managed herds of the Roman era[7]. The sheep and pigs, too, were comparatively large animals by Roman and Medieval standards.

The patterns indicate a regulated agricultural cycle. This is not altogether surprising as some Anglo-Saxon and Carolingian laws indicate that kings were as much farmers as warriors, and concerned about legislation on crop-rotation and stock-breeding as it affected tributes in kind made each year to them[8]. Interestingly, the age profiles of the stock are much the same in the emporia as they are in the countryside. Clearly, a mixture of common sense, central authority and low taxes helped to sustain good standards of husbandry at all levels of society. This contrasts with the last days of Roman control not only in Italy[9], but all over western Europe, by which time high taxes in kind had effectively destroyed stock management. □

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Richard Hodges is in the Department of Prehistory and Archaeology, University of Sheffield, Sheffield S10 2TN.

Control of translation

Enzymes and toxins that regulate protein synthesis

from Mike Clemens

DIPHTHERIA toxin and toxin A of *Pseudomonas aeruginosa* produce their effect in eukaryotic cells by inactivating elongation factor 2 (EF-2), an essenial factor in protein synthesis. This protein of about 93,000 molecular weight catalyses the translocation of the growing polypeptide chain from the aminoacyl-tRNA site to the peptidyl-tRNA site on the ribosome each time an amino acid is added during chain elongation. The mRNA template is also shifted (by a distance of one codon), in a reaction that requires energy derived from the hydrolysis of guanosine triphosphate. Inactivation of EF-2 by the toxins is achieved by the transfer of a molecule of ADP-ribose from nicotinamide adenine dinucleotide (NAD^+) to a modified amino acid on the factor, 2[3-carboxyamido-3-(trimethylammonio)propyl]histidine[1,2] (Fig.1), commonly known as diphthamide. Synthesis of this amino acid involves post-translational modification of a histidine residue in EF-2 by at least three enzymes[3,4]. The assumption that diphthamide is not present in EF-2 solely for the purpose of allowing protein synthesis to be shut down during diphtheria infection is justified by recent results[5].

Lee and Iglewski report that polyoma virus-transformed baby hamster kidney cells (pyBHK) contain an endogenous ADP-ribosyltransferase with a similar specificity for the diphthamide residue[5]. The enzyme from pyBHK cells appears to be functionally analogous to, but immunologically distinct from, fragment A of diphtheria toxin — the portion which has the mono(ADP-ribosyl)transferase activity. Similar enzymes may occur in a variety of other cell types since Lee and Iglewski have also identified an EF-2-specific mono-(ADP-ribosyl)transferase in beef liver. It is unclear whether these enzymes have any relationship to the cellular enzymes or microbial toxins capable of ADP-ribosylating other protein substrates, such as adenylate cyclase[6] or histones[7], but the absence of diphthamide residues from such substrates suggests that the new ADP-ribosyltransferases represent a separate group.

Since ADP-ribosylation of EF-2 totally inactivates it (by inhibiting GTP-dependent translocation on the ribosome), it is possible that the enzyme identified by Lee and Iglewski has a function in the regulation of protein synthesis. Such a possibility is supported by the observation that the covalent modification of EF-2 by the enzyme is reversible, at least *in vitro* in the presence of fragment A and nicotinamide, and by the fact that pyBHK cells also contain an endogenous inhibitor of the EF-2-specific ADP-ribosyltransferase[5]. The presence of this inhibitor presumably ensures that a catastrophic inactivation of all the EF-2 in the cell does not normally occur. Reversible covalent modifications of protein synthesis factors by, for example, phosphorylation are implicated in translational regulation in a number of cases[8], although control of protein synthesis is normally exerted at the stage of polypeptide chain initiation rather than elongation.

The subcellular distribution and activity of EF-2 changes in cells in different physiological states. For example, there are differences between exponentially-growing and non-growing cells in culture[9]. Variations in EF-2 activity have been attributed to changes in the amount of the elongation factor protein. However, since quantification of EF-2 in those studies was based on the number of acceptor sites available for diphtheria toxin-catalysed ADP-ribosylation, another look at these phenomena may now be warranted. In the light of the new data, it is possible that ADP-ribose may already have been present on a fraction of the EF-2 as a result of the activity of the cellular enzyme, resulting in an underestimation of the total EF-2 levels.

Whatever the role of ADP-ribosylation of EF-2 in normal cellular physiology, it is clear that the diphtheria toxin fragment A represents a further example of a microbial product which exerts its effects by mimicking a normal cellular control process and subverting it to its own ends. Such a mechanism is consistent with the suggestion of Pappenheimer and Gill[10] that the *tox* gene of the *Corynebacterium diphtheriae* bacteriophage β, which codes for the diphtheria toxin, was originally derived from a eukaryotic gene. □

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Mike Clemens is a Cancer Research Campaign Career Development Award holder at St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE.

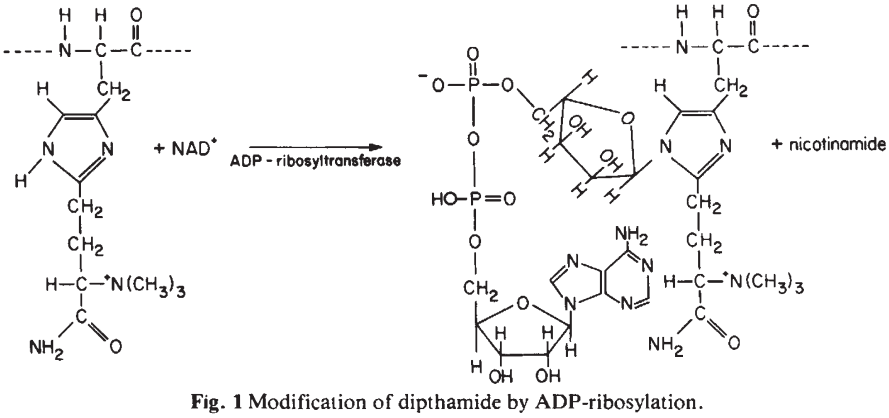

Fig. 1 Modification of dipthamide by ADP-ribosylation.