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## ANTI-PROTEINASE 3 (PR3) ANTIBODIES UTILISE INNATE SIGNALLING PATHWAYS THAT LEAD TO INFLAMMATION

*Sir,*

The paper by Kluth and Hughes discusses the direct pathogenic role of ANCA in the vasculitic syndromes.[1] Bacterial and viral infections may be important in triggering disease activity. New studies have shown that anti-PR3 antibodies prime monocytes and neutrophils via the CD14 membrane receptor and upregulate TLR and NOD receptor expression.[2,3] The widely expressed TLR and NOD proteins detect pathogen receptors and initiate proinflammatory activation. Dysregulation of these mechanisms (NOD mutations) result in auto-immune inflammatory diseases such as Crohn's disease.

Lipopolysaccharide and LTA are cell-wall components of bacteria recognised by CD14/TLR2 and TLR4 respectively. Incubation with anti-PR3 antibodies of monocytes and neutrophils alone led to mild release of chemokine IL-8, but preincubation with anti-PR3 antibodies followed by LPS and LTA challenge resulted in markedly increased levels of proinflammatory cytokines, IL-8, TNF-alpha and IL-6.[2] Cell surface expression of CD14 surface expression on monocyte and neutrophils was increased during anti-PR3 priming. A recent study has now shown that anti-PR3 antibodies prime monocytes by increasing cell surface CD14, TLR2/4 and intracellular TLR3/7/8/9 and NOD expression in a protease-activated receptor-2-dependent manner.[3] Protease-activated receptors are transmembrane G-protein coupled receptors and are activated by serine proteases. Anti-PR3 antibodies use this pathway to activate oral endothelial cells in periodontitis.[4] RNA interference studies targeting PR3 mRNA abolished antibody-mediated cell activation and down-stream inflammatory events with inhibition of NF-kappa B activation.[3,4]

These studies provide proof-of-concept that anti-PR3 antibodies prime granulocytes and upregulate innate immune receptors and bacteria use these receptors to amplify the response on further stimulation. This unwanted cooperation between anti-PR3 antibodies and bacterial cell-wall components may be the cause of vasculitic flare-ups during infections and may well contribute to sustained inflammation and granuloma formation that is seen in Wegener's granulomatosis.

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### *Authors' response*

We are grateful to the comments from Dr Khan which usefully highlight the complex interaction between the innate and adaptive immune response that occurs in AASV. A number of studies have demonstrated that neutrophils up-regulated cell surface PR3 in sepsis and when activated in response to pro-inflammatory stimulation by TNF-alpha, IL-8 and IL-6. As the letter outlines, anti-PR3 antibodies increase leucocyte TLR expression and TLR stimulation increases cell surface PR3 expression. Both of these mechanisms are potentially synergistic in maintenance of the inflammatory response. The clinical relevance of this is shown from the benefit of co-trimoxazole in Wegener's granulomatosis, the association of infections with disease exacerbations and our anecdotal experience that long-term use of rotating courses of antibiotics promotes disease control in pulmonary Wegener's granulomatosis.

D Kluth[1] and J Hughes[2]

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***Abbreviations*** Anti-neutrophil cytoplasmic antibodies (ANCA), ANCA associated systemic vasculitis (AASV), interleukin 8 (IL-8), Lipopolyscaccharide (LPS), lipotechoic acid (LTA), nucleotide binding oligomerization domain-like (NOD), toll-like receptor (TLR)

## ATRIAL FIBRILLATION

No account of AF[1] would be complete without mention of the contribution that early detection and treatment of hypertension could make towards reducing the incidence of this arrhythmia. Such a strategy would entail screening for hypertension, notwithstanding the fact that universal screening of adults is not current UK policy, and notwithstanding the fact that National Institute of Clinical Excellence guidelines do not cover screening.[2] Screening

confers an excellent opportunity, to provide, to hypertensive subjects as well as to normotensive subjects, lifestyle advice which either retards the onset of hypertension or generates some reduction in blood pressure levels.[3] Screening also identifies those hypertensive subjects who have electrocardiographic stigmata associated with high risk of subsequent AF such as bifid 'p' waves, prolonged 'p' wave duration, and atrial ectopic beats[4,5] so that they can be placed under increase surveillance for early detection of new-onset AF. As a result of screening, hypertensive subjects with LVH will also be identified, and the evidence is that treatment which results in regression of LVH can significantly reduce the likelihood of subsequent development of AF.[6]

OMP Jolobe
*Retired Physician, Manchester, England, UK*

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### *Response from authors*

We thank Dr Jolobe for his interest in our article. He is correct that hypertension is a common comorbidity associated with AF being involved in the pathogenesis of the arrhythmia, and its complications.

In population studies, hypertension is highly prevalent, and is a predictor of AF, especially if associated hypertensive left ventricular hypertrophy is present.[1] Indeed, pulse pressure is a strong predictor of subsequent AF.[2] Moreover, uncontrolled hypertension is a major associate of stroke and systemic embolism, even in anticoagulated AF patients, emphasising the need for good BP control. [3] Treatment of hypertension, especially with an agent that blocks the renin angiotensin system, may reduce the onset of new AF,[4] as well as adverse events.[5] Clearly, AF is yet another manifestation of hypertensive heart disease, given the intimate relationship of hypertension to AF and its complications, and that appropriate detection, treatment and control of BP would have major implications for AF management.

Whilst screening may seem one way to detect more AF and/or hypertension, the role of screening for AF was recently addressed in the *Screening for Atrial Fibrillation in the aged* (SAFE) study,[6] which determined epidemiology and the most cost-effective method of screening for AF in the population aged more than 65 years. Also, SAFE evaluated the relative cost-effectiveness of different methods of recording and interpreting the ECG within a screening programme. In SAFE, the baseline prevalence of AF was 7·2%, with a higher prevalence in males (7·8%) and patients aged more than 75 years, with an incidence of 0·69–1·64% per year, depending on screening method.[6] Importantly, the only strategy that improved on routine practice was opportunistic screening, rather than targeted screening.

Of note, a further analysis from the SAFE study also showed that many primary care professionals cannot accurately detect AF on an ECG, and interpretative software is not sufficiently accurate to avoid this problem, even when a general practitioner helps with interpretation. Thus, the diagnosis of AF in the community – or any screening strategy – needs to factor in the reading of electrocardiograms by appropriately trained people.[7]

Given that AF is the most common sustained cardiac arrhythmia, much can be done to improve its management,[8] particularly with stroke prevention.[9] Things can only get better.

GYH Lip
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***Abbreviations*** Atrial fibrillation(AF), blood pressure (BP), electrocardiogram (ECG), left ventricular hypertrophy (LVH)

## CONTRAINDICATIONS FOR INFLUENZA VACCINATION

***Sir,***

Roberts *et al* have given an up-to-date summary of influenza and pneumococcal vaccination in the recent issue of the *Journal*.[1] They raise some pertinent issues with respect to contraindications for influenza vaccination and indications for PPV versus PCV.

The authors state that the contraindications to inactivated influenza vaccine include egg allergy and acute febrile illness. This needs qualifying as it is frequently misunderstood. If an individual is acutely unwell, immunisation may be postponed until they have fully recovered. This is to avoid confusing the symptoms of any acute illness with adverse effects of the vaccine. Egg allergy is considered as a contraindication only if there is a confirmed anaphylactic reaction to egg products. Many people report symptoms of intolerance to egg, which are not a contraindication for immunisation. A careful history will often distinguish between true IgE mediated anaphylactic hypersensitivity and a non-allergic symptom. Specific IgE tests (RAST) to Egg (or anything else) are useless in the absence of a relevant history, there are plenty of people who have outgrown their egg allergy who still have positive tests. The risk to the individual of not being immunised must be taken into account. The local immunology/allergy specialist will be able to investigate and advise when there is uncertainty.

It is difficult to reach firm conclusions about the effectiveness of PPV, but overall efficacy in preventing pneumococcal bacteraemia in observational studies is reported to be 50 to 70% , although protection shown in RCTs is much lower and is around 40%. [2, 3, 4] Current evidence suggests that PPV is not effective in protecting against non-bacteraemic pneumococcal pneumonia. It does not prevent otitis media or exacerbations of chronic bronchitis. The vaccine is relatively ineffective in patients with impaired immunity including multiple myeloma, Hodgkin's and non-Hodgkin's lymphoma (especially during treatment) and chronic alcoholism.[4] The length of protection is not known and may vary between capsular types. Post-immunisation antibody levels usually begin to wane after about five years, but may decline more rapidly in asplenic patients and children with nephrotic syndrome.[5]

The current Department of Health recommendations for PPV are open to debate. As listed by the authors, it includes asplenic patients, immunosuppressed patients, and patients with chronic liver and renal disease. Paradoxically, these cohorts of patients make a poor response to polysaccharide antigens, yet are most in need of effective vaccination. Giving a PCV in the first instance, followed by un-conjugated vaccine (PPV) to maximise memory T cell help optimal vaccine response, makes immunological sense, although remains to be proven.

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***Abbreviations*** Protein conjugated vaccine (PCV), pneumococcal polysaccharide vaccine (PPV)

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***Authors' response***

The authors thank Dr Sargur and Dr Egner for their valid comments. The additional information, particularly with regard to reported egg allergy is very useful when considering the practical aspects of vaccination in this group.

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## DYSARITHMOTAXIA

*Sir,*

The numerical data generated by a research study are at the very core of any published report. Statistical analysis of the data by computer then calculates a plethora of secondary numbers (percentages, means, confidence limits, etc) which, and I am sure I am not alone in this, can readily generate mathematical dyspepsia in the reader. This is particularly so because the derived figures often incorporate the spurious precision of one or more decimal places.

My plea is that this arithmetical over-elaboration, so off-putting to the reader, should be sensibly pruned as part of the preparation for publication. For example, in the article 'Use of proton pump inhibitors in upper gastrointestinal bleeding' which summarises a paper from the *New England Journal of Medicine* (Lee and Dwarakanath, 2007; *J R Coll Physicians Edinb* **37:**218–9) we read:

> 'Sixty out of three hundred and forty-one (19·1%) of patients in the omeprazole group compared to 90/371 (28·4%) in the placebo group required endoscopic therapy ...'

Is the 0·1% and the 0·4% meaningful, or worth committing to paper and memory? Whole numbers would be clearer. But hey! Sixty out of 341is actually 18%, not 19·1%, and similarly 90 out of 371 is actually 24%, not 28·4%. Something is wrong somewhere! The College Librarian responded speedily with a copy of the original *NEJM* paper, and all was revealed. The actual numbers of subjects in the two subgroups, 314 and 317, have been transcribed into the College Journal as 341 and 371. Is this the first example of a new syndrome – Dysarithmotaxia?

P Myerscough
*Retired Fellow, RCPE*

***Authors' response:*** We apologise to Dr Myerscough for our typographic error and reassure him that it does not affect the conclusions that can be drawn from the paper. In reply to his appeal to round data up or down to the nearest whole number, we feel that such 'dumbing down' risks reducing the accuracy of presented data. For example, he suggests that 0·4% be removed from the figure of 28·4% of patients in the placebo group (n=317) requiring endoscopy. This is equivalent to 1·3 patients requiring endoscopy. If that is your patient then clearly the number of decimal places is important.

T Lee, AD Dwarakanth
*University Hospital of North Tees, Stockton on Tees, England, UK.*

## EDITORIAL – DOCTORS AND TERRORISM

*Sir,*

I found your *Editorial* in the RCPE *Journal* (2007; **37:**193–4) very interesting. It must have have come as a shock to my colleagues in Scotland to find that some of our own were prepared to maim and destroy other humans, rather than heal them. Alas, history is full of medical graduates who when all else fails are prepared to use violence to achieve their ends, ends which they see as eminently ethical.

May I remind you that Algerian medical graduates not only tended to their wounded but literally took up arms against the French. The distinguished Dr Morch of Denmark carried a gun to aid his resistance against the Germans in World War Two. There was even a doctor or two among the liberation theology activists of south and central America, who felt that as a last resort they might have to resort to violence; and in Nicaragua did so. Only the verdict of history can tell if a colleague like Ernesto Che Guevara will be seen as freedom fighter or terrorist. Having lived through the 1970s and all that entailed I have to admit that Guevara is one of my heroes and must disagree with your listing of him as a terrorist. Would you also condemn the young medical student (who later came to Australia) who chose to help blow up power lines as part of the ANC campaign of resistance (or terrorism) against the Afrikaaner government of South Africa? We may feel that in Australia we are isolated from all this.

On the other hand, we have been confronted by the official persecution of a young colleague alleged by an overenthusiatic security service to be a terrorist.

John Thompson
*Canberra, Australia*

***Editor's Note.*** Dr Thompson's letter neatly illustrates the blurred interface between freedom fighters and terrorists. Indeed, the terms are often used interchangeably, and the judgment of history on an individual is usually determined by those who win. Would that I was able to differentiate clearly between these terms, but all I can do is give an opinion.

What can individuals do against those seen to be oppressors who are not amenable to persuasion and where the ballot box is not an option? Non-violent resistance can work but can also be costly in human suffering. Would Ghandi have fared as well against Stalin's Soviet Union as he did against a post-WW2 British Government subject to the views of its electorate? Winning support from international opinion can also work, but such support usually involves rewarding or posing no threat to potential supporters. In the end, and it should be 'in the end', those who want freedom may



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have to take up arms and fight for it, though observers should recognise minorities determined to impose their will on majorities.

When it comes to separating freedom fighters from terrorists, I can only say that as regard for life, particularly the lives of those not involved in a dispute, diminishes, one is looking more and more at terrorism. Of course, terrorists often say whole populations are complicit in opposing them and are therefore legitimate targets, but this is hard to swallow when the dead and injured include children. On these grounds, the doctors you quote from WW2, the Algerian struggle against France, the South American liberation theologists and the ANC resistance in South Africa, look to have been freedom fighters.

So what about doctors? Should we be expected to meet standards different from other people? Our profession should be dedicated to the care of the sick, the injured and the distressed, and they should be able to trust doctors to act in their best interests even in the case of enemies (as with wounded soldiers). I think this standard does allow a doctor to be a freedom fighter but not a terrorist. You mention Ernesto Che Guevara whose charisma, personal courage and leadership abilities are widely accepted. However, a man who has been implicated in sham trials and executions and who has been quoted as saying 'Hatred is an element of struggle; relentless hatred of the enemy that impels us over and beyond the natural limitations of man and transforms us into effective, violent, selective, and cold killing machines.' has surely crossed a line taking him out of our profession. The doctor allegedly involved in the indiscriminate Glasgow airport attack also crossed the line into terrorism.

Your closing point, that we should be careful before labelling people as terrorists is a good one. Hasty and ill-considered decisions which turn out to be wrong may well create the very thing we condemn.

As I read your letter, I felt that in reality we are probably not far apart (except, perhaps, over Che); thank you for a welcome letter that has certainly made me reconsider my thoughts on this issue.