chromatographed enzymically active fraction[10]. There was an unequivocal immunoreactivity of 23% compared with that of the enzyme obtained from modern autopsy. Furthermore, no microbial contamination of the bones was detectable[7].

The wealth of pine wood compounds and sodium in the bones support the proposal that IDU II has been defleshed or skeletonized at least in part before embalming[1]. Desiccation with natron and embalming was thus being practised at least one thousand years earlier than previously thought. This 4,000-year-old conservation has been most beneficial for preserving the functional and structural intactness of bone alkaline phosphatase.

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What can stochastic resonance do?

Stochastic resonance[1–3] is often defined as a noise-induced rise (and then fall, for higher noise intensities) of the signal-to-noise ratio (SNR) of a weak narrow-band signal in a nonlinear system. Various applications of this phenomenon are being explored, in particular the possibility that stochastic resonance might help enable biological cells to respond to weak 50–60-Hz electromagnetic fields, far below the thermal noise level[4,5]. We therefore feel that its place within the broader physics context should be specified more clearly. Specifically, what stochastic resonance can, and cannot, be expected to do.

The idea of stochastic resonance might seem counterintuitive. However, soon after its discovery in bistable systems, it was realized that the idea amounted to a fairly straightforward extension of earlier work by Debye[6] on reorienting polar molecules, and that the occurrence of stochastic resonance in the general case could be treated[7] with a traditional technique of statistical physics[8]: linear response theory (LRT). It is well known in the LRT context that the response of a system to signals in certain frequency ranges can be strongly increased by noise, for example by raising the temperature. Examples range from currents in electron tubes to optical absorption near absorption edges in semiconductors. The threshold-less model considered by Bezrukov and Vodyanoy[9], the subject of recent discussions[4,5], displays noise-induced increases in both the signal and the SNR. Their formula for the SNR represents a special case of the general LRT expression given earlier[7] and subsequently applied to many different systems[7,10–12].

An important consequence[10,13] of LRT, relevant to the recent discussion[4,5], is that, for a system driven by a signal and Gaussian noise, the SNR at the output, R_{out}, does not exceed that at the input, R_{in}. For a linear system $R_{out} = R_{in}$, and the SNR decreases with increasing noise intensity. For a nonlinear system R_{out}/R_{in} can be small; then the provision of additional noise can sometimes help to increase the SNR at the output, back towards its value at the input. This latter effect constitutes stochastic resonance. Quite independently of parameter choice[4,5], therefore, the SNR of the 50–60-Hz signal inside the biological cell (output signal) cannot be expected to exceed that of the external signal coming from the environment (input signal).

Stochastic resonance can decrease quite markedly the SNR degradation of a noisy signal caused by its transduction through a nonlinear element, but it does not provide a mechanism by which the SNR of the weak input signal can meaningfully be enhanced.

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CCR5 is characteristic of Th1 lymphocytes

$CD4^+$ lymphocytes can be assigned to two subsets[1]. Th1 lymphocytes secrete interferon gamma (IFNγ) and lymphotoxin, promoting cell-mediated immunity to intracellular pathogens; and Th2 lymphocytes secrete interleukins 4 and 5 (IL-4 and IL-5), which function in allergy and humoral immunity to parasites. Th2 lymphocytes preferentially express the chemokine receptor CCR3 (refs 2,3). We have studied the occurrence of two additional chemokine receptors, CCR5 and CXCR3, in human, antigen-specific $CD4^+$ Th1 and Th2 cell clones[4].

CCR5 was expressed at high levels in Th1 and was virtually absent from Th2 lymphocytes; CCR3 was undetectable in Th1 and moderately expressed in Th2 cells (Fig. 1a, c), but both were highly positive for CXCR3. When we assessed receptor function by measuring chemotaxis in response to selective chemokines[5], Th1 lymphocytes responded to MIP-1β and IP10 but not to eotaxin, and Th2 lymphocytes responded to eotaxin and IP10 but not to MIP-1β (Fig. 1b, d), as expected from the receptor expression data. Analysis of a panel of T-cell clones[4] confirms that CCR5 is characteristic of the Th1 phenotype, being expressed at high levels in nine of nine Th1 clones. Only one of nine Th2 clones was positive for CCR5. Most Th2 clones expressed moderate to low levels of CCR3, responding accordingly to eotaxin. The presence of CXCR3 was detected in all clones tested, but expression and chemotaxis were higher in Th1 clones.

Flow cytometry and function analysis were performed on naive cord-blood T lymphocytes, polarized towards the Th1 phenotype[6]. Whereas naive cord-blood T lymphocytes were negative, Th1-polarized cells expressed moderate levels of CCR5 and high levels of CXCR3 but were CCR3-negative, and migrated towards MIP-1β and IP10 but not towards eotaxin (Fig. 1e, f).

Receptor expression and function were studied in T lymphocytes from rheumatoid joints, which acquire the Th1 phenotype *in vivo*[7]. T-cell areas of the rheumatoid synovium, defined by staining with anti-CD3, showed high levels of CCR5 and CXCR3 and only borderline staining for CCR3 (Fig. 2). The same staining pattern occurred in the characteristic lymphocytic infiltrates around microvessels (Fig. 2, insets).

In addition, T lymphocytes recovered from the synovial fluid of rheumatoid joints, which exhibit a Th1 phenotype, expressed high levels of CCR5 and CXCR3 and low levels of CCR3, and were responsive to MIP-1β and IP10.

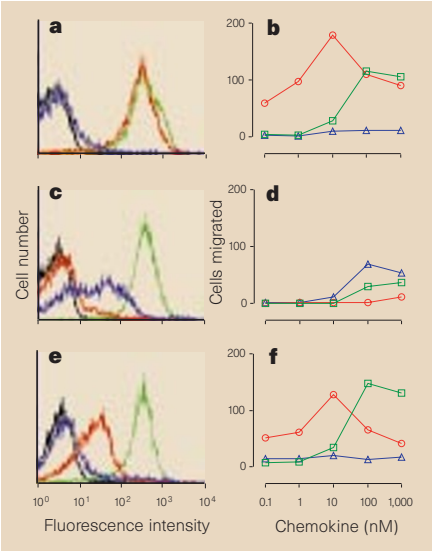

Figure 1 CCR5 is preferentially expressed in Th1 lymphocytes. Flow cytometric analysis of CCR5 (red), CXCR3 (green) and CCR3 (blue) expression and chemotaxis in response to MIP-1β (red), IP10 (green) and eotaxin (blue) is shown in Th1 clones (**a**,**b**), Th2 clones (**c**,**d**) and Th1-polarized cord blood cells (**e**,**f**). Isotype-matched control immunoglobulins are shown in black. Cloned Th1 and Th2 lymphocytes were re-stimulated with phytohaemagglutinin in the presence of irradiated feeder cells and cultured for 10–12 days[4]. Cord blood cells were subjected to two rounds of polarization towards Th1 with IL-12 and anti-IL-4 (ref. 6). For flow cytometry, cells were stained with anti-CCR5 (5C7) (ref. 8), anti-CXCR3 (1C6.2) (ref. 13), anti-CCR3 (7B11) (ref. 14) and control IgG followed by phycoerythrin-conjugated goat anti-mouse IgG. Chemotaxis was performed as described[10]. Cells were counted in five randomly selected fields at a magnification of ×1,000.

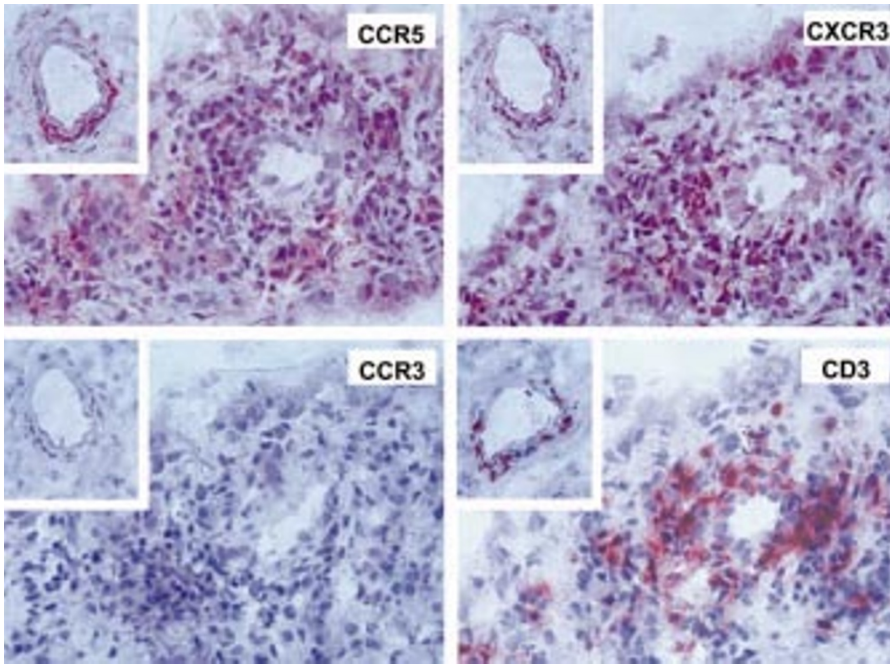

Figure 2 Expression of CCR5, CXCR3 and CCR3 in rheumatoid arthritis. Immunohistochemical analysis of serial sections of synovial tissue from rheumatoid arthritis patients stained for CCR5, CXCR3, CCR3 and CD3 (ref. 3). Cryostat sections were fixed and stained with anti-CCR5 (5C7) (ref. 8), anti-CXCR3 (1C6.2) (ref. 13), anti-CCR3 (7B11) (ref. 14) or anti-CD3 followed by biotin-labelled sheep anti-mouse antibodies and streptavidin-biotin-alkaline phosphatase. The colour reaction was developed with New Fuchsin containing levamisole. The slides were counterstained with Mayer's haematoxylin. Representative fields are shown. Insets show perivascular infiltration of CCR5-, CXCR3- and CD3-positive cells.

The study adds weight to the notion that chemokine receptors are expressed in T lymphocytes depending on their state of activation or differentiation[5]. Naive and memory T lymphocytes do not respond to chemokines that are frequently produced in inflammation. The expression of CCR1, CCR2, CCR5 and CXCR3 and chemotactic migration depends on activation, in particular with IL-2 (refs 8–11). In contrast, CXCR4 is present and functional in resting and stimulated T lymphocytes[5].

In T-cell lines generated from human donors by culture with IL-2 (ref. 10), we observed a marked variation in CCR5 expression and responsiveness to MIP-1β between donors. Like CCR1 and CCR2 (ref. 10), CCR5 is rapidly lost in the absence of IL-2, and activation by anti-CD3 and anti-CD28 antibodies results in CCR5 downregulation and loss of migration (not shown). CXCR3 is present on Th1 and Th2 cells and on T cell lines that are cultured with IL-2, whereas CCR3 is restricted to Th2 cells[2]. Like CCR1, CCR2 and CCR5, CCR3 is downregulated on T-cell activation[2]. Levels detected in this study were moderate and variable; thus CCR3-bearing lymphocytes might constitute a Th2 subpopulation. This receptor is characteristic of T lymphocytes recruited into eosinophil-rich sites of allergic inflammation[3]. Chemokine receptor expression could constitute a major regulatory element for the composition of the lymphocytic infiltrates in different types of inflammatory pathology. In fact, Th2 lymphocytes bearing CCR3 are frequent in allergic infiltrates[3], whereas CCR5- and CXCR3-positive Th1 lymphocytes predominate in the rheumatoid synovium.

The recruitment of CCR5-positive $CD4^+$ T cells to sites of inflammation and immune reactions might contribute to the spreading of monocytotropic HIV-1 strains that use CCR5 as co-receptor. This suggestion is in agreement with the observation that in HIV-positive individuals microbial infections, which induce a Th1 response, are followed by a burst in viraemia[12].

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Straining the prion hypothesis

Aguzzi and Weissmann in their News and Views feature[1] correctly state that research on the molecular genetics of PrP protein has contributed greatly to our knowledge of the transmissible spongiform encephalopathies (TSEs). But their firm belief that these diseases are caused by rogue proteins ('prions') leads them to misrepresent alternative hypotheses of the nature of the agent, dismissing all non-believers as "the die-hard pro-virus faction"[1]. In fact, the prion hypothesis is far from proven: