damage cell membranes, including those of endothelial cells [8]. Further, endothelial-bound myeloperoxidase and proteinase 3 can be recognized by ANCA [8] and, although extensive immune complex deposition on vascular walls has rarely been observed in systemic vasculitis, it remains a possibility that small numbers of highly phlogistic antigen-antibody complexes could contribute to the injury. The same is true for the anti-endothelial cell antibodies that have been described in primary vasculitis and which appear to have different reactivities to ANCA [9]. There are reports also that proteinase 3 is expressed by endothelial cells after TNF stimulation and, if confirmed, could be another link between ANCA and direct endothelial cell injury [10].

It is likely that T lymphocytes lie behind the ANCA-neutrophil-endothelial cell cascade and the breakdown of self-tolerance since the characteristics of the autoantibody response suggest that it is T cell driven (see [11] for review). We have hypothesized that self-reactive T cells to myeloperoxidase, proteinase 3 and other ANCA autoantigens may engage in antigen-specific interactions with endothelial cells in the peripheral vasculature. Endothelial cells that have been activated by interferon-γ and which express MHC class II antigens are capable of stimulating both $CD4^+$ helper T cells and $CD8^+$ cytotoxic T cells [12]; indeed, endothelial cells can process and present peptides to $CD4^+$ T cell lines (Savage *et al.*, see Abstract No. 16). Cationic antigens are taken up particularly well by potential antigen-presenting cells and it is likely that the cationic ANCA autoantigens, either in active or inactive form, are present in abundance at the surface of endothelial cells. These could be internalized and processed for expression within the groove of MHC class II molecules, the restriction elements used by antigen-presenting cells when they present peptides to the T cell receptors of autologous $CD4^+$ T cells. Therefore MHC class II expressing endothelial cells within the microvasculature may contribute to $CD4^+$ T cell activation and thence to recruitment of additional $CD8^+$ T cells, allowing amplification of the immune response in the periphery, i.e. outside lymphoid tissue. The possibility that endothelial cells may possess endogenous proteinase 3 is particularly interesting in this regard since antigens presented via MHC class I molecules to cytotoxic $CD8^+$ T cells are generally of endogenous origin.

In summary, endothelial cells possess many properties which allow them to focus inflammatory, humoral immune or cellular immune mediated mechanisms of injury towards themselves or towards other elements of the vascular wall. Therefore, it is unlikely that endothelial cells are truly innocent bystanders but the extent of their contribution to the development of vasculitic lesions has yet to be fully evaluated.

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The clinical relevance of ANCA in vasculitis

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Since antineutrophil cytoplasmic antibodies (ANCA) were first recognized in patients suffering from vasculitis [1], the spectrum of ANCA-fine-specificities and of ANCA-associated diseases has increased dramatically. Whereas cANCA are mainly found in Wegener's granulomatosis (WG), pANCA have been detected in several disorders, such as primary and secondary vasculitis, collagen vascular diseases and recently also in inflammatory bowel diseases, including primary sclerosing cholangitis.

Evaluation of the clinical relevance of ANCA findings in vasculitis proved to be a major problem. This was due first to the lack of a universally accepted definition and classification of these closely related diseases, and second to the fine-specificity of antibodies inducing the fluorescence pattern (e.g. cANCA: PR3-ANCA). Efforts were made by the American College of Rheumatology in 1990 (ACR-1990-criteria) [2] and the Chapel Hill Consensus Conference in 1992 (CHC-1992-definition) [3] to classify vasculitis. The scientific community concerned with ANCA-immunology achieved a standardization of the indirect immunofluorescence technique (IFT) and later discovered the main target antigens for ANCA associated with vasculitis. Proteinase 3 (PR3) is the main target antigen of cANCA, which is seen in WG, and myeloperoxidase (MPO) is the primary target antigen of pANCA associated with microscopic polyangiitis (MPA). However, pANCA are directed against target antigens other than MPO, such as cathepsin G (CG), human neutrophil elastase (HLE), lactoferrin (LF)

and lysozyme (LZ). Lately, eosinophil peroxidase and β-glucuronidase were described but not confirmed as additional target antigens for ANCA [4,5].

ANCA assays

ANCA screening is usually performed by IFT, which allows differentiation into two distinct types of staining pattern, the classic 'cytoplasmic' (cANCA) and the 'perinuclear' (pANCA) patterns. Additionally, a peculiar type of staining possessing characteristics of both cANCA and pANCA has been designated 'xANCA'; this pattern, however, should be subsumed under pANCA until further studies on its unidentified fine-specificities have clarified matters.

Besides IFT, solid phase immunoassays (such as ELISAs) can be employed to identify the fine-specificity of ANCA (e.g. PR3-ANCA, MPO-ANCA, etc.). Using highly purified lysosomal proteins as target antigens, ELISAs can be utilized to complement the IFT method. The available ELISA assays are currently being standardized by a multicentre study sponsored by the European Community.

cANCA-associated diseases

As described elsewhere, cANCA are highly sensitive (81%) and specific (97%) for WG [6,7]. If disease is restricted to the upper and lower airways (initial phase, limited WG), only 55% of patients are cANCA positive, whereas in generalized disease (systemic WG) 88% are positive. In some cases, cANCA can be found in vasculitis closely related to WG, such as MPA (Wegener's vasculitis; 15%), Churg-Strauss syndrome (25%) and polyarteritis nodosa (2%) [7]. These diseases often show similarities with WG and may overlap both clinically and histologically.

False positive cANCA (i.e. cANCA in disorders completely different from WG) are very rare. We and others have found cANCA mostly in poorly defined syndromes (e.g. sinusitis, episcleritis, glomerulonephritis) that possibly represent monosymptomatic WG. Many patients with these disorders did progress to full-blown WG as determined by the CHC-1992 definition or the ACR-1990 classification [7-10].

Other authors have reported on cANCA findings in infectious disorders, such as HIV-infection [11] and pneumonia [12], and in malignancies [13]. It should be emphasized that these reports dealt with only a very small number of patients and that the description of the cANCA fluorescence pattern did not always accord with the criteria for cANCA set by the 1st International Workshop on ANCA (Copenhagen, Denmark, 1988) [14].

Interestingly, cANCA have also been described in coexistence with other autoantibodies. Two percent of patients with suspected rapidly progressive glomerulonephritis (RPGN) were found to be simultaneously positive for anti-GBM antibodies and cANCA [16]. ANCA-positive Goodpasture's syndrome seems to have a more favourable course [17].

cANCA and disease activity

cANCA titres are reported to follow disease activity [6,8]. Based on a prospective randomized study, Cohen Tervaert *et al.* [18] suggest that relapses may be prevented by treating patients with rising cANCA titres but without clinical illness. Recent findings of Kerr *et al.* [19] seem to question this proposal. In only 24% of patients was disease activity preceded by a rise in cANCA titres. Changes in serial titres correlated with a change in disease status in 64% of patients. Thus rising titres alone do not justify initiation or intensification of therapy; it seems advisable, rather, to observe clinical development carefully and to base treatment on symptoms of disease activity. Conversely, disappearance of ANCA is usually associated with absence of disease activity [20].

The main target antigen of cANCA in WG is PR3 (90%). Other target antigens such as HLE only play a minor role [21]. The role of CAP 57 as a further cANCA-target antigen is still unclear, since large numbers of serum samples have not yet been investigated [22]. In the search for the association between cANCA titres and disease activity, no major difference has been found between the results using IFT and PR3-ELISA [6].

pANCA and disease association

pANCA are not specific for a single disease entity but tend to be associated with disease groups which share several clinical and histological features. The most important target antigen of pANCA is MPO.

MPO-ANCA are mainly (70%) found in MPA and necrotizing glomerulonephritis [23,24,20]. MPA additionally involves - in contrast to the classical form of polyarteritis - small vessels, including capillaries of the lung and kidney [25]. The most life-threatening clinical manifestations of MPA are pulmonary hemorrhage syndrome (PHS) and/or RPGN. pANCA findings can facilitate the differential diagnostic procedure in clinical situations with PHS and/or RPGN, which occur in a variety of disorders (e.g. Goodpasture's syndrome). ANCA-associated 'renal-pulmonary syndrome' - in contrast to Goodpasture's syndrome - responds well to early treatment with cyclophosphamide and prednisolone [26].

pANCA are found in 5% to 50% of patients with Churg-Strauss syndrome and they even occur in up to 5% of patients with WG [27,7]. To a lesser extent classical polyarteritis nodosa (cPAN), as specified by the CHC-1992 definition (excluding glomerulonephritis), also presents with MPO-induced pANCA (less than 10%).

MPO-ANCA have been described in association with hydralazine-induced RPGN [28,29] and silica exposure [30]. Occasionally, pANCA occur in Goodpasture's syndrome induced by anti-glomerular basement antibodies [17] and in systemic lupus erythematosus (SLE) [31]. Possible target antigens for pANCA in SLE may be MPO [32], LF [33] and HLE [30,34].

pANCA have been described in rheumatoid arthritis (RA) and associated disorders (e.g. Felty's syndrome) by several groups [35-37]. Metzger *et al.* [38] found a significant correlation between pANCA and rheumatoid factor. In rheumatoid vasculitis (RV), pANCA directed against LF were described by Coremans *et al.* [36]. LF-ANCA titres were 11 times higher in RA complicated by secondary vasculitis than in RA alone. Others reported a higher incidence of LZ-ANCA in RV [39].

ANCA of uncertain fluorescence pattern are seen in chronic inflammatory bowel diseases and associated conditions. This pattern appears to be a mixture of the cytoplasmic and perinuclear pattern and is named differently by various groups (snowstorm pattern, atypical ANCA, xANCA). It is mainly found in ulcerative colitis (in 60-75% of patients) and, less often, in Crohn's disease (in 10-20%) [40,41]. The correlation of disease activity with ANCA titres is controversial. Some authors have described this pattern also in autoimmune liver diseases, such as primary sclerosing cholangitis (in 60-85% of patients) [42,43] and chronic active hepatitis (in 60-70%) [44]. Nässberger *et al.* have proposed β-glucuronidase as a possible target of ANCA in inflammatory bowel disease [5]. Their findings could not be confirmed by Kaneko *et al.* [45]. Studies performed by us revealed that neither the β-glucuronidase in *E. coli* nor recombinant human β-glucuronidase was identical with the β-glucuronidase present in human neutrophils (unpublished observation). Halbwachs-Mecarelli *et al.* described CG as the main target for ANCA in ulcerative colitis, Crohn's disease, and in primary sclerosing cholangitis [46]. Further studies need to be performed in this direction.

Recently, Dolman *et al.* found ANCA directed against eosinophil peroxidase in patients suffering from heterogeneous inflammatory disorders [4]. Their diagnostic value is not yet clear.

Pathogenesis

Evidence exists that ANCA may play a major role in the pathogenesis of ANCA-associated diseases. Three models try to explain the mecha-

Table 1. Diseases producing false-positive ANCA tests as described in the literature (from Gross *et al.* [15])

Disease group	Diseases
1. Infectious disorders	HIV*, Mycobacteriosis**, Endocarditis**, Pneumonia**, Hepatitis**, Viral enteritis**, Mucoviscidosis* (with secondary infection)
2. Neoplasms	Atrial myxoma**, Bronchial carcinoma*, Hypernephroma**, Colonic cancer*, Myelodysplasia**, Non-Hodgkin-Lymphoma**
3. Others	Eosinophilia-myalgia syndrome**, Sweet syndrome**, Anti-glomerular-basement membrane disease*

* Reported by at least two different research teams.
** Unconfirmed case reports.

Table 2. Three hypothetical models explaining the mechanisms of ANCA-mediated vasculitis (from Gross *et al.* [15])

ANCA-target cell	Target structure	Pathomechanism
PMN	PMN-proteases	PMN-proteases (=ANCA-target antigens) are expressed on the cell surface of cytokine-activated PMNs. Thus, PMNs are the targets for the autoimmune reaction. After adhesion of PMN to (cytokine-) activated EC via adhesion molecules (LFA-1, ICAM-1), ANCA activation induces degranulation and generation of toxic oxygen radicals, subsequently leading to EC destruction (ANCA-cytokine sequence theory).
EC	EC-proteases	EC express proteases (ANCA-targets) on their cell surface. ANCA bind to EC, which then become direct targets of the autoimmune reaction.
EC	PMN-proteases bound to EC-cell surface	Activated PMNs release proteases into the intravascular space that bind to the EC-cell surface. EC are direct targets of the autoimmune reaction.

PMN=polymorphonuclear neutrophils, EC=endothelial cells.

nisms of ANCA-mediated vasculitis (Table 2).

The ANCA-cytokine sequence theory proposes a translocation of PMN proteases *in vivo* (ANCA-antigens) to the surface of cytokine-activated PMN, thus making them accessible to ANCA. Cytokines also lead to the expression of adhesion molecules on endothelial cells (EC), allowing a close contact of PMN with EC. ANCA bind to and further activate PMN, which results in a respiratory burst and degranulation, thus inducing vasculitic injury [47,48]. Another hypothesis suggests that the expression of proteases on EC membranes itself leads to direct binding of ANCA to EC and thus to EC damage and destruction of the vessel [49]. Similarly, in the third model EC membranes become direct targets for the autoimmune reaction: activated PMN first release proteases, which then bind to EC membranes [50].

Conclusion

In view of their high sensitivity and specificity, the presence of PR3-ANCA is highly indicative of the diagnosis of WG, especially when the ACR-1990 criteria and/or the CHC-1992 definition are used. However, correlation studies of ANCA with histopathologic features of WG and related forms of vasculitis have shown that subclassification still depends on the presence of distinctive clinical or pathological features [51]. Since cANCA seem to correlate with disease activity, they provide an additional but not the only tool for deciding whether and how treatment should be administered. Patients repeatedly positive for cANCA but with clinically non-specific signs and symptoms (e.g. episcleritis) may well have monosymptomatic WG and should be closely followed.

pANCA are associated with a variety of disorders, including vasculitis. pANCA are of major diagnostic interest in patients with suspected MPA. The demonstration of MPO-ANCA in extreme clinical situations with PHS and/or RPGN ('renal-pulmonary syndrome') may be an indication for immunosuppressive therapy. However, the specificity of MPO-ANCA for MPA is not as high as the specificity of PR3-ANCA for WG. On the other hand, MPA is sometimes associated with antibodies directed against CG, HLE, LF and LZ! Today we do not know whether the clinical picture and/or course is different in MPA associated with MPO-ANCA or with, for example, HLE-ANCA. In any event, pANCA facilitate further division of the polyarteritis syndrome into immunocomplex-mediated and ANCA-associated diseases, and appear to be associated mainly with the microscopic variant of polyarteritis (MPA).

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Large vessel vasculitis

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Inflammation of the large arteries such as the aorta and its major branches is seen on occasion in several vasculitic syndromes, such as Behçet disease and Kawasaki's muco-cutaneous lymph node syndrome; but it is a characteristic feature of two entities, giant cell (temporal) arteritis (GCA) and Takayasu arteritis (TA). These arteritides have similar histologic abnormalities, but are usually quite different in their presentation and course [1- 4].

In TA the large elastic arteries are involved primarily, while in GCA the changes are seen most often in the medium sized muscular arteries which possess well developed internal and external elastic laminae, such as temporal artery and other extra-cranial vessels of the head. It should be noted that the intracranial arteries, which lack the external elastic lamina, are seldom affected. In 10-15% of GCA there is involvement of the large elastic arteries including the aorta, its major branches and larger pulmonary arteries. Rarely the process spreads the other way to small muscular arteries, arterioles and even capillaries (vasa vasorum) throughout the body.

In both diseases the inflammatory changes are probably centered on the arterial media, but extend into the intima and adventitia. The infiltrate is granulomatous in character, consisting mainly of lymphocytes and monocytes or histiocytes, with addition of plasma cells, neutrophils and eosinophils. Multinucleated giant cells are characteristic but are not always present. In GCA, these giant cells lie close to the fragmented internal elastic lamina, and sometimes contain fragments of elastic tissue. By electron microscopy the elastic lamina is abnormal; it is dense and granular, rather than fibrillar.

In GCA as well as in TA the elastin of large arteries is also damaged with patchy disappearance of the elastic-smooth muscle layers. Actual infarct-like necrosis with neutrophilic infiltration has been observed in TA. Healing of inflammation is by fibrosis, with striking thickening of the adventita and intima and smooth tapering narrowing or even complete occlusion of the lumen. Thrombosis, diffuse dilatation and aneurysm formation, particularly in the aorta is much more common in TA than in GCA.

Clinically, GCA occurs almost exclusively in the older population, over the age of 50. It is probably the most common form of vasculitis in North America and Western Europe. Women are affected much more often than men, with a ratio of 2:1 to 5:1 in various series. There is a rare variant in young people with predominantly eosinophilic inflammation. Cranial (extracranial) arteritis is present in some 90% of patients, causing headaches, dizziness and vertigo, visual disturbances including blindness, claudication of the jaw, pain, necrosis of the tongue, and facial neuralgia. All these symptoms are usually accompanied or preceded by systemic manifestations, such as fever, weight loss, arthralgias, and laboratory changes, especially high erythrocyte sedimentation rate and anemia. ANCA is rarely positive [5]. There is often a characteristic syndrome known as polymyalgia rheumatica (PMR), but probably due to synovitis of large joints, with morning stiffness and pain of neck, shoulders and hips. PMR accompanies, precedes or follows GCA in 1/2 to 3/4 of cases, but also occurs independently. However, in 15- 40% of patients with PMR who have no clinical evidence of temporal arteritis, biopsy of the artery shows granulomatous inflammation. Hypertension is uncommon in GCA or PMR.

Involvement of large arteries, with or without cranial arteritis, causes clinical symptoms in about 10 -15% of patients with GCA. Most often the symptoms are those of the aortic arch syndrome, producing claudication of arms, absent or asymetrical pulses, paresthesias and Raynaud's phenomenon. Abdominal aortitis can accompany the aortic arch syndrome or occur independently. There are also rare cases of disseminated GCA, affecting many organs. Localized forms of GCA also exist, with arterial lesions in the female breast, ovaries and uterus. On occasion they are accompanied by systemic manifestations, and represent the initial or the more obvious phase of a generalized disease.

Although major pulmonary artery branches often show inflammatory changes, they seldom produce clinical manifestations. Dry cough, hoarseness, chest pain or choking sensation may occur, sometimes accompanied by nodular or interstitial infiltrates on X-rays. Biopsy may demonstrate non-caseating giant cell granulomas in the intersititium or in the bronchial walls [6].

Cardiac disease in GCA is quite rare compared with that in TA, although anatomical changes and clinical symptoms are similar, including coronary arteritis, myocardial infarction, myocardial fibrosis, granulomatous myocarditis, aortic regurgitation and congestive heart failure.

Cerebral manifestations are not uncommon in GCA and are usually due to inflammation and narrowing of the intracerebral vessels, causing transient ischemic attacks, or hemorrhage and infarction. Seizures, depression and confusion also occur.

Loss of vision is usually caused by inflammation of posterior ciliary arteries (which possess the external elastic lamina) and only occasionally by thrombosis of the central artery of the optic nerve or the retinal artery both of which have only the internal elastic lamina. There is also a variety of other ophthalmic manifestations, including those due to malfunction of ocular muscles.

TA also affects women much more often than men, by a ratio of perhaps 10 to 1. It occurs at a much younger age with the peak incidence of onset between 15 and 20 years and as young as 6 months, but rarely past the age of 40. It often begins with non-specific symptoms similar to those of other vasculitides: fever, weakness, weight loss, myalgias, arthralgias and skin lesions, e.g. erythema multiforme. Laboratory