A Clinical Guide to Inherited Metabolic Diseases

This user-friendly clinical handbook provides a clear and concise overview of how to go about recognizing and diagnosing inherited metabolic diseases. The reader is led through the diagnostic process from the identification of those features of an illness suggesting that it might be metabolic through the selection of appropriate laboratory investigation to a final diagnosis.

The book is organized into chapters according to the most prominent presenting problem of patients with inherited metabolic diseases: neurologic, hepatic, cardiac, metabolic acidosis, dysmorphism, and acute catastrophic illness in the newborn. It also includes chapters on general principles, laboratory investigation, neonatal screening, and the principles of treatment.

This new edition includes much greater depth on mitochondrial disease and congenital disorders of glycosylation. The chapters on neurological syndrome and newborn screening are greatly expanded, as are those on laboratory investigation and treatment, to take account of the very latest technological developments.

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A Clinical Guide to Inherited Metabolic Diseases

Third Edition

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Reviews of first edition

'should be read thoroughly by any pediatric resident, genetic resident, or clinical fellow caring for patients with metabolic disorders'

American Journal of Medical Genetics

'In short, this is an excellent guide to metabolic disease; it represents good value for money and, I suspect, will be more likely found in the owner's pocket rather than on the shelf. It is recommended not only to the 'busy physician' and trainee, but to all those with an interest in metabolic disease.'

Journal of Inherited Metabolic Disease

'The writing is lucid, direct and salted with personal observations. Clarke's teaching skills shine forth from each page . . . It succeeds admirably, effectively demystifying the anxiety-provoking world of inherited biochemical illness.'

Canadian Medical Association Journal

'J. T. R. Clarke has performed the amazing feat of distilling practical knowledge about the diagnosis of metabolic diseases into a small, yet ultimately pragmatic 280-page clinical guide . . . On the whole, I found this to be an amazing book which contains a vast amount of information presented in a concise, logical and well-organized fashion . . . I would recommend this book wholeheartedly to anyone involved in the diagnosis of inherited metabolic diseases.'

Journal of Genetic Counseling

Reviews of second edition

'Dr Clarke's enthusiasm and erudition are evident on every page of this book.'

Archives of Diseases of Childhood

'An excellent book for physicians who find inherited metabolic diseases intimidating . . . The information is presented in such a clear and simple fashion that few people would find this book difficult to read . . . Clarke teaches a complex subject in a simple but complete manner.'

Canadian Medical Association Journal

'This book's strength lies in its simple straightforward clinical approach to this difficult area of medicine.'

Doctors.net.uk

'If your clinical work brings you into contact with patients who may be hiding an inherited metabolic disease, Clarke's *Guide* is clearly for you.'

Journal of the Royal Society of Medicine

'To guide the reader in this assessment, a compact volume such as has been written by Dr Clarke is invaluable. Dr Clarke has succeeded in providing the reader with a user-friendly, inexpensive book that is up to date, and provides directions for further reading.'

European Journal of Paediatric Neurology

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Preface

In this enlarged third edition of *A Clinical Guide to Inherited Metabolic Diseases*, I have preserved the basic, clinical approach first developed in the first edition of the book. However, advances in many fields over the past 5 years have made it necessary to add significantly in some areas, such as mitochondrial disorders and the congenital disorders of glycosylation. The challenge continues to be to find ways to translate discoveries made in research laboratories, which understandably focus on biochemical and genetic principles, into a clinically relevant format organized in a way to facilitate the early recognition of the disorders by clinicians. For example, inherited defects in mitochondrial electron transport (ETC) may present as neurological syndromes (encephalopathy, myopathy, movement disorder), cardiac syndrome (cardiomyopathy), hepatic syndrome, metabolic acidosis, or catastrophic illness in the newborn. The challenge has been to develop and present a clinical approach to mitochondrial ETC defects without being unnecessarily repetitious. The chapter on 'Laboratory investigation' is important in this respect because it provides an approach to the transition in thinking between the recognition of various clinical signs and the biochemical and genetic investigation of possible causes of disease. By the very nature of laboratory investigation, it is also organized biochemically, which draws together the consideration of all those disorders presented in various different chapters as clinical problems. The book should, therefore, be viewed as a series of clinical chapters, which overlap in terms of biochemical and genetic organization and content in the chapter on 'Laboratory investigation'. It follows that reference to any topic presented in a clinical chapter ought to be considered also in the light of the appropriate section on the chapter on 'Laboratory investigation' – they go together.

I have added significantly to the chapter, 'Neurologic syndrome', as new mechanisms of disease are discovered, such as inherited disorders of neurotransmitter metabolism and the channelopathies. The chapter on 'Newborn screening' has also been expanded as this field grows, along with experience with the application of tandem mass spectrometry as a screening technology. The chapters on 'Laboratory

investigation' and 'Treatment' have had to be modified significantly in the light of new technological developments in these areas. I have also added to and updated the bibliographies at the end of each chapter, though the number of publications cited is still a tiny fraction of the literature on the subjects discussed. In many cases, I have sacrificed some outstanding articles focusing on advances in basic research for articles I thought would be more relevant to clinicians dealing daily with patient problems.

For intellectual support and stimulation during the preparation of this edition of *A Clinical Guide*, I am again grateful to my colleagues, Annette Feigenbaum, Susan Blaser, Bill Hanley, Brian Robinson, John Callahan, and Eve Roberts, and to the people who slave away in the diagnostic labs, all at the Hospital for Sick Children. In addition, however, I owe a great deal to colleagues in other centers, scattered throughout the world, who read the second edition and suggested some changes which I am convinced will make this edition even better. I owe Charles Scriver special thanks for comments on the last edition of this book which have resulted in some important additions to the current edition. As usual, I am indebted to the large number of residents and fellows who rotated through the genetic metabolic service at the Hospital, stimulating me to think clearly about the clinical problems we tackled together. Gustavo Maegawa, from Brazil, Nouriya Al-Sannaa, now in Dhahran, Saudi Arabia, Aneal Khan, now at McMaster University in Hamilton, Pranesh Chakraborty, who is now at the Children's Hospital of Eastern Ontario, Nicola Poplawski, at the Adelaide Women's and Children's Hospital in Adelaide, and Julian Raiman, now at Guy's Hospital in London, merit special mention in this regard.

Many colleagues provided material for the figures in the book: Jim Phillips provided the electron micrographs of the liver, and Venita Jay supplied the electron micrographs of conjunctival epithelium and the photomicrograph of muscle. The photographs of patients with carbohydrate-deficient glycoprotein syndrome (now called congenital disorders of glycosylation) and mevalonic aciduria were provided by Jaak Jaiken and Georg Hoffmann, respectively. Jaak Jaiken also supplied the photograph of the isoelectric focusing of plasma transferrin shown in Chapter 6. Joe Alroy kindly provided the original electron micrographs showing the changes in skin in patients with lysosomal disorders appearing in Chapter 9. Margaret Nowaczyk and Chitra Prasad provided photographs of patients with Smith-Lemli-Opitz syndrome (Chapter 6), and Eric Shoubridge provided the photograph of the blue native PAGE in Chapter 9. I am again particularly grateful to Susan Blaser for the neuroimaging studies reproduced in Chapter 2 on 'Neurologic syndrome'.

Peter Silver, at Cambridge University Press, continued to provide moral and technical support during the preparation of the book. And once again, my wife, Cathy, encouraged and supported me throughout the project, often at great personal cost.