Comparison of clinical signs between 3p deletions and unknown syndrome: abnormal facies, hypothyroidism, postaxial polydactyly, and severe mental retardation

	Cavalcanti ³	Young and Simpson ¹	Fryns and Moerman ²	Buntinx and Majeswski ⁵	Our case	Nienhaus et al ⁶ 3p deletions
Microcephaly	+	+	—	+	+	11/14
Growth retardation	+	+	+	+	+	16/16
	(<3rd)	(<3rd)	(<3rd)			
Blepharophimosis	+	+	+	+	+	16/16
Blepharoptosis	+	+	+	+	+	16/16
Epicanthus	+	+	+	+	+	10/12
Hypertelorism	+	+	+	?	+	6/14
Long philtrum	+	+/-	+/-	—	+	11/11
Flat nasal bridge	+	?	?	+	+	10/14
Bulbous nasal tip	+	+	+	+	+	10/14
Thin upper lip	+	+	+	+	+	10/16
Micrognathia	+	+	+	+	+	10/12
Malformed or apparently low set ears	+	+	+	+	+	15/15
		Right preauricular pits				
Postaxial polydactyly	+	—	—	+	+	10/14
Clinodactyly	—	—	—	—	—	<50%
Scoliosis	—	—	—	—	—	<50%
Prominent heel	—	—	+	+	—	<50%
Cleft palate	—	—	+	—	—	<50%
Hypothyroidism	+	+	+	—	—	<50%
Hearing loss	—	—	+	—	—	<50%
Heart malformation	—	Ventricular defect	—	—	—	<50%
Cryptorchidism	—	+	+	—	+	<50%

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Genetic Factors in Drug Therapy: Clinical and Molecular Pharmacogenetics. D A Price-Evans. (Pp 657; £120.00.) Cambridge: Cambridge University Press. 1994.

Professor Price-Evans has taken on a formidable challenge in attempting a comprehensive single author text on pharmacogenetics. Nevertheless, he has proved equal to the task and this impressive book represents an exhaustive review of publications up to and including papers published in 1992. Recent research in pharmacogenetics has focused primarily on genetic polymorphisms of drug metabolism and a large part of the book is devoted to the enzymes involved and their genetic determinants. The cytochromes P450 (CYPs) are dealt with first, since they represent the most important group of drug metabolising enzymes. Two major polymorphisms in this gene superfamily have been identified, affecting CYP2D6 (the "debrisoquine/sparteine" polymorphism) and CYP2C19 (the "mephenytoin" polymorphism). The list of drug substrates of CYP2D6 is growing rapidly (presently about 40), many of them in widespread clinical use. These chapters bring home the vast amount of information that has been gained on the molecular genetics, biochemistry, and substrate selectivity of these enzymes. Clinical data on population and ethnic aspects, pharmacokinetic consequences, and disease susceptibility in relation to phenotype and genotype are also considered in depth. However, a more critical evaluation of the clinical significance of the debrisoquine/sparteine polymorphism could perhaps have been expected. Most reports of unwanted drug effects in one or other phenotype are from single case studies, many of which have not been substantiated. There is a similar exhaustive

treatment of other drug metabolising enzymes which show evidence of polymorphism, N-acetyltransferase, S-methyltransferase, and pseudocholinesterase being the ones that have received the most clinical attention.

It is good to see that the difficulties of interpreting pharmacogenetic data are covered, an area that has often been neglected. For example, distinguishing between unimodality and bi- or trimodality in population distributions is a fundamental problem in pharmacogenetic studies of drug metabolism and, in an Appendix, the author summarises the main mathematical techniques proposed for its solution.

The remainder of the book is devoted to a discussion of adverse drug effects having an inherited pharmacodynamic or receptor basis. Well characterised disorders, such as glucose-6-phosphate dehydrogenase deficiency, the porphyrias, and malignant hyperthermia, would be expected to be included but the author has scoured published reports for less well known adverse reactions that may have a genetic basis. For example, in a report of one patient described as "a green man after indomethacin" it was suggested that inhibition by this drug of a rare genetic variant of biliverdin reductase caused his skin, urine, and serum to turn green owing to the accumulation of biliverdin. Unfortunately, this was not followed up with family studies.

From this book it should be abundantly clear to the reader that genetic variability in pharmacokinetics and pharmacodynamics has obvious implications for drug therapy, but with a few exceptions this knowledge has yet to be applied to clinical practice. The debrisoquine/sparteine polymorphism is a good example in that, although the phenomenon was discovered 17 years ago, few controlled prospective studies to evaluate its clinical significance have been performed. The recent emphasis on molecular genetics needs to be augmented by a more determined effort to define phenotypic differences in drug response.

All chapters are clearly written and the text and graphics layouts make the book easy to read. It is also extremely well indexed. There is a danger that, like all works of reference covering an active research area, particularly one in which molecular genetics has made such an impact, this book could become out of

BOOK REVIEWS

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date rather too quickly. Although publications on pharmacogenetics have expanded considerably in the two years since the book was written, I am sure it will continue to be a valuable text not only for those who are new to the field but also to those of us with a strong research interest in the subject. Perhaps Professor Price-Evans will take on the further challenge of producing a second edition in a few years time.

MARTIN LENNARD

ABC of Clinical Genetics. 2nd edition. Helen M Kingston. (Pp 73; £13.95.) London: BMJ Publishing Group. 1994.

Having read the first edition, which happened to be the first text book of genetics I have managed to read from cover to cover (because of its size and its reader friendly presentation), I was not disappointed with the second edition.

This is an introductory review of clinical genetics as implied in the title. The second edition is similar in its presentation and contents to the previous one, with a few new additions. It has 17 short chapters crammed into 73 pages, which summarise the cytogenetic and molecular genetic background to clinical genetics, the application of risk calculation, and an introduction to the common problems in clinical practice, including well illustrated chapters on dysmorphology and cancer genetics. Included in the book are chapters on the methods of prenatal diagnosis, the molecular diagnosis of some of the common genetic diseases, and treatments available at present (and the near future) for genetic disorders. Some of the diagnostic and ethical problems encountered in clinical practice are also discussed briefly.

The presentation is still very user friendly, with the text kept to a minimum and with numerous colour illustrations. There is a surprising range of subjects covered in this deceptively simple and short textbook, including mitochondrial inheritance and gene therapy. My criticisms are minor quibbles. The placing of the chapters is difficult to follow in a logical order, and this is particularly true for the chapters at the end of the text. There are also some typing errors, the most important of which is on page 46, when cordocentesis and the risk associated with the procedure is quoted differently as 1%, and in the next line, as 3%. The presumably Americanised spelling of "dysjunction" is also a minor irritation.

This is an excellent introductory text for those interested or involved in clinical genetics. It would be particularly useful for medical students and also for doctors, midwives, and nurses as a book which can update them quickly on the basics of clinical genetics. As such, it would be a useful addition to any genetics library.

D DE SILVA

Genetics and Medicine in the United States 1800 to 1922. Alan R Rushton. (Pp 209; £37.00.). Baltimore, London: Johns Hopkins University Press. 1994. ISBN 0-8018-4781-8.

The period covered by this book involved considerable changes in regard to genetics and medicine in the United States. Up to

the rediscovery of Mendelism in 1900, the general assumption was that much disease had a significant hereditary component and that there was a hereditary predisposition, or diathesis, to most conditions. Physicians were fond of expressing the view that "like begets like". The concept was embedded in terms such as "heredo-familial" which persisted in some textbooks until relatively recently. When a parent was also affected the term "hereditary" was used, when sibs were affected the disorder was considered "familial". There was much debate and interest in the subject but there was no way of studying the problem further. At this time American physicians often turned to Europe for training in science where interest largely centred on microscopic pathology, especially in neurology, which added very little to the understanding of the role of heredity in a particular disease.

With the rediscovery of Mendelism at the beginning of the century it is generally assumed in most textbooks that problems of human inheritance then immediately became clear. But this was not so. Though Mendelian principles could be shown by plant and animal breeders, this was far more difficult in humans. Controlled matings were impossible and generation times long. The physician could only observe a pedigree and draw inferences from it. Appropriate statistical methods, such as segregation analysis, had to be developed. (The precise modes of inheritance for Duchenne muscular dystrophy and cystic fibrosis were not incontrovertibly established in fact until around 1960.) Furthermore physicians often found Mendelian concepts puzzling and of little relevance to their practice. The profession was understandably concerned more with the problems of infectious diseases, the basis for which began to be understood from around 1880 but for which there was still little effective treatment. Some scientists with no such concerns, however, attempted to apply Mendelian principles to almost all human traits. The argument that hereditary factors could be involved in such traits as criminality, prostitution, and mental defect led to the Eugenics movement and Davenport's Eugenics Record Office established at Cold Spring Harbor in 1904. Towards the end of this period the importance and relevance of genetics in medical practice slowly began to be appreciated, and has been a continuing process ever since!

The author argues that the situation in Britain has been different. From the beginning of the century British geneticists led developments in the field. He plans therefore to write a subsequent volume concerned with the role of genetics in British medicine up to 1920. Meanwhile the present well documented and well written analysis of the scene in America will no doubt be read with considerable interest on both sides of the Atlantic.

ALAN E H EMERY

From Genetics to Gene Therapy. Editor D S Latchman. (Pp 261; £55.00.) Oxford: BIOS Scientific Publishers. 1994.

This book consists of 12 reviews that give the reader a flavour of the scope and potential of molecular medicine/pathology. The book is true to its title as some chapters focus primarily on the molecular and cell biology of various diseases (apolipoprotein B and heart

disease, X linked immunodeficiencies, Duchenne muscular dystrophy, leukaemias, neuroendocrine tumours, breast cancer, membrane protein processing in neurodegenerative diseases, herpes simplex) and mention gene therapy options only briefly, while others deal exclusively with topics directly related to gene therapy technology (gene therapy for cancer, retrovirus receptors on human cells, viral vectors for gene therapy, direct gene transfer for treatment of human disease).

Each chapter is written by recognised authorities. The reviews are clear, concise, and up to date. The authors enthusiastically convey the power of contemporary molecular and cell biological techniques as tools that can unravel the fundamental processes involved in the pathogenesis of various diseases. The importance of an in depth understanding of the molecular pathogenesis of diseases as a basis for therapy is appropriately stressed.

The format of this book may be considered by some to be unsatisfactory as the chapters are independent and do not generally look like they will amount to a coherent whole, even though they are loosely linked by a common theme. For instance, one may argue that this book provides neither a comprehensive review of the principles involved in the pathogenesis of genetic diseases, nor is it a primer on gene therapy. However, the quality and accessibility of the reviews more than compensate for this shortcoming. After reading this book I felt that I had a better understanding of the different approaches to gene therapy and their current limitations and was stimulated by the elegant studies that have led to deeper understanding of some of the diseases that are reviewed. I agree with David Weatherall's final remarks in his foreword: "This book should be read by young medical and non-medical scientists who are thinking about a career in this field, or those who wish to find out what is going on and about the current state of progress in some of the more important areas of molecular medicine."

DAVID RUBINSZTEIN

Clinical Genetics Handbook. 2nd edition. Editors A Robinson, M G Linden. (Pp 615; £32.50.) Boston: Blackwell Scientific Publications. 1993.

Initially this handbook was developed by the National Genetics Foundation and the editors of this second edition acknowledge the efforts of previous contributors and restate their aims of allowing the primary care physician to have ready access to genetic information when practical questions arise in a clinical setting. To this end the handbook is divided into two sections. The first, Applied Genetics, covers fundamental genetic topics and includes a chapter on issues related to genetic screening. The larger section, Disorders in Clinical Genetics, allows easy reference by organ system to reflect clinical presentation. Molecular genetic information provided is limited with each chapter concentrating on clinical detail, diagnostic confirmation, pathogenesis, empirical risks, and management. The style and terminology are very American and the quoted resources at the end of each clinical chapter are exclusively so. Overall it does fulfil its stated role as a useful first port of call for the clinician