Letters to the Editor

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CD4+CD28NULL T CELLS AND TOLL LIKE RECEPTOR INTERACTION: A NEW LINK TO RHEUMATOID ARTHRITIS AND ATHEROSCLEROSIS?

Sir,

We read with great interest the article on statins in rheumatoid arthritis by GD Kitas and N Sattar.[1] Accelerated atherogenesis is now a recognised feature of diseases associated with chronic inflammation like systemic lupus erythematosus and rheumatoid arthritis (RA).[2] Traditional risk factors do not appear to explain the high incidence of atherosclerosis in these patients with accompanying increased morbidity and mortality. Both the blood of RA patients and atherosclerotic lesions contain increased numbers of an unusual subset of CD4+ T cells with absent surface expression of CD28 (CD4+CD28null cells). Since microbial antigens can activate CD4+CD28null cells,[3] this may explain the link between these two conditions.

The CD4+CD28null cells express high levels of IFN-γ and are rarely found in young, healthy individuals (< 40 years old) but are increased in the elderly and in patients with chronic inflammatory disease. CD4+CD28null cells express Natural Killer cell markers, the stimulatory killer Ig-like receptor and cause target cell death (for example, endothelial cell) through release of perforin on activation. They are highly oligoclonal, which suggest that they arise due to chronic antigenic stimulation. They are long-lived, as they are more resistant to apoptosis than their normal CD28+counterparts.

A recent study has confirmed that CD4+CD28null cells cause perforin-mediated damage following engagement via the toll-like receptor 4 (TLR4) in patients with ankylosing spondylitis, psoriatic arthritis and RA.[3] This receptor binds lipopolysacharide and CD14, and so is triggered by microbial cell walls. Numbers of these CD4+CD28null T cells are significantly higher in patients with coronary artery disease and co-existent RA, than in controls with stable angina.[4] New evidence suggests that the expression levels and mean mRNA copy number of TLR4 on peripheral-blood mononuclear cells is increased in patients with coronary atherosclerosis disease.[5] A recent double-blind, placebo-controlled study on healthy human volunteers showed that simvastatin (80 mg/day) can suppress endotoxin-induced upregulation of TLR2 and TLR4 *in vivo*.[6] Thus, it seems that TLR-activated CD4+CD28null T cells provide an immunological link between RA and atherosclerosis, and statin drugs could inhibit this process in the future.

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DIAGNOSING CLINICAL PHOTOGRAPHS

Sir,

Many readers must have been fascinated by the clinical photograph of 1853 and the accompanying case history as described by Malcolm-Smith in the October issue of the *Journal*.[1]

It is almost certainly cancrum oris (noma). As Malcolm-Smith says, it is unlikely to have been the result of necrotising fasciitis as this would have been rapidly fatal. Cancrum oris is relatively common in sub-Saharan Africa. It begins as an acute necrotising ulcerative gingivitis[2] destroying the facial soft tissues and is associated with poor oral hygiene in children who are immunosuppressed and malnourished, e.g. with kwashiorkor and often followed measles or other severe infections.

In the mid 1960s, when I was paediatric registrar at University College Hospital, Ibadan, Nigeria, I saw a number of cases, some of which were successfully operated on by Mr Michael Tempest, consultant plastic surgeon. Treatment was prolonged, firstly improving nutrition and then raising pedicles and skin flaps before a series of operations.

How common was cancrum oris in eighteenth- and nineteenth-century Britain? Probably not all that common, as evidenced by this unique clinical photograph which suggests that it was something unusual, worthy of recording, and presenting a real clinical challenge to Professor Syme.

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References

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AUTHOR'S RESPONSE

Sir,

I appreciate being asked to comment on the letter from Dr Barnes which supports the provisional diagnosis of cancrum oris in the patient portrayed in the photograph.

In the early nineteenth century, causes of inflammatory disease were poorly understood and description and diagnosis were confused. The term 'lupus' was applied to destructive facial disease as was the term '*noli me tangere*', which Syme (and others) considered to be an alternative name for 'lupus' but which some used to refer to as malignancy.[1,2,3] Other authors describe conditions fitting a descriprion of cancrum oris using these terms and further alternatives.

The actual incidence of cancrum oris could only be estimated by reviewing existing case notes and reviews in the literature of the time. The case notes of Syme only mention one other case of 'lupus' before 1853 and unfortunately the surgical clerk has failed to enter any details of the patient. A case in St Bartholomew's Hospital in 1850 diagnosed as 'lupus exedens' has been reported and has very similar characteristics to Syme's case. He was treated conservatively and made a satisfactory recovery after four-and-a-half months.[4] The fact, however, that descriptions appear in the textbooks and journals suggests that destructive facial disease was not uncommon.

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PROFESSOR RONALD HAXTON GIRDWOOD

Professor Girdwood was President of the College from 1983 to 1985. He died on 25 April 2006 in his ninetieth year.

His presidency saw the building of the new Conference Centre, the establishment of *The Chronicle*, the forerunner of *The Journal*, and the first MRCP(UK) exams in Hong Kong. He took a keen interest in the College throughout his medical career, and this included serving on Council twice, holding the Vice-Presidency, and being Chairman of the Symposium Committee for 21 years. His medical service in World War II took him to India, where he developed a strong affiliation with that country and its people, and during his presidency, he travelled extensively in support of the College's overseas Fellows.

His memoirs, *Travels with a Stethoscope*, are a remarkable record of his life. The Fellows and Collegiate Members remember his College contributions with gratitude. His obituary is to be found on the College website.

Niall Finlayson