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Persistent polyclonal B lymphocytosis with Epstein-Barr virus antibodies and subsequent malignant pulmonary blastoma

Lawlor and colleagues have reported a case of persistent polyclonal B lymphocytosis (PPBL) and subsequent malignant pulmonary blastoma and suggest a possible aetiological role for Epstein-Barr virus (EBV).¹ This conclusion was based on a single EBV viral capsid antigen (VCA), IgG titre of 1/1280, for which the method was not given. We cannot agree with this conclusion.

EBV antibody titres are usually measured by indirect immunofluorescence and a great deal has been published which describes this serological screening in normal persons and patients with EBV related diseases. Antibodies to EBV are present in most adults worldwide.² The extent of antibody responses to EBV antigens varies with age and immune function, with the prevalence of high antibody titres increasing with age in healthy persons.³ Overrepresentation of high titres of VCA specific IgG antibodies, compared with appropriate controls, has been observed in a large variety of non-malignant and malignant diseases.² Patients with the EBV associated malignancies, such as Burkitt's lymphoma and nasopharyngeal carcinoma (NPC), have substantially higher titres and a broader spectrum of antibodies to EBV determined antigens. Titres obtained in various laboratories are not always directly comparable and it is unfortunate that the method was not given in Lawlor's study.

Results obtained in our laboratory of EBV serology in various patient groups are presented in the table. Although the geometric mean titres of anti-EBV VCA IgG are higher in infectious mononucleosis and NPC, where EBV has a specific and well documented role, it is clear from the considerable overlap in the range of titres in all groups that individual measurement is a poor indicator of EBV disease. It is thus unacceptable to use a single titre of antibodies to any one antigen as a basis for implicating EBV.

The profile of antibody response to a range of EBV antigens is more reliable and may

assist in identifying potential aetiological roles for the virus.

In Lawlor's case report a role for Epstein-Barr virus in the pathogenesis of PPBL and malignant pulmonary blastoma has not been adequately established.

We agree with Sumaya⁴ that there is an urgent need for a collaborative effort by diagnostic and research laboratories to standardise the limits of "normal" EBV serological responses.

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Dr Lawlor comments:

I fully agree with Wyatt and Coyle that there may be considerable overlap between EBV titres in a variety of conditions and that a wider antibody profile to EBV antigens where available is desirable. I would also support their comments on the necessity of standardisation of methods of EBV serology, particularly immunofluorescence, the method used in this case.

A number of apparently normal subjects can have a raised IgG VCA titre for some years after infectious mononucleosis.¹ In this particular patient, a middle aged woman with a benign lymphoproliferative disorder who subsequently developed a rare pulmonary tumour, the occurrence of a raised titre IgG VCA in the absence of evidence of generalised non-specific immune stimulation² (CMV 1/8, herpes 1/32, Toxoplasma (1 gM) 1/64 and IgG titres at the lower limit of normal), while not a definite indicator of EBV disease, suggest that the role of EBV should be considered in the aetiology of one or both of these conditions.

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BOOK REVIEWS

All titles reviewed here are available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the United Kingdom and for members of the British Forces Overseas, but overseas customers should add £2 per item for postage and packing. Payment can be made by cheque in sterling drawn on a United Kingdom bank, or by credit card (Mastercard, Visa or American Express) stating card number, expiry date, and your full name.

Markers for Neural and Endocrine Cells. Molecular and Cell Biology, Diagnostic Applications. Ed M Gratzl, K Langley. (Pp 222; 48 figs; £67.) VCH. 1991. ISBN 3-527-28167-3.

It is a stated hope of the editors that the book should act as a bridge between fundamental research workers and clinicians by reviewing the latest data on the molecular biology, biochemistry and cell biology of various marker proteins for neural and endocrine cells. In large measure this has been achieved by uniformity of style and presentation which have made the text attractive to both basic scientists and clinicians. The usefulness of this book is greatly enhanced by a liberal number of illustrations and a list of relevant up to date references.

For those who have a particular interest in the relation between the nervous and endocrine systems, this book is to be recommended.

This multi-author book comprises seven chapters divided into three main sections: ontogenetic relations; molecular and cell biology; and applications of marker substances useful for characterising neurones and endocrine cells.

While neurones and endocrine cells share many properties they also differ in important respects (chapter 1). For example, they do not all share a common embryological origin from the ectodermal germ layer: examples include the endocrine cells associated with the digestive tract.

Further characterisation of membrane proteins of synaptic vesicles has allowed major progress to be made in the understanding of the biogenesis and life cycles of the various types of synaptic vesicle and the development of new concepts for neuronal secretion in the context of established pathways of exocytosis in other cells (chapter 2).

Chapter 3 reviews the biochemical, cell biological, and molecular biological features of neuroendocrine granules, and the immunohistochemical data of these proteins are summarised and compared in normal and human tumours of neuroendocrine cells.

Chapter 4 concentrates on aspects of cellular expression and describes the likely functions of a family of related glycoproteins collectively known as neural cell adhesion molecules (NCAM). It is now apparent that NCAM is not confined in adults to neurones

Titres of anti-EBV VCA IgG antibody in four patient groups

Patient group (n =)	Geometric mean titre	Titre range
Infectious mononucleosis (21)	353.3	80-10,240
Other suspected viral illnesses (29)	232.7	<10- 1280
NPC (35)	1358.3	160-10,240
Other head and neck tumours (19)	297.5	20- 5120

as there is clear cut evidence of its expression by other neural cells in both the peripheral and central nervous system and also by endocrine cells, independent of whether their embryological origin is neuroectodermal.

In chapters 5 and 6 the diagnostic usefulness of neurone specific enolase S100 and chromogranin A is reviewed. As the brain is probably the most differentiated of all organs, theoretically if the function of all the proteins specific to a given cell type were known, then we would fully understand how that cell performs its specific tasks.

In chapter 7 details are given of a diagnostic algorithm in which antibodies of increasing specificity can be used to characterise tumours.

DI GRAHAM

Clinical Applications of TGF- β . CIBA Foundation Symposium 157. (Pp 234; £39.50.) John Wiley & Sons Limited. 1991. ISBN 4-7192-811-9.

The Ciba Foundation organise about eight international multidisciplinary symposia every year on topics that seem ripe for discussion by a select group of invited scientists. *Clinical applications of TGF- β* deals with the role of transforming growth factor β in the control of cell differentiation and proliferation, with special emphasis on its unique role in the formation, remodelling, and destruction of the extracellular matrices.

This book follows the established Ciba format with each chapter culminating in a reported discussion among participants. At first glance this approach appears rather disruptive, a feature clearly counterbalanced, however, by the valuable insight it gives into the current thinking and planned experimentation of the field's elite. The initial chapters outline the growth factor's biochemistry, receptor binding, and mechanisms of action. This is followed by the book's forte—the pivotal role of TGF- β in the pathogenesis of pulmonary, hepatic, and renal fibrosis. The potential clinical applications—namely, as an adjuvant to chemotherapy and as a wound healing agent—are briefly highlighted.

In summary, clinicians should not be hoodwinked by the optimistic nature of the title—in all probability a mercantile ploy. Nevertheless, this is not a volume deserving of dust collection on the shelves of academe, but begs perusal by all those with more than a superficial interest in the biology of extracellular matrices and the pathogenesis of fibrosis in particular—be they gastroenterologists, immunologists, nephrologists or haematologists.

JT REILLY

Clues to Diagnosis in Dermatology. AB Ackerman, M Jacobson, PA Vitale. (Pp 426; \$204.00.) Raven Press. 1991. ISBN 0-89189-296-6.

The principal author has put his regard for the forensic methods of Sherlock Holmes into practice, and produced an entertaining and attractive book. The "clues" of the title are

histological shibboleths that can be used as guides or triggers for diagnosis, such as the "tadpoles" of syringoma and the "dilapidated brick wall" of Hailey-Hailey disease. A photomicrograph clue is provided, followed overleaf by the answers, a page of discussion, and a page of differential diagnosis or amplification of the clue. This format is followed for each of the 100 entries.

The illustrations are of very high quality, which makes it the more frustrating that there is so much unused white space in the book. Most of the clues are well illustrated and solvable. A few photomicrographs have been taken at too low a magnification to resolve the feature that is the clue, or at so high a magnification that the feature cannot be seen in context. From a high power picture of an abscess in an island of neoplastic squamous cells we are expected to diagnose solitary keratoacanthoma; a low power picture of apparently normal skin is a clue to urticaria or vitiligo. It would be unwise to think that, "when you have excluded the impossible, whatever remains, however improbable, must be the truth," applies to dermatopathology.

I enjoyed the book, but having read it through I wonder how often I will consult it in future. It is also very expensive, and I would have to put it low on the list of priorities for a departmental library. If it is any consolation to the authors, this review copy will be kept in the room at St Bartholomew's in which, Conan Doyle tells us, Sherlock Holmes first met Dr Watson.

DAVID LOWE

Corneal Angiogenesis. A Comprehensive Critical Review. GK Klintworth. (Pp 135; DM 68.00.) Springer. 1991. ISBN 3-540-97440-7.

The naturally occurring causes of corneal vascularisation are legion and the author of this review adds over 100 experimental ways of achieving the same end. In which case it is proper to ask whether there is a common pathogenetic pathway. This is the question that underlies a thoroughgoing analysis extending to over 800 references and few are better qualified to undertake such a task than the author, who has himself contributed greatly to research in the matter. An advantage of this sort can, however, be double-edged and it may be wondered whether his firm commitment to the hypothesis that inflammatory factors are of prime importance has introduced a bias, albeit unintentional. I think he has avoided the risk—just! Most of the pieces in the jigsaw have now probably been identified, but putting them together is proving a daunting assignment and the author has done well to achieve a synthesis that is neither simplistic nor overelaborate. One message that does come over loud and clear is that those who use the cornea as an assay system for presumed angiogenic factors do so at their peril: most substances giving rise to corneal vascularisation do so through an indirect and non-specific inflammatory response.

The review has been published from camera-ready copy provided by the author and this has probably helped to expedite publication (there are several 1990 referen-

ces), although at the cost of some aesthetic appeal. But that is a minor complaint and this compact volume is essential reading for any serious student of corneal angiogenesis.

ALEC GARNER

A Colour Atlas of Trauma Pathology. H Fischer, CJ Kirkpatrick, ME Aronson. (Pp 136; £48.) Wolfe Publishing Ltd. 1991. ISBN 0-7234-1566-8.

This is one of those atlases that has about six small colour photographs on each page and a page or two of text at the beginning of each of the 15 chapters. Most of the illustrations are photomicrographs of variable standard and often of low magnification. Much of what they illustrate is very straightforward, such as normal brain with a haemorrhage in the centre showing apparently no more than that haemorrhage consists of extravasated red cells.

The first sentence in the main text reads "Sharp instrument injuries are usually caused by a knife, glass fragments or sharp metal edges," and the book continues in this vein. It is said to be written for both pathologists and therapists but it is difficult to see who would use it. The introductions at the beginning of the chapters contain useful information but only culled from other sources. The index is rudimentary and none of the really difficult aspects of subject is tackled.

AC HUNT

Forensic Pathology. B Knight. (Pp 584; £130.) Edward Arnold. 1991. ISBN 0-7131-4550-1.

This is the most comprehensive textbook to appear for many years. It departs from tradition, confining itself strictly to forensic pathology—no clinical forensic medicine or law. The traditional format of description, references, and anecdotes has been abandoned in favour of a step by step guide, copiously illustrated and selectively referenced.

The book is intended as a comprehensive work of reference for pathologists worldwide. For the full time forensic expert there is academic discussion, even controversy; for the less experienced pathologist or other doctor called on to perform only occasional medicolegal necropsies, there is clear basic advice. There are refresher notes on forensic anatomy, advice on dissection techniques, and numerous high quality line diagrams.

The whole spectrum of violent and suspicious death is encompassed; so is procedure at the scene, the obscure necropsy, and the selection of samples for toxicological analysis. The book also contains useful tables, formulae, and nomograms—for example, for body temperature and skeletal remains stature assessment—removing the need to consult other specialised texts which are not always readily available.

This is an excellent book and I heartily recommend it. It should be in the library of every histopathologist and will be of value worldwide, irrespective of variations in local judicial systems. It will retain its value for