and Mönckeberg's disease (7) calcospherites are precursors of calcified lumps, eventually supported by the secondary appearance of bone-like apatite indicating a biphasic calcification process. Thus, it may be summarized that the calcification in temporal arteries does not differ from the same process occurring in blood vessels not prone to the development of vasculitis. Therefore, we assume that the appearance of two different age-related tissue alterations – calcification on the one hand, arteritis on the other hand – does not necessary implicate a causal relationship.

W. MOHR, *Prof. Dr. med.*

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Reply

Sirs,

We have read the letter from Professor Winfried Mohr concerning our paper with the title "Calcification of the internal elastic membrane in temporal arteries: its relation to age and gender" which was published in *Clinical and Experimental Rheumatology* 2001; 19: 565-8. We do not agree with Professor Mohr's conclusion that calcification of the internal elastic membrane (IEM) and giant cell arteritis (GCA) are not causally related.

Firstly, we have presented ample light- and electron microscopical evidence that, in the course of the inflammatory process in GCA, foreign-body giant cells do attack, engulf and degrade IEM calcifications in temporal arteries. These giant cells express HLA-DR, and IL-2R-expressing lymphocytes gather around them and may be found in pockets on the giant cell surface (1-5). Furthermore, morphological evidence indicates that this occurs in the initial phase of the inflammatory process (1). We are well aware of the fact that,using special staining methods, finely dispersed calcification may be found also in the media of temporal arteries. However, the assessment of such media calcification was beyond the scope of the present investigation, since the foreign-body giant cell reaction was constantly, and without exception, directed at IEM calcifications.

Secondly, although more common in cranial arteries, GCA is a generalized inflammatory disorder which may affect any medium-size or large artery in the body. As vascular pathologist and rheumatologist, repectively, we do see GCA not only in temporal arteries but also in the aorta and other arteries. Thus, we recently examined a case in which the femoral arteries were affected, causing vascular stenosis and threatening bilateral gangrene of the lower extremities. IEM calcification and foreign-body giant cell reaction was noticed at the border between media and intima. In the aorta, the inflammatory reaction in GCA is directed at calcified, atrophic lesions within the media. We did not have the opportunity to do electron microscopy on aortic tissue, but light-microscopically the granulomatous and foreign-body giant-cell reaction is found at the margins of such atrophic lesions, in which there is loss of smooth-muscle cells, loss of undulation of the elastic lamellae and heavy calcification (6). Thus, also the morphology of giant cell aortitis, indicates the pathogenetic relationship between calcification and GCA.

The similarities in terms of age and sex distribution between the temporal IEM calcifications and GCA do support our previous morphological observation that calcification of elastic membranes, be it in temporal arteries, the aorta or elsewhere, is involved in the pathogenesis of GCA.

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The central role of actinically degenerate elastic tissue

Sirs,

We thoroughly enjoyed the article "Calcification of the internal elastic membrane in temporal artieries: Its relation to age and gender" by C. Nordborg, E. Nordborg, V. Petursdottir and I.M. Fyhr. Their emphasis on the internal elastic membrane or lamina (IEM) in temporal artieries as being a target for the inflammatory process in giant cell arteritis (GCA) is a proposition with which we would agree. We are not so convinced that calcification is necessary and would regard it as coincidental to the cause.

In several articles (1-4) John O'Brien and I have drawn attention to the central position of the IEM in the pathology of GCA, postulating that degenerate elastic tissue due to elastosis/elastolysis is the prime antigen with flow-on consequences to the elastic laminae of arteries elsewhere. We further postulated that actinic radiation over a lifetime acting upon the elastic laminae of superficial vessels such as the temporal arteries is a significant, if not the prime cause of this elastic tissue damage leading to GCA in those predisposed. Like the authors we do not dispute age, sex, racial or hereditary factors, but we wholeheartedly agree that the IEM is the prime target.

Elastic tissue can be difficult to investigate. The interest of cosmetic firms is engaged in relation to wrinkling and respiratory physicians also have an interest, but we are not aware of many basic studies on elastic tissue and its autoimmune potential with flow-

on consequences to arteries.
Whilst our view has been refuted scholastically, to our knowledge no one, having investigated elastic tissue and its autoimmune potential, has produced scientific evidence to rebuff it.

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Reply

Sirs,
We have read the letter from Dr. W Regan concerning our article with the title "Calcification of the internal elastic membrane in temporal arteries: Its relation to age and gender".
We do not agree that calcification of the internal elastic membrane (IEM) should be a co-incidental finding in giant cell arteritis (GCA). Instead, our previous observations have shown that it is involved in the pathogenesis of GCA. We have presented ample light- and electron microscopical evidence that, in the course of the inflammatory process in GCA, foreign-body giant cells do attack, engulf and degrade calcified IEM fragments in temporal arteries. These giant cells attract lymphocytes which may be found in pockets on their surface (1-5). Morphological and morphometrical evidence indicate that this occurs in the initial phase of the inflammatory process (1). The foreign-body giant cells are HLA-DR-positive and the surrounding lymphocytes express IL-2R, which may indicate that antigen presentation is taking place. This type of inflammatory reaction is found only in patients with giant cell arteritis and not in controls, which excludes the unlikely explanation that there should be two parallell and coincidental inflammatory processes.
When examining semithin plastic sections and ultrathin sections, we found that the foreign-body giant cell reaction in GCA is constantly, and without exception, directed at IEM calcifications. Portions of the IEM, which were not calcified were never attacked by foreign-body giant cells. On the other hand, during the ensuing stage of diffuse, heavy mononuclear cell invasion of the arterial wall, there may be further degradation of non-calcified parts of the IEM, the nature of which requires further elucidation. In this phase you may find multinucleate giant cells of the Langhans type which, however, never include or degrade calcified fragments in the way foreign-body giant cells do.
Although GCA is more common in cranial arteries, it is a generalized disorder which may affect any medium-size or large artery in the body. According to our observations, the inflammatory reaction is directed at calcified tissue also in other locations than the temporal artery. Light-microscopically the granulomatous reaction and foreign-body giant-cell reaction in giant cell aortitis is found at the margins of atrophic media lesions, in which there is loss of smooth-muscle cells, loss of undulation of the elastic lamellae and heavy calcification (6). Thus, also the morphology of giant cell aortitis, indicates the pathogenetic relationship between calcification and GCA.
When it comes to the relationship between calcifications in the aorta and temporal or other arteries, we believe that they are all the result of generalized arterial ageing; there is no reason to believe that temporal artery calcification should induce secondary calcification in other arteries such as the aorta. The epidemiology of GCA as well as the distribution of calcifications contradicts that they should be of actinic origin.
The similarities in terms of age and sex distribution between the temporal IEM calcifications and GCA do support our previous morphological observation that calcification of elastic membranes is involved in the pathogenesis of GCA, be it in temporal arteries,the aorta or elsewhere. We firmly believe that the focal foreign-body giant cell attack on such calcifications is the initial inflammatory reaction in this disorder. In our opinion, one key question when it comes to the etio-pathogenesis of GCA is why some individuals react by forming giant cells against their IEM calcifications whereas others do not.

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