Leader

Microorganisms in the aetiology of atherosclerosis

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Abstract
Recent publications have suggested that infective pathogens might play an important role in the pathogenesis of atherosclerosis. This review focuses on these microorganisms in the process of atherosclerosis. The results of in vitro studies, animal studies, tissue studies, and serological studies will be summarised, followed by an overall conclusion concerning the strength of the association of the microorganism with the pathogenesis of atherosclerosis. The role of the bacteria *Chlamydia pneumoniae* and *Helicobacter pylori,* and the viruses human immunodeficiency virus, coxsackie B virus, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and measles virus will be discussed.
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The pathogenesis of atherosclerosis is a subject of much debate, but it is now generally thought to be a chronic inflammatory disease.[1] The initiation and progression of atherosclerosis seems to be related to the location and extent of the inflammatory reactions.[2–4] Recent publications suggest that infective pathogens also play an important role in the process of atherosclerosis. Thus, local infection could either react directly with the vessel wall or indirectly through initiation of immunological responses.[5]

In this review we will discuss the role of microorganisms (bacteria and viruses) in the process of atherosclerosis.

Bacteria

Chronic dental bacterial infections are strongly associated with atherosclerosis.[6–8] Although the chronological sequence of infection and the initiation of atherosclerosis is still not clear, it can be argued that atherosclerosis is the cause and not the consequence of dental infections because individuals with coronary atherosclerosis might also have compromised arterial circulation in the peridontium. However, a recent study by Adams *et al* strongly argues against this explanation.[9]

Nevertheless, Meier *et al* have shown retrospectively that previous use of tetracyclines and quinolones was associated with a lower risk of acute myocardial infarction, providing indirect evidence that infection with microorganisms susceptible to tetracycline antibiotics might be involved in the aetiology of ischaemic heart disease.[10]

We will focus on the role of bacteria with the supposed strongest association with atherosclerosis, namely *Chlamydia pneumoniae* and *Helicobacter pylori*.

CHLAMYDIA PNEUMONIAE

In vitro studies

In vitro experiments have shown that *C pneumoniae* induces human macrophage or foam cell formation, a key event in early atheroma development, via chlamydial lipopolysaccharide, suggesting a role for *C pneumoniae* in atherogenesis.[11 12] Furthermore, it has been found that endothelial cells, smooth muscle cells, and macrophages are capable of supporting the growth of *C pneumoniae*.[13] In addition, an association between *C pneumoniae* infection and a specific immune response has been suggested.[14] Studies in men with coronary heart disease suggest that *C pneumoniae* possibly contributes to the process of coronary atherosclerosis by chlamydia specific, cell mediated responses, predominantly induced by antigenic structures that are similar among different species of chlamydia.[14] Indeed, a coronary strain, *C pneumoniae* A-03, has been isolated and shown to stimulate production of monocyte chemotactic protein 1, interleukin 8 (IL-8), and soluble intercellular adhesion molecule 1 in vitro.[15] In surgical specimens of human carotid atherosclerotic plaques, induction of macrophage functions by *C pneumoniae* was also found.[16] Interestingly, percutaneous transluminal coronary angioplasty also induces stimulation of the humoral immune response against *C pneumoniae* and supports the idea that plaque disruption during angioplasty might expose hidden *C pneumoniae* antigens to the immune system.[17]

These humoral immune reactions might be related to bacterial heat shock proteins (HSPs), such as chlamydia HSP60, which may play an important role in the process of vascular endothelial injury, a key event in the pathogenesis of atherosclerosis.[18]

Animal studies

In vivo experiments in rabbits showed that intranasal *C pneumoniae* infection accelerates intimal thickening (which could be inhibited by azithromycin) and inflammatory atherosclerosis like changes in the aorta.[19 20] In addition, intranasal inoculations of *C pneumoniae* in ApoE deficient transgenic mice and C57BL/6J mice (these mice develop atherosclerosis on an atherogenic diet) resulted in *C pneumoniae* localisation in atheroma, suggesting a tropism of *C pneumoniae* to the lesion.[21] In a murine model system, both *C pneumoniae* strains, AR39 and MoPn, were detected in the aorta of mice infected with the corresponding strain. However, only mice infected with AR39 had enhanced atherosclerotic lesions, suggesting that this *C pneumoniae* strain might possess a unique atherosclerotic property.[22] Thus, these animal studies strengthen the aetiological link between *C pneumoniae* and atherosclerosis.

Serological studies

Serological studies and the detection of *C pneumoniae* in atheromatous lesions were the first indications of an association between *C pneumoniae* and atherosclerosis.[23] Seropositivity for *C pneumoniae* was associated with an increased risk for future cardiovascular disease, namely stroke,[24] carotid wall thickening,[25] and coronary heart disease.[26]. Chronic *C pneumoniae* infection seemed to be associated with a serum lipid profile considered to increase the risk of atherosclerosis, supporting the hypothesis that infections do play an (indirect) role in the pathogenesis of atherosclerosis.[27] In addition, *C pneumoniae* DNA can be detected in circulating white blood cells by the polymerase chain reaction (PCR).[28 29] Using this technique, an association between coronary heart disease and circulating *C pneumoniae* DNA in men, but not in women, was found.[30]

However, in a large scale study, Ridker *et al* found no evidence of an association between *C pneumoniae* IgG seropositivity and risk for future myocardial infarction.[31] Furthermore, Altman *et al* found that the presence of IgG antibodies to *C pneumoniae* in the serum is not predictive of acute arterial complications.[32] Therefore, seroepidemiological studies are contradictionary with respect to the role of *C pneumoniae* in atherosclerosis.

Tissue studies

By means of immunohistochemistry, PCR, and nested PCR, *C pneumoniae* was detected in carotid endarterectomy specimens, within atherosclerotic plaques, and in endothelial cells, macrophages, and smooth muscle cells, suggesting a direct role of *C pneumoniae* in carotid artery atherosclerosis.[33–36] Using PCR and immunohistochemistry, *C pneumoniae* was detected in arterial biopsies from femoral, popliteal, and coronary arteries, as well as in the aorta, indicating that the organism is widespread in atherosclerosis of the vascular system.[37–42]. Bartels *et al* even found that occluded aorta-coronary venous grafts harbour *C pneumoniae* (but not cytomegalovirus).[43]

Others have demonstrated viable *C pneumoniae* by means of cell culture in coronary atheromas, carotid endarterectomy specimens, and abdominal aneurysm.[15 34 44–46] *Chlamydia pneumoniae* has also been demonstrated in many tissues by electron microscopy, supporting the true evidence of *C pneumoniae* particles.[34 45–48]

In contrast, in another study of carotid endarterectomy specimens, bacterial and viral cultures in plaques were negative.[49] An Autralian study using PCR in postmortem material did not detect *C pneumoniae* in coronary arteries or carotid endarterectomy specimens.[50] In addition, Lindholt *et al* could not detect *C pneumoniae* in symptomatic aneurysms of the abdominal aorta. Therefore, they suggested that these aneurysms and atherosclerosis might be two different disease entities.[51]

Finally, Andreasen *et al* could not detect *C pneumoniae* in calcific or degenerative atherosclerotic aortic heart valve disease.[52] However, Nystromrosander *et al* did detect *C pneumoniae* in aortic valves using electron microscopy.[48]

Treatment

Pilot studies have shown that antibiotic treatment (azithromycin and roxithromycin) improves the clinical outcome in patients with myocardial infarction and acute non-Q wave coronary syndromes.[53 54] Recently, the final ROXIS study showed that roxithromycin appeared to extend the clinical benefit of preventing death and re-infarction for at least six months after initial treatment.[55]

In contrast, Anderson *et al* have shown that in patients with coronary heart disease, positive for *C pneumoniae* antibodies, global tests for C reactive protein (CRP), IL-1, IL-6, and tumour necrosis factor α (TNF-α) improved at six months with azithromycin. However, no differences in antibody titres and clinical events were seen.[56] Thus, controlled trials are needed to establish the therapeutic role of antibiotics in peripheral arterial disease.[57]

Conclusion

The Koch-Henle criteria for proof of the aetiology of *C pneumoniae* infection in atherosclerosis seem to be largely fulfilled: correlation of atherosclerosis with antibodies against *C pneumoniae*; detection of *C pneumoniae* in atheromas with different techniques; international studies with macrolides in coronary heart disease were successful; target cells of atherosclerosis can be infected with *C pneumoniae* in vitro; and animal experiments have been positive.[58] However, several studies reported that no *C pneumoniae* could be detected in atherosclerotic lesions. It is not known whether this is related to technical problems, the specimens that were studied, or geographical differences. Furthermore, it is unclear whether *C pneumoniae* initiates the process of atherosclerosis, facilitates progression of existing plaques, or merely colonises the lesions.[59]

HELICOBACTER PYLORI

In vitro study

In an in vitro study it has been shown that polyunsaturated fatty acids inhibit the growth of *H pylori* and prevent/arrest atherosclerosis.[60]

Serum studies
Laurila *et al* found that serum triglyceride and total cholesterol concentrations were significantly higher in men with IgG and IgA against *H pylori* than in men with no signs of infection, supporting the hypothesis that chronic infection with *H pylori* might modify the serum lipid profile in a way that increases the risk of atherosclerosis.[61]

In duplex ultrasound studies that established carotid atheroma load in combination with serum *H pylori* measurements, it was concluded that chronic *H pylori* infection is an independent risk factor for ischaemic cerebrovascular disease and may act, at least in part, by increasing atherosclerosis.[62] Another study suggested that it is possible that exposure to *H pylori* and other microorganisms leads to an increased risk of clinically manifest coronary artery disease by an autoimmune process (anti-HSP 60/65 antibodies), in patients submitted for routine angiography.[63 64]

In contrast, in other prospective case cohort designs among middle aged men and women, *H pylori* seropositivity was not associated with coronary heart disease, or with increased mean intima-media thickness of the carotid artery, suggesting that *H pylori* is probably not an important contributor to clinical coronary heart disease events.[65 66]

Tissue study
In patients with aortic aneurysms, seropositivity for *H pylori* was found. However, PCR for *H pylori* was negative, making the possibility of a direct involvement of *H pylori* in atherosclerotic aortic aneurysms less tenable.[38]

Conclusion
To date, there is no convincing evidence supporting the presence of *H pylori* within atherosclerotic plaques, and seroepidemiological evidence is contradictionary.

Viruses
Pesonen *et al* investigated 175 children (0–15 years of age) who had undergone necropsy and found that infections in general and viral infections in particular seem to be associated with intimal thickening, which might predispose coronary arteries to atherosclerosis.[67] We will focus on the role of human immunodeficiency virus, coxsackie B virus, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and measles virus in atherosclerosis.

HUMAN IMMUNODEFICIENCY VIRUS (HIV)
Serological studies
Constans *et al* have shown that, although no clinically relevant atherosclerotic lesions were found, plaques occurred more often in patients with HIV than in controls.[68] During postmortem examination of eight HIV seropositive male patients, Paton *et al* found major atherosclerosis in coronary arteries in the absence of an associated cardiovascular risk factor.

They concluded that viral infection, either HIV or coexisting herpesviruses, played a role in the development of the coronary lesions.[69]

Conclusion
It is difficult to establish whether HIV itself, or an opportunistic pathogen, or both, are causally related to the process of atherosclerosis.

COXSACKIE B VIRUS (CBV)
Animal study
Recent murine model work support the idea that CBV, a member of the enterovirus genus, and immune cells cooperate and play a role in arterial lipid accumulation, possibly acting as initiating factors for atherosclerosis.[70]

Serological studies
One of the most recent studies on CBV showed that high concentrations of enterovirus specific antibodies were associated with a risk of myocardial infarction in men.[71] However, an association between antibodies to CBV and myocardial infarction has not been found in all studies.[72 73]

Conclusion
Further studies are needed to evaluate whether, and by which mechanism, enterovirus infections are involved in the pathogenesis of atherosclerosis and the development of myocardial infarction.

CYTOMEGALO VIRUS (CMV)
In vitro studies
In vitro studies have shown that CMV infection can potentially lead to infection of blood vessel endothelium, thereby inducing damage to endothelium, and infection of smooth muscle cells, suggesting a role in atherosclerosis.[74–78] Indeed, in cultures of smooth muscle cells of carotid artery plaques, CMV (but not herpes simplex virus 1 or 2) was detected by means of immunohistochemistry in 25% of cells.[79] However, no replicating CMV was found by electron microscopy, suggesting that the artery walls might be a site of CMV latency[79].

Animal studies
Inoculation of BALB/c mice with CMV resulted in the development of atherosclerosis; that is, immune injury and high low density lipoprotein cholesterol.[80] In rats, it was found that an active CMV infection of arterial smooth muscle cells can be established in vivo. Interestingly, neointimal smooth muscle cells were far more susceptible to CMV infection than medial smooth muscle cells.[81]

Serological studies
In a case control study and the ARIC (atherosclerosis risk in communities) study, an association was found between the serum CMV antibody titre and carotid intimal-medial thickness, which is in line with a causal role for CMV in atherosclerosis.[82 83] CMV infection has also been identified as an independent risk factor in re-stenosis after coronary angioplasty.[84 85] In men undergoing vascular surgery for atherosclerosis, the prevalence of CMV antibodies was higher in the surgical group than in the control group (not significant for herpes simplex virus 1 or 2), suggesting that periodically activated virus might have a role in the

pathogenesis of atherosclerosis.[86] In addition, serum CMV antibody titres were higher in patients with atherosclerosis and diabetes than in patients without diabetes, suggesting that CMV might play a role in the development of clinical atherosclerosis in patients with diabetes mellitus.[87]

In contrast, in serological studies of immune responses to CMV, combined with the correlation of angiographically assessed atherosclerosis, it was concluded that multiple reactivation of latent viruses might be a consequence rather than a cause of atherosclerosis.[88] Furthermore, another study showed that prior infection with CMV is not a major risk factor for angiographically demonstrated primary coronary artery atherosclerosis.[89] In addition, Tiran *et al* found that anti-CMV positivity is not a major risk factor at the time of disease manifestation, implying that CMV does not play an important role in the pathogenesis of atherosclerosis.[90]

Tissue studies

Using PCR, 90% of the samples obtained from patients with grade III atherosclerosis were shown to contain CMV viral nucleic acids, compared with 53% of patients with grade I atherosclerosis, indicating a role for this virus in the pathogenesis of atherosclerosis.[91] However, CMV was also found (by means of in situ hybridisation and immunohistochemistry) in abdominal aortas, femoral, and coronary arteries in atherosclerotic as well as control material, suggesting that the human arterial wall might be a site of latency of this virus.[92] Other findings suggest that the persistent expression of CMV immediate early genes in the vessel wall might play a role in the vascular cellular responses, including progression of atherosclerosis or vasculitis in vivo.[93]

Transplantation

Heart transplant recipients who are immunosuppressed and who are also actively infected with CMV are prone to develop accelerated atherosclerosis in the transplanted organ,[94] with more frequent rejection.[95] In serological tests after cardiac transplantation CMV infection was found in 77% of patients, suggesting a relation between CMV infection and rapidly progressive coronary atherosclerosis after cardiac transplantation.[96] Another study of patients with cardiac transplants found serological evidence of past *C pneumoniae* and CMV infection. However, *C pneumoniae* does not appear to have an independent role or synergistic relation to CMV in the development of transplant associated atherosclerosis.[97]

Conclusion

In vitro and immunohistochemical studies have provided mainly circumstantial evidence for the involvement of CMV in human atherosclerosis, whereas seroepidemiologic studies suggest that a periodically activated latent infection of CMV is present in patients with atherosclerosis.[98] In general, the conclusions of seroepidemiological studies are contradictionary.

EPSTEIN-BARR VIRUS (EBV)

Serological studies

A study of antibodies against EBV in sera, combined with angiography, suggested that reactivation of latent EBV is a consequence rather than a causal factor of atherosclerosis.[99]

Tissue study

Using immunohistochemistry and PCR, EBV could not be found in early and advanced atheromatous changes in coronary arteries, or in lesion free areas in the thoracic aorta of young trauma victims.[100]

Transplantation

An association between atherosclerosis and a previous EBV infection was demonstrated in heart transplants.[101]

Conclusion

Although seroepidemiological studies implicate a role of EBV in atherosclerosis, to date, EBV has not been found in atherosclerotic lesions.

HERPES SIMPLEX VIRUS (HSV)

In vitro studies

An in vitro study in HUVEC cells (cultured primary endothelial cells from the human umbilical vein) indicated that latent infection of vascular cells with HSV might play a pathogenic role in the development of human atherosclerosis.[102] Another study suggested that the efficiency of HSV-1 infection of smooth muscle cells derived from adult rats is greater than of those from pup rats. This could be important because age is a risk factor for the development of atherosclerosis.[103] It has also been shown that HSV infection leads to lipid accumulation in vascular cells. Furthermore, HSV infection of endothelial cells attracts leucocytes, with subsequent inflammatory damage. HSV also induces procoagulant changes on endothelium, with increased thrombin generation and platelet adhesion. These changes are more or less characteristic for atherosclerosis.[104–108]

Animal study

It has been shown that HSV causes atherosclerosis in experimental animals.[94 109] These authors suggest that lipid depositions in atherosclerosis may result in part from virus induced changes in the cholesterol metabolism of host cells, as was found in cultured smooth muscle cells.

Tissue studies

Histological studies and in situ DNA hybridisation in young trauma victims have shown HSV associated with areas showing early and advanced atheromatous changes in coronary arteries and with lesion free as well as lesional areas in the thoracic aorta. This supports the concept that HSV might play a direct or indirect role in the pathogenesis of human atherosclerosis.[100] In coronary biopsies obtained during coronary artery bypass graft surgery, immunohistochemistry and situ hybridisation demonstrated HSV-2 in 45% of biopsies and also one case of HSV-1.[110]

Table 1 Studies supporting the aetiological link between microorganisms and atherosclerosis

Microorganism	*Key references* *In vitro studies*	*Animal studies*	*Serological studies*	*Tissue studies*	*Treatment*
Bacteria					
Chlamydia pneumoniae	11, 12, 13, 15, 18	19, 20, 21	24, 25, 26, 27, 30	33, 36, 37, 39, 41, 43	48, 49, 50
Helicobacter pylori	55	–	56, 58, 59	–	–
Viruses					
Human immunodeficiency virus (HIV)	–	–	63, 64	–	–
Coxsackie B virus (CBV)	–	65	66	–	–
Cytomegalovirus (CMV)	70, 72, 73, 74	75, 76	78, 80, 81, 82	86, 87	–
Epstein-Barr virus (EBV)	–	–	94, 96	–	–
Herpes simplex virus 1 and 2 (HSV)	97, 98, 99, 101, 103	89, 104	–	95, 105	–
Measles virus	108	–	–	–	–

Table 2 Studies contradicting the aetiological link between microorganisms and atherosclerosis

Microorganism	*Key references* *In vitro studies*	*Animal studies*	*Serological studies*	*Tissue studies*	*Treatment*
Bacteria					
Chlamydia pneumoniae	–	–	31, 32	44, 45, 46, 47	51
Helicobacter pylori	–	–	60, 61	38	–
Viruses					
Human immunodeficiency virus (HIV)	–	–	–	–	–
Coxsackie B virus (CBV)	–	–	67, 68	–	–
Cytomegalovirus (CMV)	–	–	84, 85	–	–
Epstein-Barr virus (EBV)	–	–	–	95	–
Herpes simplex virus 1 and 2 (HSV)	–	–	–	–	–
Measles virus	–	–	–	–	–

Conclusion

In humans, clinical, epidemiological, and molecular biology studies implicate a relation between herpesviruses and atherosclerosis.[94 111] However, it also has been hypothesised that mechanical abrasion might reactivate latent HSV (and CMV) infection in endothelial cells, particularly those exposed to high shearing forces—for example, at vessel bifurcations. This mechanism might be responsible for the endothelial damage, clotting, and atheroma formation often found at these sites.[112]

MEASLES VIRUS

In vitro study

An in vitro study in isolated endothelium/smooth muscle cells indicated that measles virus infection might be a risk factor for atherosclerosis, by means of damaging endothelial cells and initiating proliferation of smooth muscle cells.[113]

Conclusion

The role of measles virus has not been studied extensively and, to date, no in vivo data are available.

Discussion

Microorganisms as aetiological agents might provide new insights into some unexplained aspects of atherosclerosis. A higher incidence of coronary heart disease in young men coincides with the remarkable androtropism of bacterial diseases, whereas the low incidence of coronary artery disease in France could be explained by a much higher use of antichlamydial antibiotics. However, the low incidence of atherosclerosis in the tropics, despite a high frequency of chlamydial infection, is difficult to explain.[58]

It has also been suggested that low grade infections might be one of the causes of the inflammatory reaction observed in atherosclerotic lesions and acute ischaemic syndromes, reflected in raised concentrations of CRP,[109 114] suggesting that the rise in CRP is not a risk factor, but a sign of an active chronic infection. However, immunohistochemical studies of atherosclerotic lesions suggested that CRP might promote atherosclerosis locally by activating the complement system and inducing foam cell formation.[115] This contradicts the idea that the rise in CRP merely reflects baseline inflammation.

Indeed, seroepidemiological data suggest an association between pathogens and clinical events related to atherosclerosis (table 1). However, they cannot distinguish between a causal relation and secondary infection. Furthermore, both serological and epidemiological data are contradictionary in different studies (table 2).

Some tissue studies have found antigens, genetic material, or cultivatable infectious agents in association with the inflammatory lesions. However, it is unclear whether these agents initiate arterial lesions or exacerbate those lesions already present. It is also unknown whether infectious agents in atherosclerotic lesions are directly pathogenic or act through immune responses to microbial antigens, which crossreact with normal human antigens. Recently, an interesting study has shown that a peptide from the murine heart muscle specific α myosin heavy chain has sequence homology to the 60 kDa, cysteine rich, outer membrane of *C pneumoniae*, *C psittaci*, and *C trachomatis*, leading to the production of autoantibodies to heart muscle specific epitopes in mice.[116] This suggests that chlamydia mediated heart disease is induced by antigenic mimicry of a heart muscle specific protein.

Overall, *C pneumoniae* is the agent with the most evidence for a causal association with atherosclerosis (provided by seroepidemiological, pathological, and animal models, and in vitro studies). Although Koch's postulates seem to be fullfilled for *C pneumoniae* infection and atherosclerosis, definitive proof that a particular microorganism causes atherosclerosis may not come from this direction, but from the prevention of primary infection by vaccination or the eradication of the agent by antimicrobials. However, if successful, there is a danger that an increase in prescription of these antibiotics could result in an increase in resistence to antibiotics.

In animals, polyclonal immunoglobulin preparations inhibited atherosclerosis via modulation of T cell activity and/or antibody production. Therefore, immunomodulation might be another effective way to prevent and/or treat atherosclerosis.[117] In addition, studies of the prophylactic use of antiviral agents, such as ganciclovir or CMV vaccine, especially in patients at high risk of developing atherosclerosis (such as heart transplant patients), will allow an alternative prevention strategy for coronary heart disease.

If antibiotic, antiviral, and/or immunomodulatory agents do appear to attenuate the atherosclerotic process, the public health implications will be enormous.

In conclusion, arguments for and against the role of infection in atherosclerosis have appeared with equal regularity. However, for some of these infectious agents (CMV, but especially *C pneumoniae*), evidence for their role in atherosclerosis seems relatively strong. Nevertheless, the mechanism by which they induce their pathological effect is still unclear. A direct effect would have important implications for this widespread disease because adequate antibiotic treatment is possible. If the effect is indirect—for example, by the process of molecular mimicry, as has been postulated recently, innovative ways of exploring the pathogenesis of human disease in general will be needed.

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Book reviews

Biopsy Interpretation of Bone and Bone Marrow; Histology and Immunohistology in Paraffin and Plastic. Cytogenetics in collaboration with Rothman, R. 2nd ed. Frisch B, Bartl R. (£95.00.) Arnold, 1999. ISBN 0 340 74089 2.

This book is beautifully produced and, as one would expect from these two authors, is generally very well illustrated. It is based largely on the authors' very extensive experience of trephine biopsy histology and is therefore not extensively referenced. In contrast to the previous edition, illustrations are now derived from sections of paraffin wax embedded as well as plastic embedded biopsy specimens; pathologists from countries where plastic embedding is little used will appreciate this feature. Illustrative diagrams are clear and helpful and the literary style is clear.

Despite the title, this book deals only with the interpretation of histological features of core biopsies (or open biopsies). Aspiration biopsy of the bone marrow is largely ignored and I succeeded in finding only a single photograph of an aspirate—a Perls's stain of ring sideroblasts. This will be a definite disadvantage for many haematologists and may encourage histopathologists to undervalue the role of aspiration cytology.

A third of the book deals with bone histology. This section is particularly comprehensive and useful. It also serves to remind the reader of the close relation between bone and bone marrow, and of the influence of bone disease on bone marrow histology. Perhaps this section of the book will encourage both histopathologists and haematologists to make a careful assessment of the bone before turning their attention to the haemopoietic tissue.

The two thirds of the book that deals with the bone marrow gives a detailed account of bone marrow histology. Although bone marrow aspirates are not discussed some consideration is given to immunophenotyping and cytogenetic analysis. There are no serious omissions.

Are there any problems with this book? I found some of the illustrations to be at too low a power to be really informative. I also regretted the lack of information on magnification; there is not always a ready point of reference so that the reader may be able to get an impression of the size of any abnormal cells. In the latter fault this book is not unique; it is one of many contemporary histopathology textbooks that do not feel the need to inform the reader of the magnification of the photomicrographs.

If one wished to find individual errors a careful reading will unearth several. The authors carry over from the previous edition the concept that paratrabecular infiltration is not seen in centroblastic/centrocytic lymphoma whereas a nodular pattern of infiltration is common; this puzzling observation is contrary to the findings of most other haematopathologists. The grouping of very diverse inherited and acquired conditions under the heading of "Langerhans cell histiocytosis" is unhelpful, and at least one of the translocations given as characteristic of malignant histiocytosis in this table is much more typical of anaplastic large cell lymphoma, indicating previous diagnostic confusion between these two conditions. The authors' use of the term "granuloma" to describe the focal lesions of systemic mastocytosis is confusing, as is their use of the term "biopsy" to describe tissue obtained after death. Nevertheless, in a book of 367 pages, covering such a large field, mistakes are probably inevitable and one can only sympathise. The authors probably became aware of many of these errors shortly after publication.

Overall, a well illustrated account of bone marrow histology with bone histology being a particular strength.

B J BAIN

Histological Typing of Ovarian Tumours, 2nd ed. Scully RE. (£49.50.) World Health Organisation, Springer, 1999. ISBN 3 540 64059 2.

The World Health Organisation's histological typing of ovarian tumours (second edition) aims to establish definitions of tumour types to aid worldwide uniformity and reporting of ovarian tumours.

This short book includes an extensive morphological classification, including FIGO and TNM systems, preceded by definitions and explanatory notes.

There then follows a collection of 150 half page (108 × 70 mm) predominantly full colour illustrations of each of the types outlined in the classification.

Most of the illustrations are excellent and help with newly described lesions, such as borderline serous tumours with a micropapillary pattern, and tricky types such as clear cell carcinoma with oxyphilic cytoplasm or containing bull's eye mucin accumulations. Occasionally, the illustrations are marred by section artefact or inconsistencies. Figure legend 98 asserts that yolk sac tumour can be distinguished from dysgerminoma by the presence of glandular spaces. Yet, fig 92 of a dysgerminoma shows similar spaces that resemble gland-like structures.

There is significant overlap with the AFIP fasicle on tumours of the ovary because the two publications share a common author. Unfortunately, every time an AFIP illustration is used the full reference is appended to the figure legend. This is unnecessarily repetitive.

It is convenient to be able to flick through the collection of illustrations but slightly tedious to refer to a preceding section for the text description. Nevertheless, this is an excellent graphical aid to correct tumour classification. It should be made available to anyone reporting ovarian surgical samples.

L J R BROWN

Calendar of events

Full details of events to be included should be sent to Maggie Butler, Technical Editor JCP, The Cedars, 36 Queen Street, Castle Hedingham, Essex CO9 3HA, UK; email: maggiebutler@pilotree.prestel.co.uk

Recent Advances in Genetics
5 July 2001, Royal College of Pathologists, London, UK
Further details: Michelle Casey, Academic Activities Coordinator, 2 Carlton House Terrace, London SW1Y 5AF, UK. (Tel +44 020 7451 6700; fax +44 020 7451 6701; www.rcpath.org)

BSCC Annual Scientific Meeting
9–11 September 2001, Majestic Hotel, Harrogate, UK
Further details: BSCC Office, PO Box 352, Uxbridge UB10 9TX, UK. (Tel +44 01895 274020; fax +44 01895 274080; email lesley.couch@psilink.co.uk)

Current Concepts in Surgical Pathology
12–16 November 2001, The Four Seasons Hotel, Boston, Massachusetts, USA
Further details: Department of Continuing Education, Harvard Medical School, PO Box 825, Boston, MA02117-0825. (Tel +1 617 432 1525; Fax +1 617 432 1562; email hms-cme@harvard.edu; web page http://www.med.harvard.edu/conted/)

41st St Andrew's Day Festival Symposium on Therapeutics
6–7 December 2001, Royal College of Physicians, Edinburgh, UK
Further details: Eileen Strawn, Symposium Coordinator. (Tel +44 0131 225 7324; fax +44 0131 220 4393; email 2.strawn@rcpe.ac.uk; website www.rcpe.ac.uk)

Correction

Microorganisms in the aetiology of atherosclerosis. Morré SA, Stooker W, Lagrand WK, *et al.* *J Clin Pathol* 2000;**53**:647–54.

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