Imprinting and Angelman's syndrome

The revision of the conclusions of two recent reports of Angelman's syndrome^{1,2} by Professor Hall³ is correct in pointing out the consistency of the observations with those expected owing to genetic imprinting. However, the importance of the results is understated even in this revision. The essential observation made was that the maternal transmission of pericentric inversions of chromosome 15 (inv(15)(p11q13)) resulted in offspring with Angelman's syndrome, while the mothers carrying the inversion were unaffected. Whereas the authors of the original reports postulated that the inversion 'unmasked' a recessive gene for the condition transmitted by the father, the role of imprinting in this parentally determined susceptibility was highlighted by Professor Hall, who predicted that the mothers would have to have inherited the rearrangement from their fathers to be unaffected. On first appraisal, this conclusion contradicts what is known about imprinting on chromosome 15, that the area deleted to yield Angelman's syndrome or Prader-Willi syndrome is identical, not only in cytogenetic (15q11-13)⁴ but also in molecular terms,⁵ dependent only on the parent of origin of the deleted chromosome (AS maternal, PWS paternal). If this were true, then the paternal inheritance of the rearrangement by the probands' mothers in these cases should have resulted in maternal Prader-Willi syndrome.

The pathological effect of imprinting apparently results from the production of nullisomy at a locus when a genetic event removes a functioning allele, the homologue of which has been rendered inactive owing to the imprinting process.⁶ In the 15q11-13 region, several (a minimum of two) such loci must exist, inactive alleles occurring on both paternal and maternal chromosomes, in order to produce the discrete phenotypes. The pericentric inversions should be interpreted in this light, while adhering to the assumption implicit in the previous assessments: that, as the mothers express the rearrangement in a non-mosaic manner in their somatic cells, they probably inherited the inversion. Firstly, if the inverted segment has led to incapacitation of the 15q11-13 region, and as it is being inferred that the individual loci giving rise to Prader-Willi and Angelman's syndromes are

distinct, it may be concluded that the locus (loci) for the former is located more distally, beyond the breakpoints in these cases. If there is indeed a submicroscopic deletion associated with the inversion, then the status of the rearranged segment is crucial. If the rearranged segment is not inactivated, which would be more consistent with viability, then the pathological consequences are mostly attributable to the deletion. In this case, the locus (loci) for Angelman's syndrome are within the deleted segment, and the Prader-Willi locus (loci) may be proximal or distal to this. Furthermore, the rearrangement could indeed be inherited from grandfathers. It is also possible that further genetic events have taken place in the Angelman patients. The final possibility is that the mothers do in fact have loci nullisomic owing to imprinting, but that the deletion is sufficiently small that compensatory mechanisms to prevent the development of Prader-Willi syndrome are effective.

Whatever the molecular event, the main conclusion which may be drawn is that, apart from the last possibility, these cases confirm the independence of the Prader-Willi and Angelman loci, suggest that if multiple loci govern Angelman's syndrome they are within a relatively restricted stretch of DNA uninterrupted by Prader-Willi loci, and confirm the importance of imprinting in the region. In short, the loci for Prader-Willi and Angelman's syndromes may be distinguishable using the DNA of these patients, and the chromosomal status of the maternal grandparents must be ascertained, a point stressed by Professor Hall.

JOHN M GREALLY

Division of Genetics,
Children's Hospital of Pittsburgh,
3705 Fifth Avenue,
Pittsburgh, PA 15213, USA.

- 1 Pembrey M, Fennell SJ, Van den Berghe J, et al. The association of Angelman's syndrome with deletions within 15q11-13. *J Med Genet* 1989;26:73-7.
- 2 Fryns JP, Kleczkowska A, Decock P, Van den Berghe H. Angelman's syndrome and 15q11-13 deletions. *J Med Genet* 1989;26:538.
- 3 Hall JG. Angelman's syndrome, abnormality of 15q11-13, and imprinting. *J Med Genet* 1990;27:141.
- 4 Magenis RE, Brown MG, Lacy DA, et al. Is Angelman syndrome an alternate result of del(15)(q11q13)? *Am J Med Genet* 1987;28:829-38.

5 Donlon TA. Similar molecular deletions on chromosome 15q11.2 are encountered in both the Prader-Willi and Angelman syndromes. *Hum Genet* 1988;80:322-8.

6 Solter D. Differential imprinting and expression of maternal and paternal genomes. *Annu Rev Genet* 1988;22:127-46.

BOOK REVIEWS

The Ichthyoses. A Guide to Clinical Diagnosis, Genetic Counselling, and Therapy. H Traupe. (Pp 253; £62.50.) Berlin: Springer-Verlag. 1989.

A book intended to bring together the modern concepts of ichthyosis is long overdue, and Dr Traupe has, almost singlehandedly, made a brave attempt to meet the challenge. His classification includes 20 genetic disorders which are grouped into 'isolated' and 'associated' forms, each with 'congenital' and 'vulgar' (meaning later onset) categories. For example, X linked recessive ichthyosis is an isolated vulgar condition, whereas neutral lipid storage disease and Sjögren-Larsson syndrome are associated congenital ones. On the whole, this didactic approach works quite well, especially as it incorporates numerous lists for sorting out the different forms according to cutaneous signs and symptoms, non-cutaneous disease manifestations, and microscopical and biochemical findings.

There is an excellent historical chapter including an illustrated account of the 'porcupine' members of the Lambert family from Suffolk. Other chapters deal systematically with the four main categories. In addition, there is a comprehensive and up to date chapter by B Melnik on epidermal lipids and the biochemistry of keratinisation. This is the only chapter not written by Dr Traupe himself.

The book is liberally illustrated with superb black and white clinical photographs, picking out the detailed topography of scaly skin, and with photomicrographs and electron micrographs, which are helpful in delineating some of the rarer forms.

The generally excellent presentation and uniformity of style will ensure this book's success with most readers. It

certainly succeeds in clarifying the muddled waters of one of the more heterogeneous groups of genetic skin diseases, but does not remove all the confusion. Ichthyosis is defined as a disorder of keratinisation, yet recent advances in the biochemistry and molecular biology of keratinisation have produced little evidence pointing to fundamental abnormalities of keratin synthesis or organisation in many of these diseases.

The tendency to revert to acronyms or abbreviations such as BIDS, IBIDS, KID, HID, and ILC is an irritating distraction, but I suppose a constant repetition of the names in full might be even more tedious!

This book will be a useful reference source for clinical geneticists, dermatologists, and paediatricians. Its price may dissuade many from buying a personal copy, but there is nothing else on the market which matches it.

R A J EADY

Maternal-Fetal Toxicology. A Clinicians' Guide. Ed Gideon Koren. (Pp 456; \$125.00.) New York: Marcel Dekker. 1990.

Clinical geneticists frequently receive enquiries from colleagues, particularly in obstetrics, about the possible teratogenic risk to the unborn child of chemical and physical agents in a pregnancy. The editor and a number of the contributors to this multiauthor text have established centres with a multidiscipline team for enquiries of

this nature, many of which come directly from the couples/women concerned. This text is said to be a result of the new approaches and clinical tools which developed.

The book is divided into four main sections covering Drugs in pregnancy, Poisoning and radiation in pregnancy, Genetic and obstetric considerations, and the Organization and operation of teratogen information services.

Particularly well written and succinct are the chapters on Ionizing and nonionizing (sic) radiation in pregnancy and Genetic aspects, which covers clinical genetics and genetic counselling.

One of the interesting aspects of the text is the chapter on Nonmedical drug and chemical use in pregnancy. The inclusion of this as a separate topic reflects the frequency of enquiries of this nature by the clientele. The rarity of such enquiries from personal experience in the United Kingdom probably reflects a difference in attitude rather than the magnitude of the problem.

One chapter, Teratology information sources, reviews in some detail other textbooks on reference sources including computer databases, an unusual practice for a textbook.

One of the important points mentioned in the introduction of many of the chapters, but explored in detail in the chapter The way women perceive teratogenic risk, is the fact that many women overestimate the degree of risk with the majority of teratogenic exposures in utero.

There are, I am afraid, a few criti-

cisms. Having read the text through rather than 'dipping into it' at random, there is repetition of material, both in the introductions of the various chapters, as well as in the topics covered in the individual chapters, something that editors of multiauthor texts should be wary of.

The index does not cross reference items and topics in enough detail. For example, if one wanted to look up epilepsy and anticonvulsants, these are covered in numerous sections of the book, but one is required to look up the individual anticonvulsants one by one to find the relevant material. The use of a hierarchical index with highlighting in the main section would have been helpful.

The text also suffers from being parochially North American in its terminology and listing of centres with experience and interest in this topic. In addition, while the reader can usually get the sense of what the authors are attempting to convey, on many occasions this requires the ability to understand what might be politely called 'neologisms' or more correctly 'North Americanisms'.

While this book might well appeal to obstetricians, paediatricians, and clinical geneticists who deal with enquiries of this nature, I am afraid the drawbacks outlined, when the cost is taken into account, might not make it a first choice for the reference bookshelf. For that price, I would expect the last word!

R F MUELLER

HEALTH EDUCATION LIBRARY
BOOTH MEMORIAL MEDICAL CENTER
MAIN ST. AT BOOTH MEMORIAL AV.
FLUSHING, N. Y. 11355