Hyperfibrinolysis

Fibrinolysis is responsible for fibrin breakdown. Hyperfibrinolysis occurs when fibrinolytic activity is potentially greater than fibrin formation such that clot integrity is threatened. The central event of fibrinolysis is the generation of plasmin which cleaves fibrin and fibrinogen with the release of fibrin and fibrinogen degradation products. Free plasmin is rapidly inhibited by its inhibitor, α-2-antiplasmin. Fibrinolytic activity is initiated by the plasminogen activators, tissue plasminogen activator (t-PA) and urokinase (u-PA) which convert plasminogen to the active serine protease plasmin. t-PA is released by endothelial cells, has a short half life of three to five minutes and is regulated by specific inhibitors, plasminogen activator inhibitors (PAI) types 1 and 2. PAI-1 is the main systemic inhibitor and is produced by several cell types including endothelial cells, smooth muscle cells, fibroblasts, and hepatocytes; PAI-2 is found in the placenta.[1] Platelets are the source of 90% of the circulating PAI-1 antigen, which is released at the site of a forming thrombus. Hyperfibrinolysis occurs when the balance of fibrinolytic activators to their inhibitors is disturbed.[2]

The consequences of hyperfibrinolysis affect other aspects of haemostasis. Plasmin may reduce platelet adhesion and aggregation by degradation of receptor glycoprotein 1b and platelet fibrinogen receptor glycoprotein IIb/IIIa.[3] The consumption of clotting factors due to the direct effect of plasmin and the formation of fibrinogen degradation which inhibit fibrin polymerisation result in poor fibrin generation.

Fibrinolytic activation has been separated into primary and secondary fibrinolysis: primary fibrinolysis represents increased fibrinolytic activity independent of other factors, whereas secondary fibrinolysis is a consequence of activation of coagulation and thus thrombin generation which stimulates the endothelium to produce increased amounts of t-PA.

Chronic liver disease is a common cause of hyperfibrinolysis, and is characterised by both primary and secondary hyperfibrinolytic changes. There is reduced clearance of t-PA, and reduced concentrations of α-2-antiplasmin due to diminished protein synthesis: both primary changes.[4] Secondary hyperfibrinolysis is due to intravascular coagulation. These changes are related to the severity of liver disease as is clearly shown by El-Bassiouni *et al*[5] in patients with hepatosplenic schistosomiasis. In cirrhotic patients ascites is frequently associated with hyperfibrinolysis; and in a multivariate analysis of risk factors for bleeding in over 100 cirrhotic patients, hyperfibrinolysis, as measured by high values of D-dimer and t-PA activity, was the only predictor of gastrointestinal bleeding, a major cause of morbidity and mortality in liver failure.[6] During orthotopic liver transplantation the precarious fibrinolytic state of chronic liver disease is exacerbated during the anhepatic phase of surgery; exceptionally high concentrations of t-PA are found when the donor liver is first perfused by the recipient's circulation.[7] This may relate to plasminogen activator release from perturbed donor liver endothelial cells caused by hypoxia and acidosis.[8]

Other surgical procedures induce hyperfibrinolytic changes, notably the use of cardiopulmonary bypass in cardiac surgery, characterised by increased t-PA concentrations during bypass: this is responsible in part for the perioperative bleeding diathesis seen in cardiac surgery patients.[9] Hyperfibrinolysis may be iatrogenic due to the use of fibrinolytic agents in removing thrombus after arterial or venous thromboembolism.

Measurement of fibrinolytic activity is difficult in the face of low fibrinogen concentrations. Increased levels of fibrin degradation product titres (usually D-dimers which are the degradation products from cross-linked fibrin) are used routinely as a quick marker of increased fibrinolytic activity. However, they are crude and in situations such as postoperative bleeding are not useful, for concentrations are increased postoperatively in all patients. In such situations it would be helpful to know the levels of plasminogen activators, but these assays are time consuming and expensive. The thromboelastograph is the most useful instrument used in the surgical setting to determine the fibrinolytic status of a patient. It is relatively simple, small, and inexpensive so that it can be used in theatre, without a pathology technician. Moreover, it has the advantage of giving a picture of all haemostatic parameters. It is criticised, however, for being crude and poorly reproducible: but often during surgical bleeding an approximate guide to the state of haemostasis is all that is required. The thromboelastograph is widely used during orthotopic liver transplantation[10] and its use is being extended to other surgical areas.

If clinical bleeding can be attributed to hyperfibrinolysis, then the use of an antifibrinolyic agent is appropriate. Aprotinin is a powerful antiplasmin agent that, when given continuously perioperatively, reduces bleeding during cardiac surgery[11] and is also used extensively during orthotopic liver transplantation.[8] In established bleeding it can be given at a dose of 500 000 KIU intravenously in an emergency. Tranexamic acid and epsilon aminocaproic acid (EACA) also have antiplasmin properties but are less efficacious than aprotinin.

Finally, hyperfibrinolysis is not always harmful; it can even be considered beneficial, notably in disseminated intravascular coagulation. In this situation the use of an antifibrinolytic agent is contraindicated as fibrinolytic activation prevents permanent end organ damage as a result of microvascular fibrin deposition.

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Cancer Medicine, 4th edn, 2 volumes. Holland JF, Bast RC Jr, Morton DI, Frei E III, Kufe DW, Weichselbaum RR, eds. (£195.00.) Williams and Wilkins. 1996. ISBN 0 683 04095 2.

Cancer medicine is a very American book with only 12 of the 346 contributors coming from outside the United States, and only one, Professor Bruce Ponder, from the United Kingdom. However, there is little cultural conspiracy and the text is readily accessible. Each section has a contribution from someone who is considered to be the field leader and all of the main institutions are reasonably well represented. The market offers two main competitors: *Cancer: principles and practice of oncology*, commonly known as "DeVita" (JP Lippincott), and *Treatment of cancer* (Chapman and Hall). To some extent the decision as to which to chose is parochial and lies between the Memorial-Sloan-Kettering in New York, the Hammersmith in London, and this volume that inclines towards Harvard in Boston.

Cancer medicine is contemporary and definitive with respect to the essential cancer curriculum. It is helpfully arranged with clinical cancer medicine in mind. The historical context is presented extremely well and the book lends itself as a resource for undergraduate lecturing. It is comprehensive enough for postgraduates and basic scientists alike. The presentation is a little cheap for the price, and lacks a certain authoritative dignity, but this is deceptive. Weighing more than 7 kg this tome is 45% heavier than the field leaders. If surgeons were still using the family bible for ganglions, then this would be a match for any cancer.

R PENSON

Oral Pathology—Actual Diagnostic and Prognostic Aspects. Seifret G, ed. (Pp 244 hardback; DM 248.00; sFr 216.00.) Springer. 1996. ISBN 3 540 60987 3.

This is a splendid book—it is well written, clear and concise, providing an excellent overview of recent advances in the field of oral pathology. The scope of the book is such that it will be of benefit to anyone with an interest in diseases of the oral mucosa or oral cancer.

The first chapter discusses the epidemiology, clinical manifestations, pathogenesis, histopathological features, and treatment of both common and rare mucocutaneous conditions affecting the mouth. This section contains an excellent review of recent developments in our understanding of the antigens associated with autoimmune diseases, and the mechanisms likely to be responsible for cell damage. This is followed by two chapters summarising viral infections with manifestations involving the oral mucosa or salivary glands. Both benign and malignant disease are included and the text is enhanced by the inclusion of excellent tables. This is followed by a summary of the oral pathology of AIDS, including a comprehensive description of the four common subtypes of orofacial Kaposi's sarcoma. The fourth chapter reviews the new concept of extranodal non-Hodgkin's lymphomas of the oral cavity, emphasising the importance of subtle histological features, together with the results of immunological and molecular studies. The book is well illustrated throughout with clinical photographs and photomicrographs.

The final chapters discuss new developments in our understanding of the carcinogenic process which occurs in the oral cavity and includes an excellent summary of recent studies looking at the possible clinical applications of proliferation markers in the diagnosis and prognosis of oral lesions. The role of oncogenes and the search for the tumour suppressor likely to be involved in the pathogenesis of oral cancer add to the wealth of new information succinctly presented. All chapters are well referenced, perhaps too well in some instances. The chapter discussing new aspects of viral disease has nearly 600 references and it would be difficult for the inexperienced reader to highlight key references. However, overall this book provides a very helpful summary of a plethora of recent information and can be strongly recommended.

M PARTRIDGE

Notices

Workshop on diagnostic pathology
Dysplasia in inflammatory bowel disease

Wednesday, May 7 1997
St Mark's Northwick Park Hospitals, Harrow

A day of practical interactive microscopy and lectures on the clinical relevance of dysplasia, diagnostic problems, and controversies. This is an intensive course for consultants and senior trainees. Using a multiheaded microscope, problem cases will be demonstrated and discussed. Faculty: Professor G T Williams, Dr A B Price, Professor I C Talbot.

Numbers are limited to 11 but if there is sufficient demand, the course may be repeated. Cost is £95.00 including coffee, lunch, and tea.

For further information and reservations, contact Mrs Elena Power, St Mark's Academic Institute, Northwick Park, Watford Road, Harrow HA1 3UJ. (tel: 0181 235 4048; fax: 0181 235 4039.)

Forthcoming meetings of the South Thames West Regional Cytology Training Centre

June 26–27 1997 Two day South Thames Breast Cytology Course

October 6–31 1997 Four week introductory gynae course for MLSOs/ cytoscreeners

November 17–21 1997 One week gynae update course for MLSOs

December 1, 2, and 4 1997 One day non-gynae courses for MLSOs

Further details can be obtained from Mrs Jennifer Walker, Department of Cytology, Royal Surrey County Hospital, Egerton Road, Guildford, Surrey GU2 5XX. (Tel: 01483 571122 ext 4374; fax: 01483 453615.)

Non-gynaecological and fine needles aspiration cytology course
Oxford Cytology Training School
John Radcliffe Hospital

June 2–6 1997

This one week course is suitable for all trainee and career medical staff and clinical scientists. It is recognised for CME purposes. Some accommodation is available. Course fee: £250. The FNA cytology component may be attended separately on June 5–6; fee £100.

Course organiser: Dr ID Buley, Consultant Pathologists, Histopathology and Cytology, John Radcliffe Hospital, Oxford OX3 9DU.

Further details from Patsy King, tel: 01865 220510.

Preparation, restoration, and maintenance of pathological museum teaching specimens

Many departments cannot justify having a dedicated technician to prepare interesting museum specimens for teaching. The Department of Pathology, University Hospital Queen's Medical Centre in Nottingham has a team of highly qualified and experienced staff in its museum workshop who can prepare and mount new material or restore existing specimens. All specimens are mounted in tailor made "perspex" containers manufactured to the highest standards. The mounting fluid complies with COSHH regulations.

For details on this service, contact Mr JE Ben, Museum Curator, Pathology Museum, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH. (Tel: 0115 970 9076; fax: 0115 970 4852.)

Corrections

The beginning of paragraph 6 in the editorial by Hunt and Segal (*J Clin Path* 1996;**49:**958) should have read:

Measurement of fibrinolytic activity is difficult. Low fibrinogen levels will eventually result due to consumption. Also there may be prolongation of clotting due to interference from elevated fibrin degradation products. Increased levels of. . .

and not as published.

Attitudes of medical students to necropsy. N J Botega, E Marques, A Cruvinel, Z V Moraes, L A R Costa. J Clin Pathol *1997;**50:**64–66.*
L Augusta was cited as an author of this paper in error.