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BOOK REVIEWS

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Technologies for Detection of DNA Damage and Mutations. Editor G P Pfeifer. (Pp 441; $95.00.) New York: Plenum Press. 1996. ISBN 0-306-45237-5.

Recent scientific advances have shown conclusively that damage to cellular DNA is the initiating event for many types of human cancer. The ability of cells to repair such damage represents a major form of protection against carcinogenesis. In the "DNA repair syndromes", a genetic deficiency in a DNA repair process results in extreme cancer proneness. Long standing examples are xeroderma pigmentosum and ataxia telangiectasia. More recently, hereditary non-polyposis colon carcinoma (HNPCC) has been shown to be caused by defective repair of DNA mismatches. An important biological consequence of unrepaired or incorrectly repaired DNA damage is the generation of mutations. Somatic mutations in oncogenes or tumour suppressor genes are critical steps in the progression of carcinogenesis. Germline mutations are the basis of genetic disease. In the field of human molecular genetics, as the genes underlying more and more genetic disorders are discovered, the need to identify disease mutations for the purposes of diagnosis, prognosis, and understanding of the disorders is mushrooming.

Technologies for the Detection of DNA Damage and Mutation is in three parts, which will be of interest to three quite disparate groups of researchers. The first part, on detection of DNA damage, covers a range of highly specialised techniques for measuring different types of DNA damage and their repair. Up until 10 years ago, DNA repair methodology was relatively crude, the techniques available being capable of assessing overall levels of damage and repair in populations of cultured cells. Techniques developed more recently have added much greater sensitivity and specificity. Single cell microgel electrophoresis (more commonly known as the comet assay), described by Singh, is a technique for measuring levels of damage in individual cells. Antibodies generated against different types of damage, such as that produced by UV light (Mitchell), alkylating agents (Thomale *et al*), and oxidative damage (Melamade *et al*), have increased the sensitivities of assays and enabled different types of damage produced by complex carcinogens to be measured.

A major advance in the mid-eighties was the development of procedures to measure repair in individual genes. These procedures are described in two chapters by the scientists who devised the techniques (Bohr, and Smith and Hanawalt). A further refinement was devised recently by Pfeifer (the editor of this volume) and Holmquist, who developed methods for measuring repair right down to the level of the individual nucleotides. Three chapters describe variations on this technique. This collection of up to date repair methodologies will be extremely valuable for advanced researchers in the field of DNA repair, but it is likely to be too specialised to be of much interest to medical geneticists. In contrast, part II describes technologies for the detection of mutations, of central importance to modern medical genetics. A variety of techniques has been developed over the last few years, all of them using variations of amplification of the target gene using the polymerase chain reaction (PCR), followed by some kind of electrophoretic separation to distinguish mutant from normal DNA. Each author is naturally a strong proponent for his own chosen technique, and all the methods (for example, denaturing gradient gel electrophoresis, single strand conformation polymorphisms, protein truncation test) are described in detail. It would have been useful to have had an overview of the pros and cons of each technique. For the relative novice, a crucial question will be the selection of the most appropriate technique to use for the problem being addressed.

Despite the similarity of the title of part III, on mammalian systems for mutation analysis, to that of part II, detection of mutations, they in fact address completely different questions and they are of interest to different groups of researchers. The procedures described in part III are used (1) to investigate the mechanisms of mutagenesis in mammalian cells, and (2) in the area of genetic toxicology to determine the mutagenicity of environmental chemicals. The systems used most widely in cultured cells, namely the pS189 shuttle vector and the *hprt* gene, are described by Seidman and by Maher and McCormick. A shortcoming of cultured cell systems for measuring mutations is that they cannot take account of the metabolism and pharmacokinetics of whole animals. In order to overcome this problem, bacterial genes (*lacZ* or *lacI*) have been integrated into mouse genomes. Following exposure of these transgenic mice to mutagens, the bacterial transgenes can be recovered from the mouse genomes from different tissues, and the mutations can be analysed by conventional bacterial molecular genetic techniques. The two systems that have been developed are described by Vijg and Douglas and by de Boer *et al*. These transgenic mouse systems have only been developed recently, and like all new techniques, they have a number of shortcomings, which are addressed by de Boer *et al*, together with future prospects and possible developments.

Despite the diverse specialists to whom the three parts of the book are likely to appeal, it has succeeded in bringing together a wide variety of the latest complex techniques, and will be of considerable value to many researchers. Most of the chapters are carefully written with theoretical backgrounds, detailed experimental protocols, and, in some cases, invaluable sections on limitations, pitfalls, and troubleshooting. It should find its way onto the shelves of many research laboratories.

A R LEHMANN

The Gene Bomb. David E Comings. (Pp 304; $25.00 pb.) Duarte, California: Hope Press. 1996. ISBN 1-878267-6.

This is the sort of book which gets geneticists a bad name. Put briefly, its thesis is easy to state: the sad, mad, bad, and the stupid are outbreeding the respectable, college educated, middle classes.

The cause is education. Ever more clever kids are getting to university where their studies distract their minds from sex (or at least reproduction) whereas the stupid start spreading their genes at a much younger age. Thus, modern society inadvertently selects for the genes associated with stupidity, sadness, badness, and madness. These genes are spreading through the population, explaining the increase in crime, alcoholism, depression, schizophrenia, attention deficit disorder, autism, and so on. This is the "gene bomb" of the title.

We are so lucky that Dr David Comings, a former president of the American Society of Human Genetics and former editor of the *American Journal of Human Genetics*, was keen eyed enough to detect this genetical epidemic, for otherwise it "could occur so gradually as to go unnoticed until it was too late to correct. However, its eventual effect on the human race could be far more disastrous than all the microbial epidemics combined."

This is hyperbole indeed. Worse than smallpox? Worse than cholera? Worse than malaria? One is tempted to ask for a reality check even before one has finished reading the introduction.

Even when the author appreciates that others might dissent from his thesis, he fails to understand why. In his discussion of intelligence, Dr Comings comments, "mention of the possibility that the IQ of the human race is beginning to turn a corner and evolve backwards to lower levels strikes a raw nerve." Not with me: laughter would seem the most appropriate response.

Let us have a reality check. In Britain today, a higher proportion of the population than ever before benefits from university or other forms of tertiary education; general literacy is higher at the end of the 20th century than it was at the end of the 19th; and a substantial proportion of the young people of the country are adept users of one of the most highly sophisticated products of human genius, the home computer.

We might worry that computer literacy is damaging traditional literacy, but that is nothing new. George Orwell complained in one of his essays that in the 1930s an entire generation was growing up intimately familiar with the workings of the magneto but ignorant of the Bible. It is boring and it is obvious, although apparently not to Dr Comings, that none of these things is consistent with a decline in IQ.

Some of his facts are simply wrong. He asserts, based on the evolutionary divide between humans and other primates, that "higher IQ appeared to require over 100 000 years to evolve". Yet our divergence from the other primates can be dated at least as far back as *Homo erectus*, nearly two million years ago. *Homo erectus* was so unintelligent it did not have language, but the point is that the period over which higher IQ developed is arguably 20 times longer than Dr Comings alleges. Consequently, we may legitimately ask for evidence of declining IQ over a time scale somewhat longer than the half century since the end of the Second World War.

Other, vital, facts are simply missing. There is no real discussion of population genetics. One looks in vain to see real figures for just how prevalent in the population such genes might be today and therefore just what fast breeders the sad, mad, bad, and the stupid might have to be in order to trigger the explosion of the gene bomb which Dr Comings so fears. There is a scrappy two page illustration of "the results of using one of the equations that calculates the rate at which the frequency of a gene with such a selective advantage will increase over succeeding generations". The equation itself is not given, nor is there any discussion of what factors might limit the spread of the gene.

In 1938, the late great J B S Haldane showed in his little book *Heredity and Politics* that eugenic programmes in the USA in the 1920s and 1930s for sterilising "mental defectives" would have had a negligible effect on the average IQ of the population. Dr Comings presents no figures on how many of the sad, mad, bad, and stupid would have to refrain from reproduction (voluntarily) before the streets of Harlem or inner city Los Angeles would once again be safe for decent, educated people to walk down.

With errors and omissions of fact go astonishing assumptions about moral and ethical values. Dr Comings tells us that "our IQ is like the core of our essence". Really? A Christian might say that the foundation of our being is our relationship to a loving God, whereas a modern secular philosopher might make "membership of the moral community" the defining characteristic of humanity. Neither of these characteristics necessarily correlates with IQ and the kingdom of heaven certainly is not a paradise of the intellectual. The point here is not who is right or wrong but that Dr Comings' initial assumption is dubious, and so much of what follows is also dubious.

The fundamental problem is that we have all been here before, many times. In the 1920s and 1930s the concern in the USA was not inner city Blacks and Hispanics but the white rural poor. Statistics put forward then by geneticists at least as respectable as Dr Comings, and with better worked out population genetics, showed irrefutably that the rural poor were significantly stupider and more fecund than the urban middle classes. But, strange to relate, the USA did not decline into a rural slum populated by village idiots. Instead, it became the world's most technologically advanced nation while the children and the grandchildren of the white trash of the 1920s turned into very capable electronic engineers and rocket scientists enabling NASA to put the first man on the moon. Now that's what I call a reality check.

TOM WILKIE

Fragile X Syndrome: Diagnosis, Treatment and Research. Editors R J Hagerman, A Cronister. (£20.00 pb, £58.50 hb.) Baltimore: Johns Hopkins University Press. 1996. ISBN 0-8018-5388-5 (pb).

The first edition of this book appeared in 1991 and is now completely out of date so that a second edition is most welcome. It was only in 1991 that the identification of the dynamic mutation responsible for the fragile X syndrome occurred. All the new information which that generated has allowed many of the authors' chapters to be written with much more precision. The chapter by Ted Brown on the molecular aspects of the fragile X syndrome includes valuable data on CCG repeat numbers and discussions of linkage have disappeared. The epidemiology section by Stephanie Shearman is immediately clearer now we can define premutations and "normal male" transmissions. Similarly the excellent chapter by Amy Cronister on genetic counselling issues is no longer clouded by being unable to identify either normal transmitting males or having to cope with the uncertainty of not being accurately able to identify carrier females. The speculative chapter on X inactivation and imprinting has given place to a chapter by Ben Oostra on the latest information on FMR-1 protein and the behavioural characteristics of knock-out mice, which includes showing hyperactivity and learning difficulties. The cytogenetic chapter remains but still includes some old fashioned guidelines for X chromosome preparation and analysis without suggesting that counts showing a low frequency of fragile X should be clarified by Southern blot analysis. It also lacks any discussion of the necessity of continuing to use cytogenetics for analysis of the proband rather than moving immediately to molecular testing because of the high frequency of identification of other chromosomal abnormalities in that population. The flow might have been improved by a combined chapter on prenatal diagnosis which is covered separately in the molecular chapter, the cytogenetic chapter, and the genetic counselling chapter, but a clear picture does not emerge to guide the reader. If there is a deficiency, it is that there is no discussion of screening in different target populations; that may also reflects this reviewer's bias.

The book is divided into two halves. The first half is on diagnosis and research and the second half on treatment and intervention. In the second half there is a chapter on molecular approaches to therapy which is, of course, still all in the area of research and perhaps is too early to include it in a book of this type. The second half contains interesting articles on pharmacotherapy, the management of behavioural problems, and educational information. These approaches are most interesting to read but not so universally applicable in different countries. They are useful, however, as reference material when these sorts of questions are raised in a genetic setting.

This book should sit on the library shelves of clinical geneticists. It is the equivalent to the Harper on Huntington's disease or the Emery on Duchenne muscular dystrophy, well written, well referenced, and should become well thumbed.

GILLIAN TURNER

Genetics in Anesthesiology. Guy Weinberg. (Pp 200; £56.50.) UK: Butterworth-Heinemann. 1996. ISBN 0-7506-9479-3.

This book is written for clinicians and aims to blend principles and methods of molecular genetics with pertinent clinical material of relevance to the anaesthetist. The book highlights the relevance of genetics to anaesthesia and the author aims "to remedy the lack of familiarity with genetics and molecular biology among anaesthesiologist colleagues".

The book is divided into two parts. Part 1 is divided into four sections. Section I provides a succinct introduction to clinical genetics, section II focuses on basic concepts in molecular biology/molecular genetics, section III describes strategies for perioperative examination of a patient with hereditary disease, and section IV addresses the increasing contribution of genetics to anaesthesia research. Part 2 is a clinical benchmarks section and covers 25 genetic diseases of relevance to anaesthetists.

In the book the common ground of genetics and anaesthesia is explored. The author points out that "professional currency demands practitioners become familiar with the basic terminology and technology of molecular biology". This book goes some way towards meeting that demand. However, given the broadness and diversity of material covered in this book, the depth of coverage on each topic is limited. Nonetheless, the book serves as a good introductory reference text that shows the common ground between genetics and anaesthesia. It also serves as a good introductory text for anaesthetists wishing to familiarise themselves with molecular medicine and its significance in anaesthesia. Overall, the book is written in an exceptionally readable style and manages to summarise the major key concepts in an interesting and concise fashion. It keeps focused on the point and does not burden the reader with minor issues.

One of the aims of the author is to bring the reader to the level necessary for understanding scientific papers with a molecular genetic basis. This is not achieved in this book and a more advanced text in molecular genetics is required.

The book falls down on some topics. In particular, section II which focuses on basic concepts in molecular biology/molecular genetics is too brief and somewhat outdated. In an era when molecular genetic research is making significant contributions in anaesthesia, the coverage of linkage analysis, association studies, molecular markers, positional cloning, and mutation detection approaches is poor or absent. Diagrams and illustrations are also lacking in this section.

The coverage on the molecular genetics of malignant hyperthermia, probably the main genetic disorder of relevance to the anaesthetist, is also disappointing and significantly out of date. Malignant hyperthermia is a major concern for anaesthetists and significant advances have been made on the genetics of this pharmacogenetic disorder and related issues concerning genetic diagnosis. The author is somewhat out of date on current knowledge on this disorder and seems to have ignored key substantiated European malignant hyperthermia genetic research from several groups while favouring some of the more speculative North American views. Diagnosis of malignant hyperthermia susceptibility by the in vitro contracture test, a major issue in malignant hyperthermia management, is poorly addressed. Also, the current situation and future prospects concerning genetic diagnosis of malignant hyperthermia susceptibility is poorly covered.

The second half of this book covers 25 genetic disorders that the anaesthetist is likely to encounter on an infrequent basis. Even though each of these disorders will be encountered infrequently, they are nevertheless of major relevance to any anaesthetist. Each disorder is dealt with succinctly under five headings: general introduction, genetics and pathogenesis, clinical features, anaesthetic management, and general bibliographical references. The examples are chosen to illustrate concepts in molecular genet-