Letters to the Editors

In search of the source of hyperprolactinaemia in systemic lupus erythematosus

Sirs,

We read with interest the recent study by Paraiba *et al*. (1). The authors: (i) confirmed the long-recognised association of systemic lupus erythematosus (SLE) with hyperprolactinaemia; (ii) did not find a significant correlation between serum prolactin (PRL) levels and clinical SLE "manifestation," and; (iii) found no significant differences in lymphocyte-derived PRL levels between patients with active or inactive SLE and healthy controls. They concluded that they had "excluded a lymphocytic source of PRL" in SLE.

The association between raised serum PRL levels and SLE was first reported over two decades ago in male patients (2). Subsequently, this finding has been replicated in females, and several studies have shown a correlation between serum PRL levels and disease activity (see Pacilio *et al*. (3) for summary). It had been postulated that lymphocytes, a well-recognised source of extrapituitary PRL production (4), contributed to systemic hyperprolactinaemia in SLE (3). Indeed, Stevens *et al*. (5) discovered a single nucleotide polymorphism in the extrapituitary PRL promoter which was not only associated with SLE, but also increased PRL promoter activity and PRL mRNA production in lymphocytes. However, the exact source, and pathophysiological significance, of increased circulating PRL in SLE has remained ill-defined (3). Therefore, Paraiba *et al*. (1) sought to clarify whether circulating lymphocytes were the source of the hyperprolactinaemia associated with SLE. However, several notes of caution must be borne in mind when interpreting these interesting results.

Firstly, in principle, PRL levels might vary dramatically between those produced by circulating peripheral blood lymphocytes and those produced by lymphocytes that form an integral part of the inflammatory milieu in the affected tissues such as skin. Secondly, the lymphocyte populations isolated from the blood may either lack the pathobiologically most relevant subset of lymphocytes that participate in inflammation in the tissues, or may contain the latter in such low numbers that their specific contribution to PRL production is easily missed. Thirdly, in contrast to other studies (3), Paraiba *et al*. (1), did not find an association between cutaneous manifestations of SLE and hyperprolactinaemia. The current study may have been underpowered to detect any such association. Fourthly, given the circadian variations in PRL serum levels (4), the circadian window during which differences in peripheral blood lymphocyte-derived PRL might have been maximal, could have been missed. Finally, contrary to the authors' assertion that the efficacy of the dopaminergic agonist bromocriptine in SLE is due to its effect on reducing pituitary PRL secretion, as there is no evidence that extrapituitary PRL secretion is inhibited by dopamine (4), Pacilio *et al*. (3) have reported the efficacy of bromocriptine in normoprolactinaemic patients (3, 6). The exact mechanism(s) of action of bromocriptine in SLE remain(s) poorly understood. It may therefore be premature to conclude that extrapituitary PRL secretion in general, and lymphocytic PRL secretion in particular, do not contribute significantly to the hyperprolactinaemia of SLE.

Another intriguing possibility is that human skin may also contribute to the hyperprolactinaemia associated with SLE. Indeed cutaneous extra-pituitary PRL production may not only derive from intracutaneous immunocytes, *e.g*. dermal macrophages (4), but also from resident skin cells; both human skin and scalp hair follicles are extrapituitary sources of PRL (4, 7-9). Given that human skin is the largest peripheral endocrine organ, harbouring around 5 million hair follicles, it is important to establish whether patients with SLE have enhanced intracutaneous PRL production. Interestingly, oestrogen and thyrotropin releasing hormone, which stimulate pituitary PRL production and release, both stimulate PRL production in human skin at the gene and protein level (9).

Human skin organ-culture (9), in addition to skin biopsies from patients with SLE, provides an ideal model system to characterise the transcription, production, and cutaneous secretion of PRL in health and chronic inflammatory disease. This can also provide valuable mechanistic insights into the local cytokine-like effects of PRL (4, 8) on epithelial tissues, for example in the cutaneous lesions of SLE. In this model system, it can be explored preclinically whether currently available pure PRL receptor antagonists (10) may have a place in the future treatment of SLE-associated skin and peripheral tissue lesions.

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Funding: E.A. Langan, is supported by a Medical Research Council Clinical Research Training Fellowship.

Competing interests: none declared.

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