Foreword

Today's medical students have a hard life. New methods of diagnosis and treatment appear all the time and the medical sciences grow at an alarming rate. I doubt if there is a medical curriculum in any university which is not overcrowded and yet each professor will assure the students that his particular discipline is essential.

Over the past thirty years Biochemistry has grown faster than any of the other basic medical sciences. One look at the chart of metabolic pathways supplied by a friendly manufacturer of biochemicals will deter all but the strongest. "Do I need to know the whole of that?" asks the medical student, who wants to be curing diseases rather than contemplating molecules. Of course he does not need to know it all, but he does need to feel at home with the major pathways. Biochemistry will contribute to the understanding and treatment of a surprising number of illnesses and the number grows each year.

There are several excellent text books of biochemistry for the science student, though I am less happy with those written for medical students. There are also many books on clinical biochemistry, but these are usually written for laboratory workers rather than students.

Dr. Schwarz's book breaks new ground, since it presents clinical biochemistry to the medical student without pretending to be a full text book of biochemistry. It shows medical students how important the subject is for clinical medicine today and does this in a clear and interesting way. In my view every med-

ical student should have at least two biochemistry texts; this one, and a comprehensive yet readable text book on the subject, not necessarily one designed for medical students.

There is at present a shortage of medical graduates with an interest in clinical biochemistry. At the same time, many of the research proposals put to medical research foundations depend on a deep knowledge of biochemistry. I believe that this book will help to solve this problem. If only a few of those who read it decide to pursue biochemistry seriously it will have been extremely useful in the progress of medicine.

J. N. HAWTHORNE
Professor of Biochemistry and Vice-Dean,
Queen's Medical Centre, Nottingham

Preface

A large number of readers' comments have guided me in producing this second edition. Many readers suggested additional topics, and I have accordingly introduced six new chapters and have substantially rewritten five. The remainder have been brought up-to-date. The new chapters deal with somewhat more advanced material which we teach in the second preclinical year.

Each chapter is followed by four to six questions, answers to some of which may require guidance from tutors or recourse to the literature. Usually, reference to one of the items under "Further Reading" will guide the student to where more extensive reading can be obtained.

I would like to record my gratitude to the following colleagues for helpful comments on individual chapters: Prof. M. E. Grant, Dr. E. B. Mawer, Prof. S. W. Stanbury, Dr. F. S. Steven, and Dr. J. B. Weiss; and to the Department of Medical Illustration for their expert help with illustrations.

V. S.
Manchester, March 1983

Preface to the First Edition

In most medical courses the basic preclinical sciences are taught in the first four to six terms, during which diseases may be referred to briefly and patients brought into the lecture theater for demonstration. This latter practice defers to students' eagerness to come to grips with "real" medicine yet fails to achieve its primary objective—to provide the stimulation and motivation to guide the student through the maze of preclinical studies. Such support is invaluable in helping to dispel doubts in the student's mind regarding the relevance of the biochemistry course, doubts which inhibit learning and sap the determination to embrace material which appears academic or at best peripheral.

In order to counteract this negative attitude, we have, for the past 2 years, given a series of "clinical biochemical seminars" during the first four terms of our preclinical course. In each seminar one or two case histories were presented which contained the most significant, representative, and biochemically relevant clinical material pertaining to the particular disease. The presentation of each case was followed by an examination of the underlying biochemical mechanisms, and, wherever possible, explanations were offered for the clinical observations. The seminars have proved popular with students and staff alike and have stimulated much useful discussion. I hope that this book may help a wider circle of students to gain insight into the close relationship between biochemistry and clinical med-

icine, which so often eludes students in the early years of their medical studies.

Many of the cases presented here are substantially in the form in which we have discussed them in our seminars. Others have been added to cover material often taught later in the second year. All have been chosen to provide the widest possible range of biochemical topics with a minimum of overlap. Carbohydrate, amino acid, triglyceride, hemoglobin, porphyrin, and nucleic acid metabolism, protein structure, enzyme action and co-enzymes, ion transport, and the biosynthesis and biochemical effects of hormones are represented.

It has not been my aim to be comprehensive, either in the description of the disease or in the discussion of the biochemistry, as this could so easily defeat the whole purpose of the venture; nor is there any relationship between the choice of diseases and their incidence or "importance."

Without reference to other works, sufficient detail has been given to enable the student to understand the underlying biochemical basis of the disease as well as the student's own knowledge or, indeed, the available knowledge permits. But, as its title suggests, this book is intended to be read in conjunction with biochemistry texts. The order of individual cases is roughly in accordance with the clinical and biochemical complexity of the material.

Inherited enzyme defects are particularly well represented. These "inborn errors of metabolism" have been described as nature's perfect experiments in biochemistry, which cannot be simulated in the laboratory. The deletion of one particular enzyme shows us not only the importance of the particular step in a metabolic sequence but also the often unsuspected effects of the accumulating intermediates on other enzymes, and hence on the functioning of the cell and of the whole body. There is no clearer or more convincing way of demonstrating the biochemical basis of many pathological lesions, from abnormal shapes of red blood cells, derangement of liver function, cataracts, and aberrations of sex organs to mental defect.

My sources have been textbooks, monographs, and original papers, from which I have synthesized case histories to make them, as far as possible, typical as well as subservient to my purposes. A few references are given to enable those who desire further insight to gain access to the literature.

I would like to record my indebtedness t my colleague in the Department of Medical Biochemistry and in other preclinical and clinical departments of the University, who have made many valuable suggestions incorporated in the text.

I am grateful to the following for providing the photographs: Drs. D. I. K. Evans, G. M. Komrower, and I. B. Sardharwalla, Royal Manchester Children's Hospital; Prof. J. H. Kellgren, Drs. J. E. MacIver, S. Oleesky, and B. R. Tulloch, Manchester Royal Infirmary; and Prof. Z. Lojda, First Pathological Institute, University of Prague; also to the University Department of Medical Illustration, Manchester Royal Infirmary, for the preparation of photographs and for permission to reproduce them.

V. S.
Manchester, April 1977

Contents

Introduction

Learning without thinking is useless.
Thinking without learning is dangerous.

CONFUCIUS

The brief case histories here presented are, as far as possible, typical of the particular diseases; they have been synthesized from cases described in the medical literature in greater detail. Some signs and symptoms have been omitted for the sake of simplicity, since this book is intended for students who have not yet studied clinical medicine; but nothing that is included is irrelevant to my primary aim, which is to generate interest in biochemistry by drawing attention to its fundamental role in the disease process, in diagnosis and treatment.

The reader should give careful consideration to every detail of the case history and should ponder, rather than commit to memory, the biochemical and other data in tables and figures, which have been selected for their pertinence and their instructive value. As far as existing knowledge, and space, permit, the phenomena described have been explained in the discussion.

Understanding the molecular mechanisms underlying disease not only lends depth to clinical studies but offers a wealth of intellectual satisfaction and stimulation to the student of biochemistry.

Some questions at the end of each chapter are offered as a challenge; the answers may be contained in the text or they may be gained from perusal of biochemistry and other books. Many more questions will present themselves to the thoughtful reader and will, I hope, stimulate curiosity to explore the subject further. Selected references are given for those whose interest and available time allow them to study the subjects discussed in greater biochemical and clinical detail.

Temporary Lactase Deficiency

Case History

Brenda J. was born after a normal pregnancy and delivery. She was breast-fed and was in good health until she was weaned at 2 months. A cow's milk preparation was then introduced. Three days later Brenda developed diarrhea, she became irritable, vomited frequently, and had a temperature of 40.5°C. She was admitted to the hospital with a diagnosis of gastroenteritis. She was treated for dehydration with intravenous fluids for 24 h, followed by glucose solution by mouth for another 2 days. Vomiting and diarrhea stopped and Brenda was much more settled. She gained weight; the urine was normal and contained no reducing substance. Her gastroenteritis had probably been caused by inadequate attention to hygiene in the preparation of the milk.

On her fourth day in hospital Brenda was given a brand of infant milk which she took avidly; but after 24 h her stools became loose and frequent. The following day her urine contained a reducing sugar which was not glucose, as indicated by a negative reaction on the glucose oxidase test strip. The stools were watery, frothy, and acidic, with much gas being produced (Table 1); they also contained a reducing substance.

In the light of these findings and pending further investigations, it was felt that Brenda's trouble might be a temporary lactase deficiency and she was put on a lactose-free diet. Her condition improved dramatically, the diarrhea ceased, the reducing substance disappeared from her urine and stools, and she gained weight.

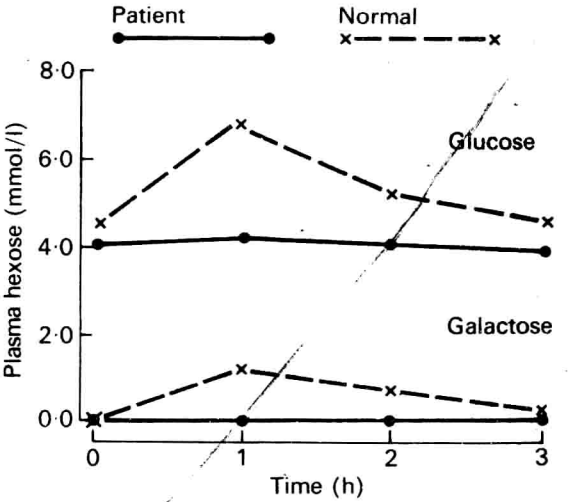

Figure 1
Lactose absorption test. A standard amount of lactose is given by mouth and the plasma glucose and galactose levels are determined at intervals.

Meanwhile the reducing substance in the urine was identified as lactose. In an absorption test the patient was given an oral dose of the disaccharide and her plasma glucose and galactose levels were determined at intervals (Fig. 1); the plasma sugars were also chromatographed on paper (Fig. 2a). An intestinal biopsy specimen failed to stain for lactase. These four tests together indicated a failure to hydrolyze lactose due to the absence of lactase from the brush border of the intestinal mucosa.

After 6 weeks on a milk-free diet, the lactose absorption test was repeated and found to be normal and a sugar chromatogram showed the presence in the plasma of galactose and the absence of lactose (Fig. 2b). A second mucosal biopsy gave a normal reaction to lactase staining (Fig. 3), confirming that the enzyme had returned. Thereafter milk did not cause any further gastrointestinal disturbances.

Table 1
Nature of patient's stools on milk diet

Stool characteristics
Frequent
Watery
Frothy
pH 5
Contain a reducing substance and volatile acids

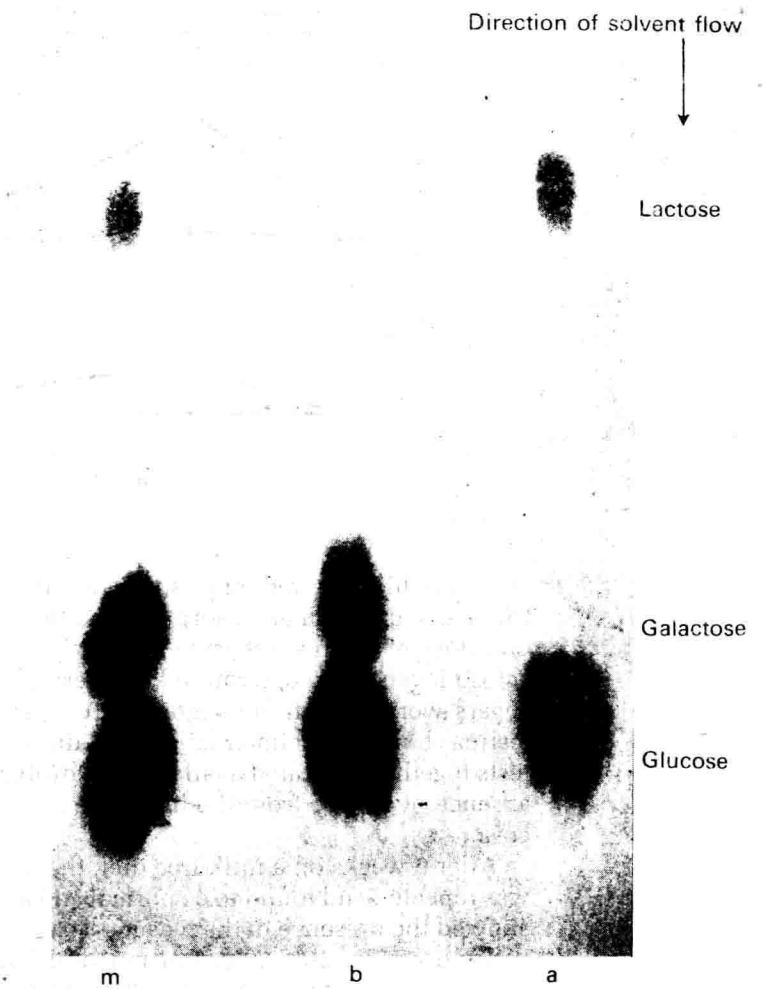

Figure 2
Chromatogram of sugars extracted from plasma after an oral lactose load. (m) Lactose, galactose, and glucose markers, 10 μg each. (a) Patient's plasma, first absorption test; (b) patient's plasma, 6 weeks later.

Discussion

This child obviously did not suffer from an hereditary lactase deficiency, since she had thrived on breast milk for the first 2 months of life. She had developed gastroenteritis when bottle feeding was begun and, as a result of the infection and the consequent malnutrition, the brush border lactase had disappeared. When she eventually took her milk feeds again, lactose failed to be hydrolyzed and thus remained largely unabsorbed; only a small proportion was passing into the circulation to be excreted in the urine. (There is no provision for the hydrolysis and metabolism of circulating lactose and hence the disaccharide, once absorbed, is excreted in the kidney.)

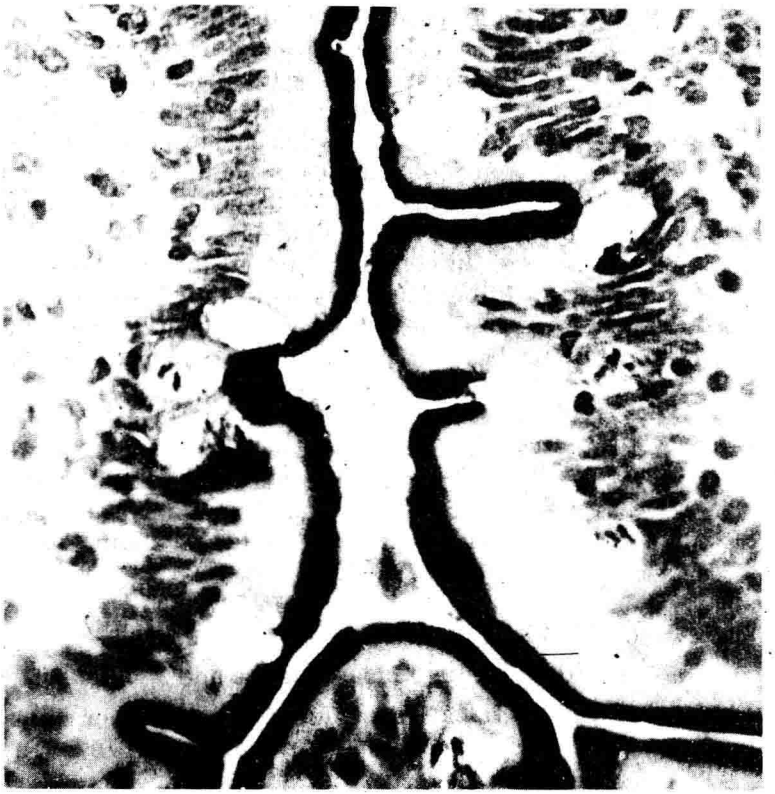

Figure 3
Biopsy of jejunal mucosa, stained for lactase. Second specimen, taken 6 weeks after admission. (Courtesy Z. Lojda, First Pathological Institute, University of Prague.)

The unabsorbed lactose attracts water into the lumen of the gastrointestinal tract, so accounting for the watery stools, and the presence of a fermentable sugar in the large bowel results in proliferation of the microflora and its metabolism of lactose to lactic and other acids and to CO_2.

In the presence of lactase, lactose is hydrolyzed to glucose and galactose (Fig. 4), which are absorbed and can be detected in the plasma in the course of the absorption test. Lactase is one of several disaccharidases in the brush border and it appears to be specially sensitive to damage by infections and other processes, not only in infants but also in adults.

If lactose fails to be hydrolyzed in the small testine, due to

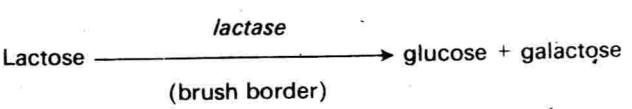

Figure 4
Action of intestinal lactase.

the absence of lactase, the disaccharide is fermented by bacteria in the large bowel with the production of a variety of substances, including hydrogen. A small amount of the gas diffuses from the gut into the circulation and is exhaled in the breath, where it can be detected by gas chromatography. Thus the presence of significant quantities of H_2 in the breath of a patient after ingesting a disaccharide is a reliable indicator of a disaccharidase deficiency.

In contrast to the temporary loss of one or more intestinal disaccharidases, as in the present case, many non-Caucasians lose their lactase permanently after infancy due to the gene becoming silent. In consequence these perfectly healthy adults do not tolerate milk.

A survey in a U.S. city revealed that 40 percent of lactase-deficient subjects were unaware of their deficiency. A Sudanese doctor described his own undiagnosed gastrointestinal symptoms of many years' standing; eventually, the symptoms were diagnosed as being due to his inability to metabolize lactose (Ahmed, 1975).

Further Reading

H. F. Ahmed: *Lancet* 1:319, 1975.

N. Kretchmer: Lactose and lactase, *Sci. Am.* 227(4):70, 1972.

D. H. Alpers and K. J. Isselbacher: Disaccharidase deficiency, *Adv. Metab. Disord.* 4:75–115, 1970.

Questions

1. On the chromatogram (Fig. 2) 10 μg of each sugar was applied as a marker. Why is the spot produced by lactose smaller than those due to glucose and galactose?

2. How can one account for the low pH and the frothy nature of the stools?

3. Why are the symptoms in adults relatively mild compared with those of Brenda J.?

4. Can you think of any other enzymes or proteins whose synthesis ceases at a certain stage of development?

5. Why are many non-Caucasians unaware of their lactase deficiency?

6. Are there any enzymes whose total absence in humans necessitates their reliance on the enzymes in plants?

7. In what circumstances would sucrose deficiency manifest itself? How could the special problem of detecting sucrose in the urine be overcome?