Deletions of the entire APC gene are associated with sessile colonic adenomas

Lynch et al have recently described four extended kindreds with an autosomal dominant inherited predisposition to cancer characterised by multiple colonic adenomas. The adenomas were usually fewer than 100 in number, predominantly sited in the colon, and often flat or sessile rather than polypoid. Linkage analysis using DNA markers for loci flanking the APC gene in two of the families showed linkage to the APC gene locus with a multipoint lod score of >3. A similar large family with variable numbers of colonic adenomas in affected persons was described by Leppert et al in 1990, where linkage between the disease and the APC locus was shown, with a lod score of 5.58

The flat adenoma phenotype is of clinical importance since these adenomas may be difficult to define at endoscopy, and because of their predominantly proximal location, colorectal cancer rather than sigmoid cancer would be required to detect them. The histology of these lesions is distinct from the classical polypoid lesion of FAP.

At Lynch’s suggestion, we have reviewed our experience of sessile colonic adenomas detected in the two cases of FAP with cytogenetic 5q deletions including the entire APC gene, which we described previously.1 In both cases, adenomas were predominantly proximally sited in the colon, and in both there were some sessile adenomas, similar to those described by Lynch et al.1 However, the majority of adenomas in case 1 were microadenomas and microadenomas were also found, and the overall histological picture was similar to classical FAP. In case 2, many adenomas in the distal colon were flat, but in the more proximal colon, pedunculated adenomas were seen in increasing numbers to the caecum.

We therefore feel that the heterozygous deletion of the total APC gene is associated not specifically with the phenotype of hereditary flat adenomas, but with a form of FAP characterised by a more proximal distribution of adenomas than usual, with some adenomas being sessile and some may be non-polypoid or flat. We could postulate that in the usual type of FAP where the mutation results in a truncated protein, this protein could possibly interfere with the function of the normal protein product of the normal allele to cause a more severe disease than seen in our patients.

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If I am to be Remembered. The Life and Work of Julian Huxley with Selected Correspondence. Krishna R Dronamraju (Pp 294; £27.00.) Singapore/London: World Scientific Publishing Co. 1993.

By any criteria the Huxley family is incredibly gifted. Julian (1887-1975), the subject of this biography, ranks among the foremost biologists of this century. He had a life long fascination with all things animate. He liked to consider himself a generalist and he certainly had interests in a wide range of subjects. I still remember vividly a lecture he gave to us as undergraduates on the intriguing metamorphosis of the axolotl and the problems of allometric growth and the demise of the Irish Elk. He was also interested in ornithology and his careful and classical studies of the courtship behaviour of the Great Crested Grebe established the new discipline of ethology. He researched marine invertebrates and for a time was employed at the world famous Stazione Zoologica in Naples.

In 1925 he became Professor of Zoology with an annual salary of £1000, a four figure income never previously offered to a British biologist! He considered himself an excellent teacher. In his work he travelled widely. He loved America and in his travels to Africa to advise on education took a great interest in the wild life and conservation. He was to be elected as a member of the Royal Society, and as a UNESCO delegate, he became involved in the notorious Lysenko affair whose work he ultimately dismissed on scientific grounds. He was a prolific writer and many of his books helped popularise science and the concept of Humanism.

What of the man himself? Huxley’s own autobiography (Memories, Vol I and II, Penguin Books) reveals little and the author admits he has been unable to discover very much. Huxley was given to “nervous breakdowns” and reading between the lines of this biography, he had difficulties with close personal relationships. Could the author have divined more by interviewing those who had known and worked with Huxley? I don’t know, but as a scientific biography this is an excellent contribution on a great biologist. It is well documented and well written and can be highly recommended.

ALAN EMERY


This is a very nicely produced book comprising 14 chapters, which deal with every aspect of new procedures (largely untried) for diagnosis of genetic disease in human oocytes and embryos in vitro. The book is divided into five sections. Although all the chapters are clear, well written, and interesting, some of them are not relevant to the title of the book and thus in the book as a whole is not well organised.

The chapters are distributed somewhat arbitrarily into five sections which I will summarise.

The first section contains three introductory chapters which give background – a rambling walk through early attempts to diagnose sperm, oocytes, and embryos (Edwards and Schulman), an excellent review of our limited knowledge of macromolecular synthesis in human embryos (Tesarik), and the logistics of the clinical application of preimplantation diagnosis (Penketh). The second section contains a useful introduction to genetics of common diseases by Schulman and Black and two chapters, which are out of place in the context of this book, on the history of prenatal diagnosis (Verlinsky and Ginsberg) and chorionic villus sampling (Pergament and Fine). The third section contains two technical chapters on methods of DNA diagnosis by Bentley et al, which would have been more sensibly organised as one chapter and included in the fourth section which addresses the main theme of the book.

The first chapter in the main text is entitled, “Can Spermatozoa be Typed?” by Gledhill and Edwards, has been answered in part, since Johnson et al (Hum Reprod 1993; 8: 1735) have recently reported fluorescence activated cell sorting of X and Y bearing human sperm. Then follows a condensed chapter on polar body diagnosis by Verlinsky and Strom (more support for the data given is needed here), another review of blastococyte biopsy and sexing by Handsides and Delhanty, a fascinating and informative review of the blastocyst and blastocyst biopsy by Harthorne et al, and a survey of the potential for the different approaches by Leese and Edwards. Finally, there is a most welcome review of the ethical and legal aspects of the work by Braham.

Overall, if you are interested in this rapidly developing field, this book is comprehensive and “intended to be an up-to-date presentation”. However, as is always the case in edited volumes of this type, chapters are prepared well before the final publishing date and inevitably the claim to “the latest technology” cannot be upheld. In this same year, we have seen significant developments such as sperm typing, the preimplantation diagnosis of the first single gene defect (cystic fibrosis), earlier prenatal diagnosis by coelocentesis and transcervical flushing, further clarification of specific gene defects (for example, fragile X), and new diagnostic techniques such as chromosomal painting.

There is also a problem in that the well organised presentation of data in a book of this type tends to give a false impression to the reader that preimplantation diagnosis of genetic disease is established and accurate. There are chapters in this book that make it look easy, especially where data are given without controls and are not placed in the wider context which would allow a realistic success rate for this approach at the present time. There are only a few centres which can offer
preimplantation diagnosis and only a small number of babies have been born from such procedures. These brave pioneers must go through the early stages of a high failure rate and errors.

It is important also to emphasise the pitfalls and dangers of the procedures. The main problems arise with the diagnostic tests, the problems of test contamination, extra sperm which may be present in the perivitelline space of the embryo, cellular mosaicism, and the presence of abnormal cells which may or may not be representative of the future fetus. Then, there are problems associated with the IVF procedure itself: low efficiency of pregnancy, multiple pregnancy, and the invasive treatments of the woman. Also, in all attempts at preimplantation diagnosis, a later prenatal diagnosis by chorionic villus sampling or amniocentesis is needed to check the accuracy of the earlier embryo diagnosis. Preimplantation diagnosis may be a safe and efficient approach to the prevention of genetic disease in the future but it has a long way to go. If you are interested to know how far along the road it has come since its recent beginnings just six years ago, this book is the best you will find to bring you up to early 1993.

Marilyn Monk


The editors describe the first edition of this book as being "at the cutting edge of the interface between clinical and basic neuroscience". This is reflected in their choices of contributors, all authorities in their fields and with high profile in the author lists in current neurology/genetics journals. The chapters are, in general, comprehensive, well written, and more than adequately referenced. The book is divided into sections, each containing between one and five chapters.

Part I, chapter 1, begins gently with descriptions of nucleic acids and DNA structure and translation, and progresses rapidly (in 17 pages) through DNA markers, restriction enzymes, and polymorphisms to linkage, cloning, and gene therapy. One small criticism is the use of the term "reverse genetics" where most would now use "positional cloning". In addition the section devoted to Lesch-Nyhan disease would seem superfluous in view of the full chapter coverage later.

Chapter 2 is a list of the chromosomal locations for genetic neurological diseases and genes of relevance to the nervous system. There are some minor omissions: tuberous sclerosis has entries at 9q34, 11q14, 12q22 (the last two are rather dubious localisations) but not chromosome 16 where there is a major locus. This is, however, mentioned in the chapter on TS. Similarly there are no listings for myotonia congenita and Becker's generalised myotonia which are associated with the skeletal muscle chloride channel at 7q32-qter. Some entries list the disorder alongside the gene product but this is not universal; dystrophin does not appear with Duchenne and Becker muscular dystrophies. Chapter 3 gives a small (three pages) taste of linkage analysis, computer programs for such, and the problem of genetic heterogeneity. It is perhaps a little too short for reader with no previous knowledge of this field.

The disease specific chapters which follow contain many highlights and very few disappointments. The chapters on metabolic disorders admirably cover the clinical, biochemical, and molecular features of the appropriate diseases. In addition they offer therapeutic protocols where available or discuss potentials for therapy. Part XI contains a single chapter; a scholarly, multiauthor review of the prion diseases of humans and animals. Frusnier and colleagues also provide ample scope for further reading on this fascinating topic, with 311 references.

Part XIII contains reviews of the muscle dystrophies and, with the exception of the chapter on FSH/limb-girdle dystrophies which contains less than two pages of text, this section amply summarises the salient clinical and molecular features of these disorders. Roses (chapter 41) has been able to incorporate some of the rapidly appearing new data on the unstable trinucleotide repeat sequence associated with myotonic dystrophy and this chapter is well referenced up to 1992. At this time it was known that expansion of another trinucleotide repeat sequence, this time in the androgen receptor gene, was the causal mechanism of bulbospinal atrophy (电机's syndrome). There is no mention of this, either in this chapter or (that this reviewer would) elsewhere in the book.

Part XIV contains again a single contribution. DiMauro's review of mitochondrial disorders is comprehensive, clearly written, well supplemented with explanatory diagrams, and excellently referenced. Part XV deals with "degenerative disorders" and begins with a chapter on heredity ataxias. Unfortunately this was a little disappointing as over half of this chapter reviews disorders given more comprehensive coverage elsewhere in the text. Part XIX (neuropathies and neuropathies) contains limited clinical information, the discussions focusing on gene mapping (for spinal muscular atrophy), mutations (transthyretin and amyloid neuropathies), and peripheral nerve physiology (axonal neuropathies). The review of the genetic epilepsies (part XX/chapter 63) is particularly thorough, including a description of the epileptic Mongolian gerbil! It also includes useful guidelines on risk estimates and prognosis for the controlling relatives of persons with epilepsy. The final chapters (gene therapy and consequences of gene mapping) conclude this volume with general discussion of future developments in the field of genetic neurological diseases, although specific examples are given for replacement therapy in animal models. The reviewer finds it surprising that there is no mention of the possible societal and political consequences of the Human Genome Project.

Is this the neurology equivalent of The Metabolic Basis of Inherited Disease? The answer must be "yes". The criticisms above are minor compared with the wealth of information provided overall and this volume will certainly fulfill its goal in being of use to clinicians caring for patients and for scientific investigators in this field. Every genetic/neurology unit should have access to this volume but most people will want their own copy and anyone with a colleague visiting North America would do well to persuade him/her to add the extra weight to their return luggage as the US price equates to £150.

John Macmillan
Preconception and Preimplantation Diagnosis of Human Genetic Disease

Marilyn Monk

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