Advances in human genetics 14. H. Harris and K. Hirschhorn (eds). Plenum Press, New York and London. 1985. Pp. xiii+399. Price $49.00(US).

Science remains unpopular among the general public because it is increasingly difficult to understand. So too within science there is the problem of comprehension between two disciplines; and in Vol. 14 of this series some writers are aware of this and others not. Those who arouse interest attract disciples, while others seem only concerned with quoting every reference—they forget that people in their own field have a habit of keeping themselves up-to-date.

Overall what is needed is crisp English, not turgid prose. It is useful to have a summary capable of being readily understood by any geneticist and one that indicates which are the important advances.

The publisher's blurb states "Like its predecessors, Volume 14 will be essential reading for those working in the areas of medical genetics, genetics and biochemistry". I will try and show how far I think this claim is justified.

Chapter 1. *Cytogenetics of pregnancy wastage.* (Boué, Boué and Gropp) 49 pages and 150 references.
The information here comes from studies on perinatal deaths, and from both spontaneous abortions and those, I suppose, induced as a result of amniocentesis findings. Almost every possible chromosome error has been observed, giving good grounds for the conclusion that abortion represents the main natural way of eliminating around 99 per cent of chromosomally abnormal conceptuses. However, just to be on the safe side, I would have liked to see a control series taken from TOPs carried out for social reasons—or are these minimal on the Continent?

Surprisingly, the chromosome abnormality rate is much lower in domestic and laboratory animals, possibly because *breeders* know how to select good stock; it would be interesting to know what happens in wild animals, particularly primates.

Androgenesis is no longer new, but it was one of the early (1973) surprises, in which the Japanese found that in the classic hydatidiform mole the apparently female 46XX complement in fact consisted of paternally derived chromosomes, the maternal haploid set having been lost. A later sequel (1982) is the interesting finding that the mole, even though from an anucleate egg, contains exclusively maternal mitochondrial DNA. There remain however many puzzles, for example, the geographical difference in the incidence of moles (less than 1 in 2000 in "developed" countries but 1 in 200 in Japan (underdeveloped?)); environmental factors are thought to be responsible. These may be socio-economic, since women from a high risk ethnic group born in a developed country only have the lower risk of their adopted home. A possible explanation is that the incidence is the same in all female populations but the time of elimination is different; in the East, women being less immunologically competent and the abnormal conceptus therefore not rejected, as it usually is in the developed countries.

With racially mixed populations (as in the U.K. and U.S.A.), combined with markedly different environments, the differential elimination of abnormal conceptuses must always be borne in mind by medical geneticists. I think for example of fluoride. The "antis" accused the "pros" of poisoning the genome in fluoridated areas, and causing an increase in Down babies. The "pros" reply is that the prophylaxis might equally well be protecting conceptuses in general—among them the Down babies!

Another interesting observation is that there is a significant concordance between the chromosome status of two consecutive abortions, particularly for trisomy, but the extra chromosomes involved are different in most cases. It therefore appears that certain couples have a higher than normal risk of producing non-disjunction during gametogenesis.

The chapter topic is of general interest which means that the authors start with an advantage, but my attention was held throughout and I agreed with most of the inferences drawn from the data.

Chapter 2. *Mutation in human populations.* (Crow and Denniston) 57 pages and 145 references.
The authors make their intentions quite clear. They concentrate on the rate of phenotypically detectable mutation and on its impact on human welfare, and on some evolutionary considerations. They do not deal in any detail with molecular studies which try and measure the amount of change in the DNA from mutation. This is because many of these have no detectable phenotypic effect, though whether they influence fitness is another matter. This being so, a large part of this chapter is familiar (including Kimura's "neutral genes") and I was more interested in some special problems, such as the explanation of paternal age effect, which is related to more cell divisions in the sperm. For example, before sperm is fully functional there are about 380 divisions at 28 years and 540 at 35, compared with about 24 divisions before the egg is ready, so that there is more opportunity for mutational abnormalities to occur in the male. Over 70 years ago Wilhelm Weinberg, evidently being pre-adapted to this knowledge, noted that children with achondroplasia tended to result from older fathers, and he thought this argued for a mutational origin. Similar findings were made much later for Marfan's syndrome and myositis ossificans, and more spectacular is the increase in the age of the maternal grandfather of sporadic haemophiliacs. Just as interesting, on the other hand, are diseases which do not have a paternal age effect even though the mutation rate is high. Possibly the cause here is not mutation in the usual sense but something akin to a high rate of meiotic recombination and this may not be dependent on the number of cell generations. Some malignancies also come into this category, *e.g.*, retinoblastoma, where the absence of a clear paternal effect may be the result of the confounding of germinal (inherited) and somatic mutations.

On the evolutionary side, the authors think that Fisher and Wright's views on selection still hold the field with their emphasis on changes of gene frequencies

resulting from changes in the environment. However, the advent of transposable genes has brought out latent Goldschmidtian tendencies in some molecular biologists, the possibility being that a transposed gene can convert a normal locus into a mutable one, and conceivably there might be an evolutionary advantage in this. However, with all this talk about jumping genes it is, as the authors say, remarkable that the gene order has remained so stable.

Chapter 3. *Genetic mutations affecting human lipoprotein metabolism.* (Zannis and Breslow) 61 pages plus 3 of addendum and 526 references.
Reference 527 should have been included. It is Lewis's chapter in David Weatherall's textbook of medicine, and the present authors should have read it to see how to present the subject in an attractive and informative way (should not the English editor have pointed a finger in this direction?). As it is, we have biochemistry and turgid prose, a daunting combination, with only occasional glimpses of the light when new single gene disorders are discussed.

Chapters on a subject such as this ought to engender interest, and yet nowhere could I find discussed whether my moderate intake of gins and tonic is influencing my HDLs and postponing atherosclerosis; nor why, in terms of those terrible "apo-s", the population of the U.S.A. has benefited so dramatically by altering its lifestyle. Because this has happened, I feel that molecular geneticists should at present stick to single factor cardiovascular disorders and not become involved with polygenes and their "commercial application" by life insurance actuaries and job selection committees.

Chapter 4. *Glucose-6-Phospate Dehydrogenase.* (Luzzatto and Battistuzzi) 85 pages plus 2 of addendum and 523 references.
Deficiency of G6PD has been on the polymorphic books for many years, and the sex-linkage has added greatly to its interest. Everyone knows about the protection which lack of the enzyme affords against *falciparum* malaria and the price that is paid in toxic reactions—and so we have a good basis from which to start.

The advances include the fact that G6PD deficient males are not protected against *Plasmodium falciparum* malaria whereas heterozygous females are—exactly the opposite of what one might expect—reason, *P. falciparum*, needing G6PD and finding none, manufactures its own in male hosts, but is confused by heterozygous females, and the metabolic point of view of the all-important mosquito is well discussed. There is also a wealth of information about what happens in many other animals, and it is important to remember that there are many G6PD polymorphic systems in non-deficient populations.

Lyonisation of the X keeps in the news, for by chance there will be heterozygous women who are very G6PD deficient, or the converse—and this can now be tested for and might have clinical relevance.

But there still remains the erratic behaviour of the G6PD deficients. Only 25 per cent of them develop favism after eating the beans, and they can often tolerate drugs, against the odds, so that infection as well as the enzyme deficiency may be necessary to produce haemolysis.

There is the splendid section defending malarial protection, contradicting "the clinical data are controversial". The authors point out that there is not a single population in which G6PD deficiency has reached a polymorphic frequency in the absence of exposure to malaria. True the Amerindians have endemic malaria and no G6PD deficiency, but geneticists have no difficulty with this. The Amerindians did not bring the Gd negative gene with them across the Bering Strait nor did it arise *in situ* by mutation.

Lastly, there is the splendid swipe at the epidemiologists who criticise the protection idea but they pool data on males and females—X-linked traits are a troublesome trap for non-geneticists!

I have picked out some bits of the chapter that I understand, but must point out that much of it is uphill work. However, it is interestingly written so that non-comprehension does not equate with boredom—one reads it again, and the paragraph headings make this easy. Most important of all, the English (by two Italians) is impeccable.

Chapter 5. *Steroid sulfatase deficiency and the genetics of the short arm of the human X chromosome.* (Shapiro) 40 pages plus 1 of addendum and 217 references.
Agreed that investigating rare conditions often pays unexpected dividends, and *STS* deficiency relates not only to ichthyosis but also to X-chromosome inactivation, X/Y interchange and the understanding of XX males and other aneuploid states. So on the first page we are all agog, but before we get to the deficiency we have to wade through ten pages of boring physiology until at last we come to the nub of the matter. Not only is *STS* deficiency responsible for X-linked ichthyosis, but the locus is on the short arm of the X close to Xg and therefore not inactivated, and in an area where crossing over between the X and the Y can occur. Does this matter? Yes, most certainly. XX men have testes, without a Y chromosome, and the explanation is now clear. Crossing over has occurred and in some cases the *STS* locus has been lost so that then these men are ichthyotic. My criticism of the arrangement of the chapter may stem from the fact that as a medical man I start with patients but nevertheless it *is* the ichthyotics who contribute most that is interesting.

In summary, buy the book, and a wet towel as well.

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