Metabolic Disease in Childhood

LEONARD SINCLAIR BSc. MB. FRCP. DCH

Foreword by
Malcolm D. Milne FRS

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LEONARD SINCLAIR BSc, MB, FRCP, DCH

Physician in Charge of the
Paediatric Metabolic Clinic,
St Stephen's Hospital, Chelsea.
Consultant Paediatrician,
Royal National Throat, Nose
and Ear Hospital,
and Westminster Hospital

Foreword by
Malcolm D. Milne FRS
Professor of Medicine,
Westminster Hospital
Medical School

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Foreword

Understanding of metabolic disease requires a mastery of many separate disciplines including clinical medicine, theoretical and practical biochemistry, genetics, endocrinology, immunology, community medicine and handicap. All too often, texts dealing with such diseases give undue prominence to one or other of these disciplines according to the special interests of the author. This book gives a more balanced view, as all these specialties are adequately covered. Dr Sinclair is primarily an experienced and able clinical paediatrician with an especial interest in metabolic and genetic disease in children. He has, however, a wide knowledge of the theory and techniques of the many disciplines necessary in writing a book of this high calibre.

Longer and more detailed texts on this subject are already available, but are more useful as works of reference than as an adequate text which can be read with pleasure in a reasonable space of time. This book is, therefore, particularly recommended to candidates for higher degrees and diplomas in paediatrics, but will also be of great value to physicians dealing with adults and faced with the prospect of taking over medical care of patients suffering from diseases more familiar to paediatricians. Advances in early diagnosis and management of metabolic disease, so well described in this monograph, are increasing the chances of survival of patients into adolescent and adult life, and are therefore enhancing the necessity for greater and more efficient clinical contact between physicians involved in consultant care of either children or adult patients.

It has been a considerable pleasure to have been allowed to read the text of this monograph during the years of its gestation, and I sincerely hope that it will give similar interest and instruction to its many future readers.

Westminster Hospital Medical School *Malcolm D. Milne*

Preface

This book sets out the principles and the practice of metabolic disease in childhood. It is divided into three sections. Section I deals with the general topics which form the basis of our study of the subject. The second section describes common metabolic problems encountered in paediatric practice and includes a chapter on clinical manifestations. The third section which is 'a new look at inborn errors of metabolism', is an innovation. It is a reclassification and clarification of those molecular disorders which affect patients and present prenatally, in infancy and in childhood. The work is fairly complete, but space has not allowed the inclusion of detailed description of diabetes mellitus, jaundice or haematological disorders.

The field probably owes its origins to Archibald Garrod's conceptions of inborn errors of metabolism in the early years of this century. It is growing rapidly and the unfortunate clinician may often feel intellectually overwhelmed by the dynamic technical and conceptual advances since then. Still, there must come a time when the whole subject requires a careful and critical review, to allow him and all those with whom he collaborates and who in turn stimulate him and his team, to take a broader perspective. I hope that this work will be helpful in this respect.

The book has a general theme, but each section and each chapter is self-contained, so that the reader may dip into it and refer to any topic appropriate to his immediate needs. Normal values are included in the text. They may vary slightly in the reader's own laboratory. Each chapter has an introduction which should facilitate subsequent reading. The clinical course of each condition is described as is the prognosis. The social consequences of life with a metabolic disorder, the family response to biochemical handicap and dietary control are of growing importance. These are problems of which clinicians are becoming increasingly aware which require his utmost sympathy, understanding and social skills, but it is not as yet easy to gain their full emphasis in an essentially clinical text.

The audience aimed at is a wide one. It should be of interest to the paediatrician, the obstetrician who is concerned with prenatal diagnosis, the chemical pathologist, the research biochemist and the dietician; not the least the latter three who are often involved in much of the hard work.

London 1978 *Leonard Sinclair*

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A quartet of secretaries, Lynette Kirby, Sue Budd, Mrs D. Davis and Mrs Jill Wellard who was responsible for much of the retyping of the text, were of inestimable help and patience. Miss N. Yaron took on the unenviable task of typing the references. Jim Pipkin, Mr D.J. Connolly and the staff of the Medical Illustration Department of the Institute of Otology and Laryngology should be thanked for their assistance with the artwork. Finally, a word of thanks to the publishers, Blackwell Scientific Publications, for much encouragement, advice and help.

Glossary of useful abbreviations

ABL: abetalipoproteinaemia.
ACH: acetylcholine.
ACP: acid phosphatase.
ACTH: adrenocorticotrophin.
ADH: antidiuretic hormone.
ADP: adenosine diphosphate.
AIP: acute intermittent porphyria.
ALA: aminolaevulinic acid.
ALT: alanine transaminase (SGPT).
AMP: adenosine monophosphate.
AMPS: acid mucopolysaccharides (MPS).
APRT: adenine phoshoribosyltransferase.
ASA: argininosuccinic acid.
AST: aspartate transaminase (SGOT).
ATP: adenosine triphosphate.

BAL: British anti-Lewisite.
BCKA: branch-chain ketoacidosis.
BEI: butanol extractable iodine.
BMR: basal metabolic rate.
BSP: bromsulphthalein.
BUN: blood urea nitrogen.

CaBP: calcium binding protein.
CAH: congenital adrenal hyperplasia.
CAMP: cyclic adenosyl monophosphate.
CDP-choline: ceramide choline phosphotransferase.
cer: ceramide.
cer-P-choline: ceramide-P-choline (sphingomyelin).
CESD: cholesteryl ester storage disease.
CF: cystic fibrosis.
ChE: cholinesterase.
CoA: coenzyme A.
CPC: cetylpyridium chloride.
CPK: creatine phosphokinase.
CPS: carbamyl phosphate synthetase.
CRF: corticotrophin releasing factor.
CSF: cerebrospinal fluid.
CTX: cerebrotendinous xanthomatosis.

1,25-DHCC: 1,25-dihydroxycholecalciferol.
DIT: di-iodotyrosine.
DN: dibucaine number.
DNA: desoxyribonucleic acid.
DOCA: desoxycorticosterone acetate.
DOPA: 3,4-dihydrophenylalanine.
DPN: diphosphopyridine nucleotide (NAD).

ECF: extracellular fluid.
EDTA: ethylene diamine tetraacetate.

FAD: flavine adenine dinucleotide.
FFAs: free fatty acids (NEFA).
FIGLU: formiminoglutamic acid.
FN: fluroide number.
FSH: follicle stimulating hormone.

GABA: gamma-aminobutyric acid.
GFK: glomerular filtration rate.
GH: growth hormone.
GLC: gas-liquid chromatography.
G_{M1}: ganglioside M1.
G_{M2}: ganglioside M2.
GOT: glutamate oxaloacetate transaminase (AST).
G6PD: glucose-6-phosphate dehydrogenase.
GTT: glucose tolerance test.

Hb: haemoglobin.
HBD: hydroxybutyrate dehydrogenase (SHBD).
25-HCC: 25-hydroxycholecalciferol.
HDL: high density lipoprotein.
HGH: human growth hormone.
HGPRT: hypoxanthine guanine phosphoribosyl transferase (PRT).
5-HIAA: 5-hydroxyindoleacetic acid.
HMMA: 4-hydroxy-3-methoxymandelic acid (VMA).
5HT: 5-hydroxytryptamine.
5HTP: 5-hydroxytryptophan.

ICD: isocitric dehydrogenase.
ICF: intracellular fluid.
IRI: immunoreactive insulin.

LATS: long-acting thyroid stimulator.
LCAT: lecithin cholesterol acyltransferase.
LDH: lactic dehydrogenase.
LDL: low density lipoprotein (β-lipoproteins).
LPL: lipoprotein lipase.
LVP: lysine vasopressin.

MCT: medium-chain triglycerides.
MIT: monoiodotyrosine.
MLD: metachromatic leucodystrophy.

MPS: mucopolysaccharides (AMPS).
mRNA: messenger RNA.
MSUD: maple syrup urine disease (BCKA).

NAD: nicotinamide adenine dinucleotide (DPN).
NADP: nictotinamide adenine dinucleotide phosphate (TPN).
NEFA: non-esterified fatty acids (FFAs).
NTP: 5-nucleotidase.

OCT: ornithine carbamyl transferase (OTC).
17-OGS: 17-oxogenic steroids.
11-OHCS: 11-hydroxycorticosteroids.
17-OHCS: 17-hydroxycorticosteroids.
OTC: ornithine transcarbamylase (OCT).

PAS: para-amino salicyclic acid.
PAS: periodic acid Schiff (stain).
PBG: porphobilinogen.
PBI: protein-bound iodine.
PEA: phosphorylethanolamine.
PFK: phosphofructokinase.
PHLA: post-heparin lipolytic activity.
PHPPA: parahydroxyphenylpyruvic acid.
PKU: phenylketonuria.
PPRP: phosphoribosylpyrophosphate.
PRT: phosphoribosyl transferase (HGPRT).
PTH: parathyroid hormone (parathormone).

RNA: ribonucleic acid.
RTA: renal tubular acidosis.

SG: specific gravity.
SGOT: serum glutamate oxaloacetate transaminase (AST).
SGPT: serum glutamate pyruvate transaminase (ALT).
SHBD: serum hydroxybutyrate dehydrogenase (HBD).

T_2: di-iodotyrosine.
T_3: tri-iodothyronine.
T_4: thyroxine (tetraiodothyronine).
TBG: thyroxine binding globulin.
TBPA: thyroxine binding prealbumin.
TBW: total body water.
TCA cycle: tricarboxylic acid cycle (citric acid or Kreb's cycle).
THAM: trishydroxyaminomethane.
THF: tetrahydrofolate.
THFA: N^6,N^{10}-methenyl tetrahydrofolic acid.
Tm or Tmax: maximal tubular transport (reabsorptive) capacity.
TPN: triphosphopyridine nucleotide (NADP).
TRF: thyrotrophin releasing factor.
TSD: Tay–Sachs disease.
TSH: thyroid stimulating hormone.

UDP: uridine diphosphate.

UDP-GlcUA: uridine diphosphate glucuronic acid.
UDP-IdUA: uridine diphosphate iduronic acid.
UMP: uridine-5-monophosphate.
UTP: uridine triphosphate.

VLDL: very low density lipoprotein.
VMA: vanilyl mandelic acid (HMMA).

XMP: xanthosine-5-monophosphate.

Contents

I • General principles

1 • The incidence of metabolic disease

Although there is enormous literature on the subject of metabolic disease, until recently our knowledge of its incidence has been somewhat limited. This is possibly because many of the disorders have been discovered in recent years and investigated in different populations. It is only in the last few years that attempts have been made to compose regional and national registries so that newly diagnosed cases may be recorded centrally. These give some idea of the national recurrence rate for metabolic diseases, and if consulted wisely, should give a certain amount of information about regional incidence. The latter is quite important, because in the British Isles the local risk rate shows marked regional variation, and a study of this may give further information about the nature of the disease and its genesis. A good example is the higher incidence of phenylketonuria in Northern Ireland than in South-east England. It is now recognised that this disease is more prevalent in people of Nordic stock, and might be attributed to this factor. If given populations show a high incidence of inbreeding, consanguinity or if there are other social factors involved, a study of regional statistics would enable one to offer a suitable local programme of investigation and genetic advice. This would also apply to diseases which show greater frequency in certain ethnic groups such as Tay–Sachs disease (see p. 294). Such a registry will have three other major advantages.

1 It will be possible to verify the numbers of those at risk, and thus help clinicians and laboratory workers in their efforts to evaluate and minimise the amount of cases that are being overlooked. It will then be easier to plan the size of a national programme for detection and management.
2 In the long-term, it will enable changes of frequency in metabolic disease to be recorded, and thus detect changes in frequency of mutations of genes.
3 Taking into account the variation in the expression of the abnormal gene, it will be possible to ascertain the prognosis for the disease in affected individuals and affected families more accurately.

Most of the above is in prospect, and one must face the reality that the incidence of many disorders is not known and that figures from which the incidence has been calculated may be inaccurate. One must also realise that certain metabolic diseases, whilst occurring predominantly in one population may be confined only to that population, so that any figures for

incidence must relate entirely to the population that has been investigated. Further, they may be subject to several other possible inaccuracies:

1 They may not be properly recorded and/or notified.
2 They may not be diagnosed, even though patients may be suspected of having died of a metabolic disease.
3 There may be uneven distribution with segregation within a population because of familial or ethnic factors, thus giving a falsely low or high figure, especially in those disorders inherited via a dominant gene.
4 Because of the natural history of some diseases, they may only express themselves in adult life, and thus the incidence may be recorded as being unusually low if only the paediatric age group is considered.
5 Figures may be affected by population mobility and its inaccurate recording.
6 The true incidence may be masked by birth control methods, birth prevention, and family planning, all of which are subject to social change. It is therefore very important to record whether a fetus removed by abortion is affected or not.
7 The reliability of the investigation used for detection of disease and the heterozygous state, must be taken into account in calculating the frequency of a gene. If the method is recognised as not having been fully reliable and is superceded, this should be noted, and ideally, the given population should be reinvestigated provided this does not involve any risk to the patients.

Taking these factors into account Table 1.1 gives the frequency of the commoner metabolic diseases in childhood. The commonest is said to be glucose-6-phosphate dehydrogenase (G6PD) deficiency which is said to occur in over 100 000 people in the world at large, but whose incidence is limited to certain ethnic groups, namely those of Mediterranean and Negro origins. Although figures are not generally available, it is quite likely that alactasia is also one of the commonest disorders, but one must take into account that it occurs most frequently in populations who do not habitually consume milk, and that several different forms are known to exist. Phenylketonuria is recognised as the commonest inborn error of amino acid metabolism amongst Caucasians, although as noted above it shows predominance in those of Nordic stock as probably does homocystinuria. The incidence of virilising adrenal hyperplasia in Switzerland (Prader 1958) and in Birmingham, England (Hubble 1966) is apparently much greater than that found in the eastern seaboard of the United States by Childs *et al* (1956) who have, however, acknowledged that many cases had not been detected. Hubble (1966) also states that patients coming in the neonatal period may not have been diagnosed so as to give a falsely low figure.

Taking into account that the paediatrician will have to look after the child until adolescence, i.e. for approximately 14 years, and that he may look after a family suffering from an inborn error of metabolism, it is nevertheless

interesting and important to point out that if he is responsible for the care of approximately 2000 newborn infants a year, in South-east England he would meet one case of phenylketonuria every 10 years, one patient with galactosaemia every 35 years, one with virilising adrenal hyperplasia every 3–4 years, and one patient with homocystinuria every 20–40 years.

In the USA his workload would depend more upon where he practised, but in general he would look after fewer newborn infants and might come in contact with one phenylketonuric every 12–14 years, one patient with galactosaemia every 20–30 years and would possibly never see a patient with homocystinuria during his years of clinical practice. Nevertheless, if he worked in New York he would be fully aware of the high incidence of the Tay–Sachs gene in the Jewish population, where it is estimated to be approximately 1 in 1000 in those of Ashkenazi origins. He would also be aware of the high incidence of type A G6PD deficiency (as much as 11%), among the American Negro population. The very high incidence of other metabolic diseases in specific ethnic groups in the United States is probably well known to investigators locally. Acute intermittent porphyria apparently has a high incidence in Lapland, but this incidence is made artificially high by one family, 135 members of which suffer from this disease, in a very sparsely populated area. The incidence is much higher than that found in the rest of Sweden, where it is comparable to the incidence found in other parts of the world.

Table 1.1 The frequency of the commoner metabolic diseases in childhood.

Disease	*Population*	*Incidence in population per 100 000*	*Individual frequency of homozygotes*	*Reference*
A-β-lipoproteinaemia	American	2.5	1 8 40 000	Farquar & Way 1966
Alactasia	Oriental	100 000	100%	Chung & McGill 1968
	Negro (USA)	70 000–75 000	70–75%	Bayless & Rosensweig 1966 Littman *et al* 1968
	African Bantu	50 000	50%	Cook & Kajubi 1966
	Caucasian (USA)	5000–19 000	5–19%	Gray & Santiago 1966 Bayless & Rosensweig 1966 Newcomer & McGill 1967 Littman *et al* 1968
	Denmark (Copenhagen)	3000	1 : 33 000	Gudmand-Höyer *et al* 1969
	Puerto Rico (San Juan)	21 000	21%	Gray & Santiago 1966
Alkaptonuria	Northern Ireland	0.3–0.5	1 : 330 000 1 : 500 000 (prob. falsely low)	Knox 1958
Adrenogenital syndrome	Switzerland (Canton of Zurich)	20	1 : 5000	Prader 1958
	England (Birmingham)	14	> 1 : 7250	Hubble 1966
	USA (Baltimore)	1.3	1 : 67 000 (probably low)	Childs *et al* 1956
Cholinesterase deficiency	England (commonest type)	36	1 : 2800	Kattamis *et al* 1962
Cystinuria	England (London)	5.0	1 : 20 000	Crawhill *et al* 1968 & 1969
	USA (Massachusetts)	5.5	1 : 18 000	Levy *et al* 1972
Cystathioninuria	USA	40	1 : 2500 (probably high)	Frimpter 1973
Fructosuria (essential)	USA	0.77	1 : 130 000	Lasker 1941
Galactosaemia	Denmark	3.7	1 : 27 000	Brandt 1969
	England	1.4	1 : 70 000	Schwarz *et al* 1961
	Europe	1.4	1 : 70 000	Public Health Committee of Europe 1970
	USA (New York)	2.8	1 : 35 000	Kelly *et al* 1970
	USA (Massachusetts)	0.45	1 : 187 000	Shih *et al* 1971
	Germany	8.0	1 : 12 000	Kaloud & Sitzmann 1972
Galactokinase deficiency (G6PD)	Switzerland	2.4	1 : 30 000	Thalhammer *et al* 1968
G_{M2}-gangliosidosis (Tay–Sachs disease)	USA	2.5	1 : 40 000	Mayes & Guthrie 1968
	USA (Jewish, New York)	11.1	1 : 900	Aronson & Volk 1962
	USA (non-Jewish, New York)	1.0	1 : 90 000	Aronson & Volk 1962
Gout	European	30.0	1 : 3300	Lawrence 1960
	USA	275.0	1 : 364	Wyngaarden 1960
Histidinaemia	England (Manchester)	4.5	1 : 23 000	Komrower 1974
	USA (Massachusetts)	2.0	1 : 50 000	Levy *et al* 1974
Homocystinuria	England (Manchester)	0.5	1 : 200 000	Komrower 1974
	USA (Manchester)	2.0	1 : 50 000	Levy *et al* 1971
Hyperprolinaemia	England (Manchester)	5.0	1 : 20 000	Komrower 1974
Hyperphenyl-alaninaemia	International mean	3.3	1 : 30 000	Scriver & Rosenberg 1973
	England	1:25	1 : 80 000	Scriver & Rosenberg 1973