response in autoantigen-specific T cells. The team are also looking at the effect of statins in RA and diabetes settings. *Exp. Biol.* (2002) Press release/conference, April 2002 *AL*

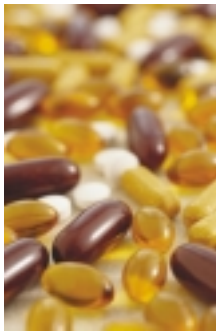
Final exams increase allergic reactions in asthmatics

Anxiety and depression have been associated with increases in asthma symptoms, which are often triggered by allergies. Now, researchers at the University of Wisconsin Hospital, WI, USA, report that the stress of final exams could worsen the symptoms of asthma. They compared the allergic reactions of students to allergens such as dust mites and cat dander during final exams to their reactions to the same substances during non-stressful times. Although the students did not feel that their symptoms worsened during exam times, the investigators found that the students experienced a higher influx of the inflammatory cells that respond to allergies, compared to non-exam periods. An increased and prolonged inflammatory response to allergens, could explain why some asthma patients' symptoms increase under stress. *Am. J. Respir. Crit. Care Med.* (2002) 165, 1062–1067 *SW*

Toxin transporters

Bacterial toxins have powerful effects on cells that line body surfaces and cavities, but how do such molecules move from the bacteria into the host? Studies using a colonic cell line demonstrated the movement of several staphylococcal superantigen molecules by active transcytosis. This process is dose dependent, with the exception of the toxic shock syndrome toxin, which showed increased transcytosis at lower concentrations. By using synthetic molecules it was demonstrated that a ten amino acid peptide conserved throughout these toxins is crucial for such transportation. However, the transport of toxins could be prevented *in vitro*, by using antisera or by saturation with this peptide. This knowledge offers a new route for the therapy of toxin mediated diseases because a peptide vaccine could be designed that produced the long-term exclusion of staphylococcal superantigens, thus potentially preventing their multiple effects and pathologies. *Infect. Immun.* (2002) 70, 2178–2186 *CM*

Vitamin A, measles and long-term protection



The effects of giving vitamin A to infants simultaneously with their vaccinations can be difficult to study and the time span of such studies is a major obstacle. However, it has now been demonstrated, by following up a longitudinal cohort, that giving this vitamin with the measles vaccine to nine month old infants results in higher antibody titers in children aged 6–8 years. The work, carried out in Guinea-Bissau, showed there was no difference in the reported number of measles cases in the vitamin A group compared with the placebo groups. However, on the grounds that higher antibody levels are more protective, vitamin A could in future be recommended for some populations in Central or Western Africa. *Lancet* (2002) 359, 1313–1314 *CM*

Papillomavirus, parity and cervical cancers

A multi-center study covering eight countries compared statistically the role of human papillomavirus with other variables such as age, parity and age of first sexual encounter. It seems possible that the presence of human papillomavirus is a crucial element in the development of cervical cancer. The analysis of pooled data showed that the risk of squamous cell cervical cancer in virus-positive women increased with parity (full term pregnancies). The age at first pregnancy was not a clear risk factor, although oral contraceptive use for over five years was. The powerful effect of parity, the mechanism of which is unclear, could explain the decline in this type of cancer in countries in which screening has yet to commence, but where birth rates are falling e.g. Latin America. *Lancet* (2002) 359, 1093–1101 *CM*

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Letters

Antimicrobial peptides are signaling molecules

Antimicrobial peptides are one of the major components of the innate immune response towards pathogen infections, and have been identified in all animals studied and also in some plants [1,2]. Five groups of natural antibiotics have been characterized in the past two decades [1–5]. This includes a huge group of cationic antimicrobial peptides [1], anionic peptides [3], aromatic dipeptides [4], processed forms of oxygen-binding proteins [5] and peptides such as enkelytin and secretolytin, which have antibacterial properties derived from neuropeptide precursors like proenkephalin and chromogranins, respectively [6].

The biosynthetic pathway that leads to the production of the biologically active neuropeptides begins with the synthesis of large inactive precursor proteins, which are cleaved at specific paired or single basic residues within the Golgi secretory pathway [7]. It is a family of subtilase-like pro-protein convertases (SPCs) that is largely responsible for these processing events, activating precursor proteins into neuropeptides and antimicrobial peptides [8]. α-Defensins are expressed in human and other mammalian neutrophils (HPN) [9] and Paneth cells of the small intestine [10]. They are synthesized as 90–100-amino acid preprodefensins, with a 19-amino acid signal sequence, an anionic propiece of ~45 amino acids, and a 29–40-amino acid C-terminal mature cationic defensin [11]. The removal of the anionic propiece is an activation step that converts the inert prodefensin to antimicrobial mature defensin [12]. In mouse small intestine, matrilysin is colocalized with α-defensins (cryptdins) in

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Table 1. Activities of defensins[a]

Antimicrobial substances	Activities
Human defensins	Chemotactic activities
	Stimulate release of IL-8, TNF, IL-1
	Decrease IL-10 release
	Associated with the lymphocyte nuclear fraction
	Inhibit phospholipid/Ca^{2+} protein kinase and phosphorylation of endogenous proteins
Murine defensins	Bind murine CCR6
	Chemoattract bone marrow-derived immature dendritic cells
Guinea-pig defensins	Increase in ICAM-1 on human neutrophils
	Induced adhesion of neutrophils
	Inhibit superoxide anion generation during phagocytosis of complement-opsonized particle

[a]Abbreviations: ICAM-1, intercellular adhesion molecule 1; IL, interleukin; TNF, tumor necrosis factor.

Paneth cell granules, and *in vitro* it cleaves the prosegment from cryptdin precursors [13]. Matrilysin functions in intestinal mucosal defense by regulating the activity of defensins [13]. The processing site of murine intestinal prodefensins contains a leucine-arginine dipeptide sequence in the P_1' and P_2' position, which is a cleavage motif of matrilysin. Cathelicidins, another class of human antimicrobial peptide found in neutrophils, are processed by neutrophil elastase [14]. In summary, the enzyme(s) currently implicated in the process of antimicrobial peptide precursors in human immunocytes are serine proteases, aspartyl proteases and metalloproteinases [13–15]. The processing of these peptides bears resemblance to that of various peptide hormones.

Defensins (HPN1–3) have also been found to be associated with the lymphocyte nuclear fraction, suggesting a cell function and regulation for these peptides [16]. They are also known to potently inhibit phospholipid/Ca^{2+} protein kinase (PKC) and phosphorylation of endogenous proteins [17]. Of the three defensin peptides, HNP-2 appears to be more potent than HNP-1 and HNP-3. Defensins, in contrast to polymyxin B (another peptide inhibitor of PKC), do not inhibit the binding of [3H]phorbol 12,13-dibutyrate to PKC; however, like polymyxin B, defensins inhibited the PKC activity stimulated by 12-O-tetradecanoylphorbol-13-acetate. Defensins had little or no effect on myosin light chain kinase (a calmodulin/Ca^{2+}-dependent protein kinase) and the holoenzyme or catalytic subunit of cAMP-dependent protein kinase, indicating a specificity of action of defensins. This suggests that defensins, which are among the most potent peptide inhibitors of PKC identified, could have profound effects on functions of neutrophils and other mammalian cells, in addition to their well-recognized antimicrobial activities, and that protein kinases are possible intracellular targets [17,18].

Taken together, these data (Table 1), in addition to the review of Oppenheim *et al.* (pp. 291–296), emphasize that antimicrobial peptides are involved in immune response modulation, not only by their antimicrobial activities but also as signaling molecules. These natural antibiotics can also modulate the immune response through paracrine or endocrine pathways. For example, data from proenkephalin and chromogranins [2,6,8] show that molecules yielded from these neuropeptide precursors (e.g. enkelytin or secretolytin) are involved in the modulation of the innate immune response. Some of the yield peptides have chemotactic activities like the methionine-enkephalin and some present antimicrobial activities like the enkelytin. This confirms that endocrine and immune markers are present in both nervous and immune systems. The recent data of Cutuli *et al.* [19], showing that α-MSH possesses antimicrobial activities, confirm that we now have to speak about the immune and nervous systems as expressing either endocrine or immune phenotypes, depending the nature of external stimuli [20].

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