

LETTERS

Endothelial apoptosis in scleroderma: comment on the article by Black et al

To the Editor:

Apoptotic endothelial cells have been found in the early inflammatory stages of systemic sclerosis (SSc) and localized scleroderma (1), and experimental data on humans suggest a possible role of anti-endothelial cell antibodies in this process (1,2). Interferon- α (IFN α) causes apoptosis of human dermal microvascular endothelial cells in vitro, in a time- and dose-dependent manner (3). Theoretically, if administered to patients with SSc, IFN α should cause a worsening of the disease. This assumption seems to be confirmed by the results of the recent trial of IFN α in diffuse cutaneous scleroderma reported by Black et al (4). Endothelial apoptosis may be of importance in the pathogenesis of SSc and localized scleroderma.

Tihomir Štefanec, MD
St. Vincent's Hospital and Medical Center
New York, NY

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Lipoprotein(a) levels and atherosclerosis in rheumatoid arthritis: comment on the article by Asanuma et al

To the Editor:

Asanuma et al (1) report an increase in levels of lipoprotein(a) (Lp[a]) and a higher prevalence of the disadvantageous S3 apolipoprotein(a) (Apo[a]) phenotype in patients with rheumatoid arthritis (RA) compared with apparently healthy controls. They report no difference in Lp(a) levels between RA patients with atherosclerotic disease and those without. They hypothesize that high Lp(a) levels may contribute to the increased incidence of vascular disease in RA.

The association of RA with increased cardiovascular mortality is well documented (2). There is, however, no direct evidence that this increased cardiovascular mortality is due to increased atherosclerotic disease, particularly coronary artery

disease. This can currently only be inferred, since other cardiac pathology in RA (such as pericarditis) rarely causes significant hemodynamic compromise (3). The finding of elevated Lp(a) levels in RA patients compared with controls is important in this respect, because they may lead to accelerated atherosclerosis and early ischemic heart disease (IHD) in these patients.

The absence of a difference in Lp(a) levels between RA patients with atherosclerosis and those without in the study by Asanuma and colleagues is not surprising, since very few patients had atherosclerotic disease as defined by the authors. The definition of atherosclerotic disease was based on “blunt” clinical end points (history of IHD, cerebral infarction, or transient ischemic attacks). These are highly specific but very insensitive. Postmortem studies (deaths from all causes) have shown rates of definite, though nonocclusive, coronary atheroma in up to 60% of young adults (4). It is very likely that in the age groups studied by Asanuma et al, atheroma would be a virtually ubiquitous finding. In addition, cardiac ischemia may be clinically silent, particularly in a population of RA patients who are limited in exertion due to their joint disease.

We have prospectively assessed 50 randomly selected hospital outpatients with RA, ages 40–70 years. On clinical grounds alone, using the Rose questionnaire (5), only one-fourth of them would have been judged to have IHD. However, the true prevalence of IHD was 50%, as assessed by combining clinical information with findings on electrocardiography and ²⁰¹thallium myocardial perfusion imaging with single-photon-emission computed tomography using pharmacologic (adenosine) stress. Half of the patients with clinically silent IHD were at high risk for a major cardiac event (6). The crude definition of atherosclerotic vascular disease used in the study by Asanuma et al may have led to the inclusion in the nonatherosclerotic group of a substantial number of patients with significant but silent atherosclerosis. This may have masked a potential difference in Lp(a) levels between the 2 RA groups.

Although it is well established that cardiovascular mortality is increased in RA, the cause remains elusive. Further studies are required to confirm whether atherosclerosis is accelerated in RA, to identify the risk factors for this, and to allow earlier intervention to prevent the complications of advanced atherosclerotic disease.

M. J. Banks, MB, ChB, MRCP
G. D. Kitas, PhD, MD, MRCP
Dudley Group of Hospitals
NHS Trust
Dudley, UK

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Reply

To the Editor:

We thank Drs. Banks and Kitas for their interest in our recent study concerning serum Lp(a) and Apo(a) phenotypes in patients with RA. They have made a detailed clinical evaluation of IHD in RA patients (Banks MJ, Flint EJ, Bacon PA, Kitas GD. Expression and prevalence of ischaemic heart disease in rheumatoid arthritis [abstract]. *Arthritis Rheum* 1998;41 Suppl 9:S209.). One-fourth of the subjects in their study were judged to have IHD based on clinical data alone. In addition, the prevalence of IHD as assessed by electrocardiography and ²⁰¹thallium myocardial perfusion imaging with single-photon-emission computed tomography was 50%. Although they mention that there was no difference in Lp(a) levels between RA patients with and those without atherosclerosis in our study, we did demonstrate that Lp(a) levels tended to be higher in RA patients with atherosclerotic complications (mean \pm SD 35.7 \pm 26.8 mg/dl [n = 11]) than in those without (26.8 \pm 22.2 mg/dl [n = 120]). The incidence of atherosclerotic disease was 8.4% (11 of 131) in our RA patients, but these patients were evaluated based on the clinically obvious outcome of atherosclerotic changes, as Drs. Banks and Kitas point out. In this context, we agree that further studies are required to confirm the relationship between atherosclerosis and Lp(a) or Apo(a) phenotypes in RA patients. However, our study showed that an increased Lp(a) level in RA patients was associated with S3 phenotype predominance, which might be genetically determined. This finding may help to improve our understanding of the genetic background of RA patients, especially those with atherosclerotic diseases.

Yu Asanuma, MD, PhD
Shinichi Kawai, MD, PhD
St. Marianna University School of Medicine
Kawasaki, Japan

Absence of human retrovirus 5 in French patients with rheumatoid arthritis: comment on the article by Griffiths et al

To the Editor:

The etiology of rheumatoid arthritis (RA) remains unknown, although several viral candidates have been pro-

posed over the last few years (1). The recent report by Griffiths and colleagues (2) describing the possible involvement of human retrovirus 5 (HRV-5) in rheumatic diseases is of particular interest in view of increasing evidence that retroviruses may be implicated in other autoimmune disorders, including Sjögren's syndrome, multiple sclerosis, and, controversially, insulin-dependent diabetes (3–6).

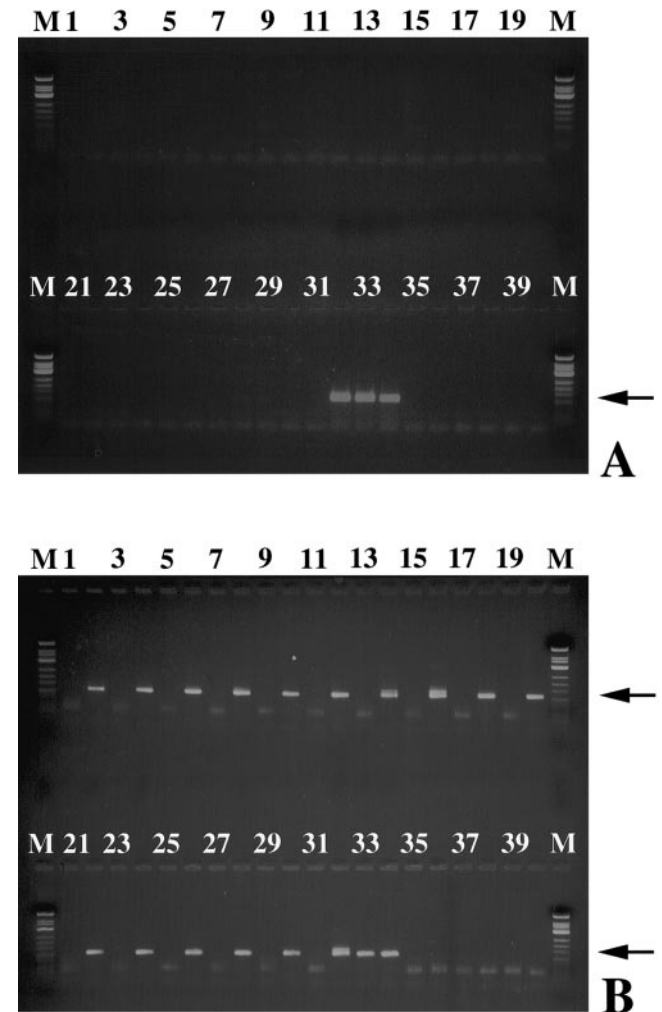


Figure 1. Ethidium bromide-stained 3% agarose gels of second-round nested polymerase chain reaction (PCR) products. The molecular weight markers (M) are *Hinf* I digests of phage ϕ 174 DNA. **A**, PCR for detection of human retrovirus 5 (HRV-5). Lanes 1–19, rheumatoid arthritis DNA samples; lanes 20–30, control DNA samples; lanes 31 and 37–40, water controls; lanes 32–36, pHRV5.1 plasmid dilution series ($\sim 10^3$, 10^2 , 10, 1, and 10^{-1} copies, respectively) used as a positive control. **Arrow** indicates the expected 157-bp bands. **B**, HRV-5-spiked PCR. Lane contents are the same as in **A**, but with 100 copies of pHRV5.1 plasmid added to alternate samples. **Arrows** indicate the expected 157-bp bands.

HRV-5 is a novel exogenous retrovirus initially identified in salivary gland tissue of a patient with Sjögren's syndrome (7). Using a highly sensitive polymerase chain reaction (PCR) technique, Griffiths et al detected HRV-5 proviral DNA sequences in 48% of synovial samples (12% of blood samples) from patients with RA and in 60% of synovial samples from patients with reactive arthritis or osteoarthritis, but in none of 13 samples of normal synovium (2). In an attempt to confirm these important findings, we conducted a PCR-based study on a cohort of 40 French patients with RA or carpal tunnel syndrome who were undergoing hand surgery (joint replacement, synovectomy, arthrodesis, tendon repair, or neurolysis) at Grenoble Teaching Hospital.

Synovial membrane was obtained from 19 patients with RA and from 21 non-RA controls during surgery for mechanical carpal tunnel syndrome. Biopsy specimens were stored at -70°C , and DNA was extracted and purified using QIAmp DNA Minikit reagents according to the instructions of the manufacturer (Qiagen, Crawley, UK). Extracted DNA was quantified by Hoechst H33258 dye binding (8), and its suitability for PCR analysis confirmed by amplification of the human single-copy gene, pyruvate dehydrogenase (PDH), as previously described (9). One microgram of the extracted DNA was tested by nested PCR for the presence of HRV-5 sequences, using the *pol* primer set and thermal cycling conditions described by Griffiths et al (2). The HRV-5 *pol*-containing plasmid pHRV5.1 (generously donated by Dr. Griffiths) was used as a positive control in each experiment. Single copies of the pHRV5.1 plasmid were detectable by this nested PCR.

HRV-5 DNA sequences were not detected in any of the 40 samples analyzed, despite testing in triplicate (Figure 1A). Reduction of the annealing temperature from 52°C to 45°C also failed to generate PCR products from the test samples. In order to exclude the possibility that the negative results might be due to copurified inhibitors of PCR, alternate DNA samples were spiked with 100 copies of pHRV5.1. No evidence of PCR inhibition was observed (Figure 1B). The suitability of the DNA for PCR analysis was confirmed by amplification of the PDH gene (data not shown).

We have thus been unable to confirm the findings of Griffiths et al in this group of patients. The reason(s) for this discrepancy is unclear because the same PCR methodology was utilized, although we cannot exclude the possibility that unrecognized technical differences may have accounted for the disparate results. However, the discrepancy may possibly be related to the different geographic areas from which the patients were selected, i.e., southeastern France versus London. It is well known that the geographic distribution of other exogenous retroviruses, such as human T lymphotropic virus type I, may be very heterogeneous (10). Alternatively, the populations studied may have differed in the duration and severity of their disease or in their treatment. The patients in our study all had had RA for at least 5 years (average 7.5 years), and all were receiving treatment with methotrexate, steroids, or other second-line drugs. Further work is clearly required to define more precisely the prevalence of this novel human retrovirus in various patient populations.

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Philippe Gaudin, MD, PhD
 François Moutet, MD
 A. Michallon Hospital
 Grenoble, France
 Philip W. Tuke, PhD
 Jeremy A. Garson, MD, PhD
 Royal Free and University College Medical School
 London, UK

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Reply

To the Editor:

Gaudin and colleagues report their failure to confirm our detection of HRV-5 DNA in synovial membranes from patients with RA. Having reviewed their methods, we can see no obvious methodologic or technical explanation for this discrepancy, and therefore it is likely that the difference in results is due to some difference in the tissue specimens studied.

The patients in our study were from the UK, whereas those studied by Gaudin et al were residents of southeastern France. We do not believe that this geographic difference can explain the data. In addition to patients from the UK, HRV-5 has been detected in individuals from France, Italy, and the US (Calvez V, Corbellino M, Patel R: personal communications), although the presence of HRV-5 in patients with RA was not studied by all of these groups. In one of these studies (Patel R et al: manuscript in preparation), HRV-5 proviral DNA was

detected in a high proportion of synovial membrane samples from patients undergoing revision arthroplasty. DNA from some of these samples was sent to us. We were able not only to confirm these findings, but also to detect sequences in the *gag* region of HRV-5, which we have recently cloned (Griffiths DJ et al: unpublished data). This confirms that the findings could not have been due to contamination.

It would be of interest to know whether any of the patients studied by Gaudin and colleagues had detectable HRV-5 in their peripheral blood, given that we detected the virus in 12% of RA patients. The suggestion that corticosteroids might activate or inhibit HRV-5 expression is worthy of discussion, especially since one of the closer relatives of HRV-5, murine mammary tumor virus, is activated by steroid hormones. Five of the 12 RA patients in our study whose synovial membranes contained detectable HRV-5 DNA were receiving steroids, although the numbers are too small to determine an effect by correlation. We believe that the effect of steroids on HRV-5 expression would be best studied by directly examining infected or transfected cell lines.

Apart from technical factors, we suggest that one explanation for the observed differences between our findings and those of Gaudin and colleagues might be the source of tissue and the way it was obtained. Samples from the majority of the patients in our study were undergoing "medical" arthroscopy, which tends to select for patients with active disease. In this procedure, synovial villae are sampled under direct visualization. Such villae are highly enriched for inflammatory cells, whereas synovium obtained at surgery from patients with RA or carpal tunnel syndrome may be more mesenchymal or fibrofatty in nature. In our study, the number of subjects was too small to examine a relationship to inflammation by seeking

clinicopathologic correlations. A more direct approach would be to examine the cellular tropism of HRV-5. This will address not only the issue of sampling, but also whether the virus is involved in the pathogenesis of arthritis or, more critically, whether it is a "passenger" that is tropic to a cell type concentrated in inflamed synovium. Such studies are currently in progress.

David J. Griffiths, PhD
University College London
London, UK
Patrick J. W. Venables, MD, FRCP
Kennedy Institute of Rheumatology
London, UK

Specificity of antineutrophil cytoplasmic antibody: comment on the article by Choi et al

To the Editor:

The case report by Choi et al in the February 1999 issue of *Arthritis & Rheumatism* (Choi HK, Merkel PA, Cohen Tervaert JW, Black RM, McCluskey RT, Niles JL. Alternating antineutrophil cytoplasmic antibody specificity: drug-induced vasculitis in a patient with Wegener's granulomatosis. *Arthritis Rheum* 1999;42:384-8.) provides further evidence that autoimmunity can be triggered by many agents, of which drugs are one. Drugs have been known to induce systemic lupus erythematosus, pemphigus, pemphigoid, and vasculitis characterized by the presence of specific autoantibodies.

Approximately 28 cases of drug-induced antineuro-

Table 1. Results of the ANCA Combi test in patients who were positive for cANCA or pANCA by immunofluorescence*

Patient	PR3	MPO	BPI	Elastase	Cathepsin G	Lysozyme	Lactoferrin	ANCA type (titer)†
1	-	-	-	-	-	-	-	c (1:320)
2	-	-	+	-	+	-	-	c (1:10)
3	+	+	+	+	-	-	-	c (1:280)
4	+	-	-	-	-	-	-	c (1:80)
5	+	-	-	-	-	+	-	c (1:160)
6	-	-	+	-	-	-	-	p (1:80)
7	+	-	+	-	-	+	-	c (1:80)
8	-	-	+	-	+	+	-	p (1:160)
9	+	-	+	-	-	-	-	p (1:40)
10	+	-	-	+	-	-	+	p (1:280)
11	-	+	+	-	-	-	-	p (1:640)
12	+	-	+	-	-	-	-	p (1:20)
13	+	-	+	-	-	-	-	c (1:32)
14	-	-	+	-	-	-	-	c (1:2)
15	-	-	+	+	-	-	-	p (1:40)
16	+	+	+	+	+	+	-	p (1:20)
17	+	-	+	-	-	-	-	c (1:40)
18	+	-	+	-	-	+	-	c (1:160)
19	-	-	+	+	+	-	-	c (1:80)

* ANCA = antinuclear cytoplasmic antibody; PR3 = proteinase 3; MPO = myeloperoxidase; BPI = bactericidal permeability-increasing protein; c = classic ANCA; p = perinuclear ANCA.

† Titers > 1:32 considered positive.

phil cytoplasmic antibodies (ANCA) have been reported in the literature. The most common association is with antithyroid drugs (Guntton JE, Stiel J, Caterson RJ, McElduff A. Antithyroid drugs and antineutrophil cytoplasmic antibody positive vasculitis: a case report and review of the literature. *J Clin Endocrinol Metab* 1999;84:13–6). Propylthiouracil (PTU), used in the treatment of Graves' disease, has been implicated in the development of ANCA in 88% of the reported cases of drug-induced ANCA in Graves' disease patients. Drug-induced ANCA, however, has also been reported in association with other drugs, such as hydralazine, sulfasalazine, and minocycline.

The type of ANCA reaction in >80% cases is of perinuclear ANCA (pANCA), with undifferentiated ANCA in ~15% of cases and classic ANCA (cANCA) in 10%. Among cases in which the specificity of the ANCA was determined, myeloperoxidase (MPO) was found in ~80%. The report by Choi et al is unusual in that the patient was already diagnosed as having ANCA-positive Wegener's granulomatosis and subsequently developed Graves' disease; in most other cases, the underlying disease was only Graves' disease. However, in this and other cases, the ANCA positivity was triggered ~3 months after treatment with PTU. The drug has been shown to accumulate in neutrophils and bind to MPO, changing its structure. This binding may result in alteration of the structure and conformation of the antigen, hence allowing initiation of an autoimmune response in genetically susceptible individuals. The immune response to drug-induced antigen alteration subsides when the triggering agent is withdrawn. Thus, it is believed that when Choi and colleagues' patient began PTU treatment after Graves' disease was diagnosed, he developed pANCA of MPO specificity. The antibody titers of cANCA in this case decreased upon immunosuppression, whereas the pANCA titer continued to increase with PTU therapy, and the reverse was true when the drug was withdrawn.

Another comment pertinent to the report by Choi et al is that alternating ANCA specificity can also occur due to the concomitant presence of several ANCA specificities. Table 1 shows results we obtained in correlating the immunofluorescence pattern pANCA with the antigen-specific response in 19 cANCA- or pANCA-positive vasculitis patients. We used the ANCA Combi test, an enzyme-linked immunosorbent assay technique developed by Orgentec (Mainz, Germany), in which a microplate was coated with the antigens proteinase 3 (PR3): MPO, bactericidal permeability-increasing protein (BPI), elastase, cathepsin G, lysozyme, and lactoferrin, which had been previously purified by affinity chromatography. The ANCA Combi test is specific for autoantibodies directed to these antigens, without cross-reactivity. The results indicated that slides read as showing cANCA or pANCA by immunofluorescence do not always show PR3 or MPO reactivity on the ANCA Combi, but do show reactivity with other antigens. ANCA BPI appears to be masked as or associated with cANCA or pANCA in a high number of cases.

In conclusion, alternating ANCA specificity could be due to transient superimposed immunoreactivity within the same disease, as well as to the simultaneous presence of 2 distinct vasculitic diseases, 1 of them drug induced, as shown in the report by Choi et al.

Sueli B. Maciel, BS
Morton A. Scheinberg, MD, PhD
*Center for Clinical Immunology
LID Laboratory
São Paulo, Brazil
Vijay Kumar, PhD
Immco Diagnostics
Buffalo, NY*

Comparison of Dutch and US patients' perceptions of the effects of Wegener's granulomatosis on health, function, income, and interpersonal relationships: comment on the article by Hoffman et al

To the Editor:

We read with great interest the article by Hoffman et al (1), in which patient-perceived effects of Wegener's granulomatosis (WG) on health, function, income, and interpersonal relationships were reported. From this investigation it could be concluded that WG has a major impact on quality-of-life issues.

Some limitations of this study, however, were apparent. One of the major limitations was that the investigation was performed as a single-site study. Whether the results are also applicable to patients in other parts of the world is still unknown. We thus studied patient-perceived effects of WG in our patient population in Groningen and compared our findings with those obtained in the Cleveland study. The questionnaire that was used by Hoffman et al was translated into Dutch and sent to 91 WG patients who are regularly seen at the outpatient clinic of University Hospital Groningen. All patients met the American College of Rheumatology criteria for WG (2). Our study design was approved by the formal ethics review committee.

Seventy-nine of the 91 patients (87%) responded (Cleveland study 60 of 100 patients). Sixty-four of the 79 lived with a partner, and 59 of these (92%) also responded (Cleveland study 43 of 44 partners). Dutch patients were comparable with the Cleveland patients with respect to sex, age, race, median duration of disease, distribution of organ involvement, and patient-reported comorbidity.

The patient-reported delay from onset of symptoms to diagnosis of WG was, however, much shorter in the Dutch patients (mean 9.4 months versus 16.8 months in the Cleveland patients), possibly due to a greater awareness of WG in our region and hence more widespread use of the antineutrophil cytoplasmic antibody (ANCA) test. Interestingly, in a study of 35 patients (3) that was performed in 1986, at the time ANCA testing had only recently been introduced in our laboratory (4), we also found a longer delay in diagnosis (17.7 months), comparable with the delay reported by the Cleveland patients. Another observed difference between our patients and those reported by Hoffman et al was that the Dutch patients were less often told that their problems were "psychosomatic" (14% versus 25% of the Cleveland patients).

Patient happiness was equally effected by WG in The Netherlands and the US (32% Dutch patients unhappy versus 33% Cleveland patients), although somewhat fewer Dutch patients reported being depressed because of their disease

Table 1. Major differences between the Cleveland Wegener's granulomatosis (WG) patient population and the Groningen WG patient population

	Hoffman et al (1)*	Boomsma et al*	Difference†
Impact on financial security	28	5	5.6
Bring the family closer together	47	16	2.9
Relationship with partner improved	50	20	2.5
Relationship with partner worsened	18	9	2.0
WG causes suicidal thoughts	14	7	2.0
Concerned about long-term effects of WG and treatment	70	35	2.0
Changed duties at work	37	90	0.4

* Values are percents.

† Differences of >1 indicate higher frequency among the Cleveland patients; differences of <1 indicate higher frequency among the Groningen patients.

(33% versus 43% of the Cleveland patients), and, additionally, fewer Dutch patients reported suicidal thoughts (7% versus 14% of the Cleveland patients).

Remarkably similar findings were found with respect to the impact of WG on employment status. Our patients missed work for long periods somewhat more frequently, and more patients worked a reduced number of hours. In The Netherlands, almost all patients changed duties at work (Table 1). Finally, 27% of our patients were disabled and receiving disability benefits (Cleveland patients 31%).

The most remarkable differences between Dutch and American patients were found in the answers to questions pertaining to interpersonal relationships. Whereas 47% of the Cleveland patients thought that their illness brought their family closer together, only 16% of our patients thought so. Not only did fewer Dutch patients believe that their relationship with their partners improved (20% versus 50% of the Cleveland patients), but fewer Dutch patients also reported a worsening of their relationship (9% versus 18% of the Cleveland patients).

Interestingly, the degree of agreement between patients and partners about the effect of the illness on their relationships was higher in our patient group than in the Cleveland group (observed agreement in The Netherlands 84.4%, chance agreement 53.8% [$\kappa = 0.66$]; observed agreement in Cleveland 52.8%, chance agreement 35.5% [$\kappa = 0.27$]).

Finally, partners of Dutch patients were less often concerned about the long-term effects of the disease and treatment (35% versus 70% of the Cleveland patients) and about implications of the disease on financial security (5% versus 28% of the Cleveland patients).

In conclusion, our study findings are consistent with those of Hoffman et al (1) and demonstrate that WG is associated with substantial medical morbidity resulting in physical and occupational disability. Important differences, however, exist with respect to the influence of WG on interpersonal relationships. We hypothesize that most of these latter differences are due to cultural and socioeconomic differences between The Netherlands and the US.

M. M. Boomsma, MD
C. A. Stegeman, MD, PhD
J. W. Cohen Tervaert, MD, PhD
*University Hospital
Groningen, The Netherlands*

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Reply

To the Editor:

We are very pleased that our Dutch colleagues have found our questionnaire helpful to study patient-reported effects of WG on health, function, and income. In an effort to ensure that patient-reported information was similar to that perceived by the primary physician responsible for the patients' care, restricting our cohort to patients who had been evaluated by the senior author was very useful. In this manner, we were able to determine that physician-recorded medical events were in fact similar to those reported by patients. This observation enhanced the credibility of patient-reported psychosocial and economic information, which was supplemented by information derived from Internal Revenue Service tax returns. This degree of rigor would have been difficult to apply to patients accrued in a multicenter study, for whom multiple physicians would have been responsible for care and documentation of disease impact.

It is not surprising to learn, from Boomsma and colleagues, that patients who have the same disease but different ethnic, socioeconomic, or cultural backgrounds may differ with regard to the impact of any specific illness. This may contribute to compliance in responding to health questionnaires, to development of coping strategies for dealing with pain, to disability, to economic challenges, and to interpersonal relationships. Despite the fascinating differences that may distinguish patients surveyed in Cleveland and those in The Netherlands, it is clear from both studies that WG exacts a dramatic toll on those who are affected. We look forward to

reading about further studies from international colleagues that explore how different cultures and medical care systems affect quality of life in patients with WG and other forms of vasculitis.

Gary S. Hoffman, MD
Cleveland Clinic Foundation
 Cleveland, OH
 Kent Kwoh, MD
Case Western Reserve University
 Cleveland, OH

Reporting of bone mineral density values as T-scores or Z-scores: comment on the article by Sowers et al

To the Editor:

We are writing in reference to the article by Sowers et al in a recent issue of *Arthritis & Rheumatism* (Sowers M, Lachance L, Jamadar D, Hochberg MC, Hollis B, Crutchfield M, et al. The associations of bone mineral density and bone turnover markers with osteoarthritis of the hand and knee in pre- and perimenopausal women. *Arthritis Rheum* 1999;42:483–9). Sowers et al define the Z-score as the difference between the subject's BMD and "the mean value in a young adult population," which is a T-score. Thus, this is either a consistent mislabeling of T-scores throughout the article, a mistaken definition of a Z-score, or misuse of standard terminology. In any case, the reader is left confused and not knowing what the authors are really trying to communicate in this otherwise interesting report.

John A. Shepherd, PhD
 Sven Prevrhal, PhD
University of California, San Francisco
 San Francisco, CA

Reply

To the Editor:

Drs. Shepherd and Prevrhal question the use of the "Z-scores" label to describe BMD in our report. They raise 2 issues: Why use a score (what is the report trying to communicate), and should the score be labeled a Z-score or a T-score?

With regard to the first issue, Z-scores have been frequently used as a mechanism to standardize data from diverse sources to a common reference. In our report, we wanted the reader to be able to readily compare BMD across the 3 anatomic locations (femoral neck, spine, and total body) where the mean absolute values of BMD (gm/cm^2) are not comparable. However, we also wanted to use the Z-score for communicating and comparing BMD differences over a 3-year

time interval across the 3 anatomic sites and between subjects with and those without hand and knee osteoarthritis.

We used the Z-score label, not the T-score label, for the following reasons. First, in the age range of this population (24–45 years at baseline) and with a population of this size ($n = 601$), the Z-score and the T-score are almost synonymous with one another. Second, the T-score syntax has not been widely applied to bone differences across time (one of the things we wanted to communicate), whereas the Z-score syntax has been widely used for communicating differences across time. Thus, we assumed readers would understand this label more readily. Third, Z-scores were the unit label in the manufacturer's database of the bone densitometer used in the study, although this manufacturer's nomenclature has since been modified to that identified by Shepherd and Prevrhal. Given that there was a rationale for using the Z-score nomenclature, we thank Drs. Shepherd and Prevrhal for acknowledging that we defined the reference for the Z-score and that we consistently applied and adhered to this definition throughout the article.

We hope our approach will encourage investigators to continue to utilize standardized scores to communicate complex comparisons.

MaryFran Sowers, PhD
University of Michigan
 Ann Arbor, MI

Rarity of reported cases of vasculitis in Africa: comment on the article by Bae et al

To the Editor:

We read with interest the article by Bae et al, in which they reviewed the epidemiology of systemic lupus erythematosus (SLE) in populations of African descent (1). Their excellent review raises a related issue, that of the epidemiology of vasculitis in Africa. The epidemiology of vasculitis in the developed world has been poorly documented until relatively recently (2). It is clear that in the developed world there are some geographic and ethnic differences, but these are proving difficult to elucidate.

Vasculitis in sub-Saharan Africa has been infrequently described, and although there are no published epidemiologic studies, descriptions of the pattern of rheumatic disease seen in hospital clinics and in the community indicate that these conditions are rarely seen, if at all (3). Indeed, one of us (AOA) has never seen vasculitis associated with connective tissue diseases in this area of the world, while working in both the hospital and the community.

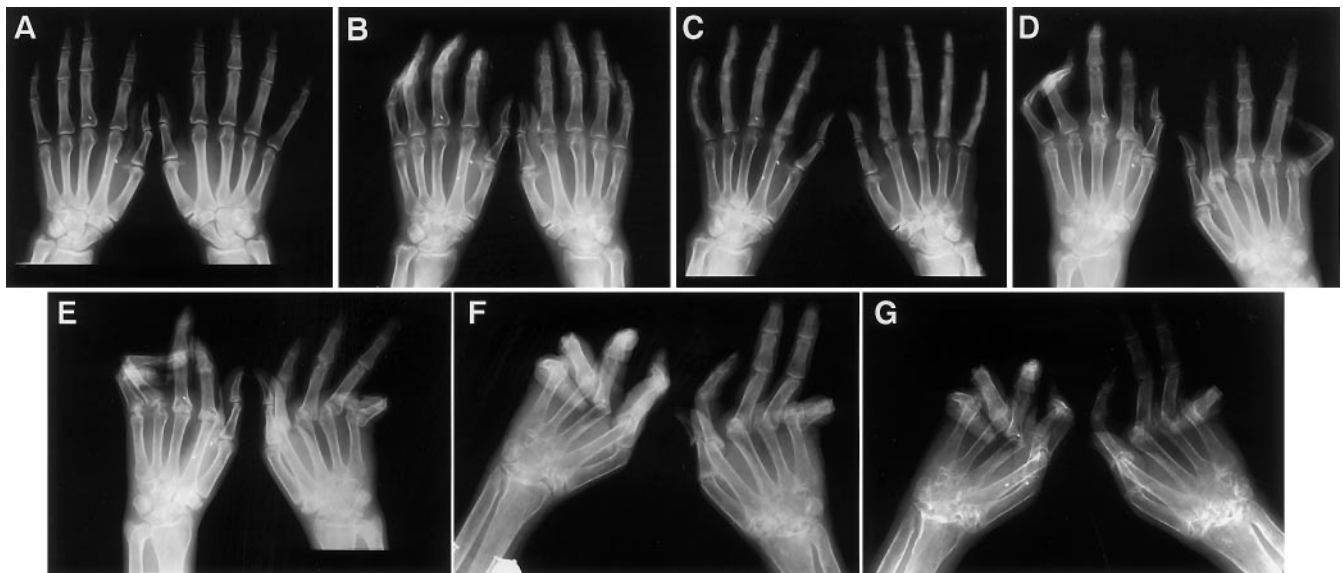
The reasons for these observations are obscure, but as with SLE, there are various possible explanations, including misdiagnosis and underreporting. Nevertheless, the high prevalence of infections such as hepatitis B ought to make some forms of connective tissue disease-associated vasculitis at least as common as in the West. Interestingly, antineutrophil cytoplasmic antibody positivity (tested by enzyme-linked immunosorbent assay) has been reported in patients from West Africa with malaria and tuberculosis who did not show any overt clinical features of vasculitis (4). One intriguing hypothe-

sis is that the putative etiologic factors relating to the prevalence of SLE in populations of African descent (the prevalence gradient hypothesis) may also apply to the prevalence of vasculitis in these populations.

A. O. Adebajo, MD
University of Sheffield
Sheffield, UK
R. A. Watts, DM
Ipswich Hospital
Ipswich, UK

1. Bae SC, Fraser P, Liang MH. The epidemiology of systemic lupus erythematosus in populations of African ancestry: a critical review of the "prevalence gradient hypothesis." *Arthritis Rheum* 1998;41:2091-9.
2. Watts RA, Scott DGI. Classification and epidemiology of the vasculitides. *Baillieres Clin Rheumatol* 1997;11:191-217.
3. Adebajo AO, Birrel FA, Hazleman BL. The pattern of rheumatic disorder seen among patients attending urban and rural clinics in west Africa. *Clin Rheumatol* 1992;11:512-5.
4. Adebajo AO, Isenberg DA. Immunological aspects: tropical rheumatology. *Baillieres Clin Rheumatol* 1995;9:215-30.

Clinical Images: Radiographic progression of rheumatoid arthritis over twenty years



The patient was diagnosed as having rheumatoid arthritis (RA) in 1977, at the age of 56 years, based on symmetric arthritis of the hands, wrists, and elbows, morning stiffness lasting 2 hours, and positive rheumatoid factor at a titer of 1:320. He did not have nodules, and a plain posteroanterior radiograph of the hands at the time of diagnosis (A) showed nonspecific diffuse joint space narrowing. Prior to the onset of RA, he had been taking clorazepate, imipramine, and diazepam, and he was reluctant to receive any other drugs. In 1979 (B), there were typical changes of early RA, consisting of soft tissue swelling symmetrically around the involved joints, joint space loss, juxtaarticular osteopenia, and marginal erosions, best seen here in the second and third metacarpophalangeal (MCP) and third proximal interphalangeal (PIP) joints bilaterally. In 1982 (C), he had multiple and extensive erosions in the MCP, PIP, and carpal joints and ulnar styloid. During 1985 (D) and 1986 (E), the erosive process progressed rapidly, with extensive destruction of the bony architecture, subluxations in the MCP, PIP, and carpal joints, and ankylosis of the second, third, fourth, and fifth PIP joints bilaterally. Ulnar deviation of the MCP joints was present mainly in the right hand. In 1994 (F), severe generalized osteopenia and resorption and fragmentation of the MCP, PIP, and carpal joints was evident, and this continued to progress through 1997 (G). Ulnar deviation of the MCP joints and radial deviation of the wrists produced the characteristic zigzag appearance (E-G). The patient was last seen by us in March 1999, when he had 30 articular deformities of 40 recorded joints, without synovitis, and was in Steinbrocker functional class III. He was treated during his >20-year disease course with aspirin 600 mg 4 times daily, naproxen 500 mg twice daily, and prednisone 5-10 mg/day, except for 5 months in 1982 when intramuscular gold was started but had to be stopped due to a rash. Of interest, he has HLA-DRB1 *1302 and *1602, neither of which has been commonly associated with skin reactions to intramuscular gold, nor do they contain the shared epitope sequences for RA.

Inmaculada del Rincón, MD
José F. Roldán, MD
University of Texas Health Science Center at San Antonio