Lysosomes and prohormone activation

SIR — The interesting *News and Views* article by Pfeffer and Ullrich[1] refers to the unexpected relationship between the structure of the low-density lipoprotein and epidermal growth factor (EGF) receptors and that of the biosynthetic precursor for EGF itself. Pfeffer and Ullrich believe that a new clue to the puzzle is provided by the letter in the same issue of *Nature*[2] reporting the detection of unprocessed EGF precursor, but not EGF itself, in mouse kidney. The authors of this letter envisaged the possibility that the EGF precursor is a membrane protein and that it might function as a receptor in the cells of the distal tubules to regulate membrane transport events. This exciting new information, together with other clues to the puzzle, invites the re-evaluation of a suggestion I made a few years ago, prompted at that time by the related problem of the existence of prohormones[3,4].

In brief, it was proposed that polypeptide hormones have evolved from the constituent proteins of the secondary lysosome of simple unicellular organisms. A key element of this hypothesis was that the membrane of the secondary lysosome must contain transport processes. Hence the agents and products of lysosomal digestion would have direct access to, and the possibility of regulating, nutrient transport processes. Regulation of nutrition is a major feature of the action of many polypeptide hormones and growth factors. (As a result of this concept a glucose transport system was searched for and found in lysosomes[5].) It was also proposed that the proteins which could act as polypeptide hormone precursors included membrane transport proteins and lysosomal digestive enzymes. "If some of the effectors arise by partial degradation of membrane proteins, then a structural relationship could exist between some effectors and receptors"[3]. A structural relationship between cobalamin binding proteins and their receptors has been recognized[6].

Further informative structural relationships between a membrane protein, transport, nutrition and growth promoting activity, have emerged around transferrin and its receptor. The transferrin receptor shows weak homologies with the EGF precursor and chicken transferrin precursor[7]. Transferrin itself appears to be structurally and functionally related to an iron-binding cell surface glycoprotein which is present in most human melanomas, fetal intestine and, in trace amounts, normal adult tissues. This protein may translocate iron[8]. Transferrin has growth factor activity and stimulates the growth of some cells independently of its iron binding[9]. Finally the nucleotide sequence of a transforming gene suggests that it encodes a protein partially homologous to the amino terminus of transferrin, suggesting possible functional similarities[10]. It is possible that this smaller peptide is growth-stimulating with a role similar to that proposed for platelet-derived growth factor in malignant transformation[10,11].

Pfeffer and Ullrich also mention that the precursor for a polypeptide homologous to EGF, transforming growth factor (TGF)-alpha, has a sequence suggestive of its being a membrane protein. It should perhaps be added in the present context that TGF-α and EGF show homology to the serine proteases urokinase and tissue-type plasminogen activator[12], and that EGF appears to be related to pancreatic secretory trypsin inhibitor[13]. The EGF precursor also appears to be structurally related to the serine protease factor X and more generally to the family of blood coagulation zymogens which includes prothrombin[14]. Thrombin itself has mitogenic activity and triggers a number of platelet reactions including secretion. These effects are not due to its protease activity but are considered to be hormone-like[15]. Other thrombin sequence homologies which have been described include those with angiotensin and the β-chain of luteinizing hormone[16]. It has recently been recognized that human γ-trace, a polypeptide having some homology with glucagon and corticotropin[17], is an extremely potent cysteine-proteinase inhibitor[18]. The K_i for γ-trace inhibition of cathepsin L is less than 0.005 nM[18]. Thus a picture of close interrelations between some polypeptide hormones, proteases and their inhibitors emerges.

The sequence information which has emerged to date is consistent with the hypothesis that the lysosomes are involved in the activation of prohormones, suggesting that it may provide a useful framework for making and interpreting structural comparisons in this area.

C.N. HALES
Department of Clinical Biochemistry, University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 2QR, UK

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Agreement between optical and radiocarbon dating

SIR — D.J. Huntley *et al.*[1] recently described a new method for dating sediments. They compared their optically dated age of 62±8 kyr for a sample with a radiocarbon dated age of 58.8±0.3 kyr. In fact, the agreement is even better than Huntley *et al.* indicated, since the radiocarbon age used for comparison is based upon the wrong half-life for ^{14}C.

For well over twenty years, it has been internationally agreed to continue to use the Libby half-life value of 5,568 years for ^{14}C (ref. 2), although the best value was acknowledged to be a factor of 1.03 larger[3]. The procedure was justified by the desire to avoid the confusion which would arise should the many thousands of published dates require revision[4]. It should be noted that all radiocarbon dates are consistent among themselves but 3% lower than the true age.

As a result, the true (radiocarbon) age for Huntley *et al.*'s specimen would become 60.6±0.3 kyr, which is in excellent agreement with their 62 kyr value.

NORMAN E. HOLDEN
National Nuclear Data Center, Brookhaven National Laboratory, Upton, New York 11973, USA

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Right-handed flagella in tumbling *Caulobacter*

SIR — In a pair of fascinating *News and Views* articles, Michael Spencer has recently discussed the remarkable case of bacteria that have right-handed helical flagella but are still able to reverse direction without tumbling, by simply changing the sense of rotation from clockwise to counterclockwise[1]. There seems some uncertainty, however, about when such bacteria were discovered. Spencer presents data from the work of Alam and Oesterhelt on *Halobacterium* species[2]. But the first bacteria to be discovered with such properties were in fact *Caulobacter crescentus* — they were studied by us in the University of Tokyo and the work was reported in an earlier edition of the same journal[3].

SHIGEO KOYASU
Department of Cell Biology, Tokyo Metropolitan Institute of Medical Science, 3-18-22 Hongomagome, Bunkyo-ku, Tokyo 113, Japan
YASUO SHIRAKIHARA
Laboratory of Molecular Biology, Medical Research Council Centre, University Medical School, Hills Road, Cambridge CB2 2QH, UK

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