tained in an extremely stable, insoluble glass-like material. In addition, the wastes once buried should be retrievable.

If one considers the problems of seismic stability and worldwide distribution and availability of salt deposits, the overwhelming need for an international solution to the problem of the disposal of high-level radioactive wastes seems obvious.

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Posttranslational Covalent Modification of Proteins

Only 20 amino acids are used in protein synthesis, yet some 140 "amino acids" are found in various proteins.

Rosa Uy and Finn Wold

The main features of the process by which amino acids are assembled into polypeptide chains in a sequence determined by the nucleotide sequence of the genes are now well established. The process, as outlined in Table 1, is generally designated the "translation" process to emphasize that this is where the polynucleotide "language" of DNA, transcribed in messenger RNA (mRNA) molecules, is translated into the polyamino acid language of the proteins. In a strict sense, the actual translation takes place in step 1, in which each of the 20 primary amino acids is covalently attached to a specific transfer RNA (tRNA) molecule. In step 2, each of the tRNA moieties of the resulting aminoacyl-tRNA complexes is matched uniquely to a given three-nucleotide codon on the mRNA, which is bound to the synthetic machinery of the ribosomes, and the amino acid moieties are thus aligned and polymerized in the appropriate predetermined sequence. At the "full stop" codon of the mRNA, the completed polypeptide chain is released from the ribosome-mRNA complex (step 3), and the resulting linear amino acid polymer finally undergoes a number of modifications as outlined in step 4. Most current discussions of protein synthesis rather surprisingly do not include step 4. It is our thesis that since the actual gene product, the one that is most readily isolated, and the one we generally wish to characterize, is the active protein in its proper compartment of action, step 4 must be included as an essential component of the complete process of protein synthesis. Indeed, if the protein in question is subject to regulatory modulation, the form of the gene product isolated will be influenced by the modulation state (step 4b) which existed at the time of isolation. Thus, in order to understand the complete process of protein synthesis, we must understand all aspects of the processing step along with the translation and polymerization steps.

As indicated in Table 1, it is convenient to consider three distinct kinds of processing: one kind involves weak, noncovalent interactions which lead to the folding of the polypeptide chain and the association of individual chains with each other and with noncovalently bound ligands, and in turn determine the proper three-dimensional conformation of the final product. Another distinct processing step is the transport of the protein from the site of synthesis to its site of action. Considering the fact that this site of action may be an extracellular compartment or a specific intracellular organelle, it is clear that the protein may have to be transported across membranes and substantial cytoplasmic distances. Furthermore, since proteins destined for very different compartments are probably synthesized at the same site, the transport system must require a sophisticated set of traffic-directing in-

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formation signals. The third distinct processing step is the one in which the protein undergoes covalent modifications. Although it is clear that some of these modifications are reversible, they nevertheless, as a group, represent distinct chemical changes, that, if the process is arrested at a given state, can be observed as permanent alterations in the original polymer chain, or in one or more of the original 20 amino acids that were used in the synthesis of the chain. While it is useful from a didactic standpoint to consider these three physically and chemically distinct kinds of protein processing steps, it may be misleading to view them as three separate in vivo biological processes. In the cell, noncovalent and covalent modification and transport probably are integrated into a single continuous process, each one unique for each individual protein, starting in each case with the aminoacyl-tRNA's assembled at the site of synthesis and ending with the chemically modified, active protein in its proper compartment of action.

Summary. A search for derivatized amino acids in proteins has shown that the extent of posttranslational modification of proteins is quite substantial. While only 20 primary amino acids are specified in the genetic code and are involved as monomer building blocks in the assembly of the polypeptide chain, about 140 amino acids and amino acid derivatives have been identified as constituents of different proteins in different organisms. A brief consideration of the questions about where and when the derivatization reactions occur, how the specificity of the reactions is established, and how the posttranslational modifications can facilitate biological processes, reveal a need for more information on all these points. Answers to these questions should represent significant contributions to our understanding of biochemistry and cell biology.

Posttranslational Covalent Modification of Proteins

It may be useful to state briefly how the terms in this heading are used in the following discussion. On the basis of the introductory remarks, we feel that the term "posttranslational" should refer to any event that takes place after the completion of step 1 in Table 1, and that is the way it is used in this article. The term protein is used to include all proteins and low-molecular-weight peptides that have been unequivocally shown to be assembled by the ribosome-mRNA (polysome) complex. Oligopeptides, peptidoglycans, and other amino acid associations that are synthesized in the absence of ribosomes without the direct involvement of genetic information have been excluded. The term covalent modification is used in its broadest sense to include any alteration that involves breaking or making formal covalent chemical bonds.

For proteins there are two clearly distinct types of covalent modifications: peptide bond cleavage and derivatization of individual amino acids. The first of these, the cleavage of peptide bonds to convert long-chain, generally inactive precursors to shorter chain, active proteins, was originally established for the zymogen-enzyme conversion in the case of the digestive proteases—pepsin, trypsin, and chymotrypsin. Subsequent studies have established a more general involvement of posttranslational peptide bond cleavage in the processing of proteins; reviews and articles have dealt with its role and significance in blood coagulation (*1*), immunoglobulin synthesis (*2*), complement fixation (*3*), collagen synthesis (*4*), hormone activation (*5*), virus assembly (*6*), zymogen activation (*7*), and the precursor to secretory protein conversion that has emerged as a general phenomenon for pancreatic secretory proteins (the signal hypothesis) (*8*). When we also consider that all bacterial proteins are synthesized with *N*-formylmethionine as the first amino acid in the chain and that very few finished proteins retain the amino-terminal formyl group or even the methionine residue, it seems reasonable to conclude that cleavage of the peptide bond could well be a very common protein processing step.

The second type of covalent modification, the derivatization of individual amino acid residues in proteins, is the main topic of this article; one of the points we wish to make is that this processing step also is much more complex and extensive than we had expected when we first started to collect the data. It becomes obvious that a number of the derivatized amino acids are found in only a few specialized proteins and perhaps uniquely in eukaryotes (for example, the cross-link derivatives in collagen and elastin). In contrast, it should become equally obvious that examples of a substantial number of the derivatives can be found for very different kinds of proteins throughout the biological world (for example, disulfide bonds, glycoprotein, acyl proteins, phosphoproteins, methyl proteins). Until very recently our methods for analyzing protein composition

Table 1. The steps in protein synthesis.

Step	Designation	Chemical processes
1	Translation	$\text{Amino acid}_1 + \text{tRNA}_1 \longrightarrow \text{aminoacyl}_1\text{-tRNA}_1$*
2	Polymerization	$\text{Aminoacyl}_1\text{-tRNA}_1 + \text{aminoacyl}_2\text{-tRNA}_2 + \ldots + \text{aminoacyl}_{20}\text{-tRNA}_{20} \xrightarrow[\text{mRNA}]{\text{ribosomes}} \left.\begin{matrix}\text{polypeptide}\\ \text{mRNA-ribosome}\end{matrix}\right\}$*
3	Termination	$\left.\begin{matrix}\text{Polypeptide}\\ \text{mRNA-ribosome}\end{matrix}\right\} \longrightarrow \text{mRNA-ribosome} + \text{polypeptide}$
4	Processing	(a) $\text{Polypeptide} \xrightarrow[\text{modification; transport}]{\text{noncovalent and covalent}} \text{active protein in proper compartment}$
	(Activity modulation)	(b) $\text{Active protein} \xleftrightarrow[\text{covalent modification}]{\text{noncovalent and}} \text{inactive protein}$

*Although in this tabular form processing is shown to occur only with the completed polypeptide chain (step 4), it is important to note that significant modification of the primary amino acids is known to occur both at the level of the aminoacyl-tRNA and in the nascent polypeptide chain.

were selected for optimal recovery of the 20 primary amino acids after complete hydrolysis of the peptide bonds. Thus, there has been a strong experimental bias against finding any derivative whose stability is equal to or less than that of the peptide bond, and the current progress in developing more gentle methods for cleaving the peptide bonds is likely to lead to the discovery of new derivatives. Even on the basis of current knowledge, we believe that there is ample justification for including the posttranslational derivatization of amino acids as an essential and general component of protein synthesis. We further believe that the grouping together of this whole broad spectrum of different chemical reactions as a single, distinct step in protein synthesis helps to focus our attention on two fundamental biochemical and biological questions that apply uniformly to all the reactions. (i) Where in the cell and at what stage of protein synthesis does the derivatization take place? (ii) What determines the specificity of the processes in which only one or few residues of a large number of like residues are selectively derivatized? (iii) What is the relationship of any given modification to a specific biological function? This last question will have to be pursued for each individual derivatization reaction.

Tabulation of Amino Acids and Derivatives in Proteins

Our current list of derivatives found in proteins (Table 2) is considerably more extensive than that presented in other recent reviews of derivatized protein amino acids. For example, Vickery (*9*) limited his list to simple, stable derivatives, and Marshall (*10*) did not attempt to present a complete listing, but rather to illustrate the variety of derivatives with typical examples from each class of modification. We have included every example that we have been able to find (Table 2), and since we are attempting to make the point that the variety and number of derivatives are much larger and more impressive than expected, our approach has been to include even those derivatives whose existence is based on deduction from chemical properties rather than on actual isolation and structural identification. Thus, some of the derivatives in Table 2 may be found to be incorrect. However, there are undoubtedly a substantial number of derivatives that we have missed or that will be added in the future, so that the current number of about 140 natural amino acids and amino acid derivatives in proteins is more likely to increase rather than to decrease with time. In fact, we invite suggestions and corrections concerning both questionable derivatives included in Table 2 and on present and future additions.

The different designations used in Table 2 are explained in the footnotes, but a brief discussion of some of the derivatives should be included here. In addition to the 20 primary amino acids, the monomers used in the biosynthesis of all genetically coded proteins, the list contains 126 natural derivatives. An additional four derivatives (lanthionine, lysinoalanine, cysteine trisulfide, and methionine sulfoxide) could be added to the list, but according to current knowledge they are artifacts produced in vitro by relatively harsh treatments of the protein during isolation (*11*) and are therefore not natural amino acid derivatives resulting from in vivo processing of proteins. Among the 126 natural derivatives, there are 17 glycosylated amino acids (Table 2, italics). These have been tabulated and counted as single sugar residues attached to a given amino acid. This method should be acceptable for the purpose of counting distinct derivatives, but is misleading in terms of the actual structures found in glycoproteins. Protein-bound single sugars are not commonly encountered; in fact, the current evidence suggests that they are not even likely to occur transiently as biosynthetic intermediates since several oligosaccharides have been found to be assembled on lipid carriers and transferred as intact oligosaccharides to the protein acceptor to form the glycoproteins (*12*). If all the simple and complex oligosaccharides attached to each of the different amino acid attachment points were known and were listed separately, Table 2 might contain several hundred items. For the sake of simplicity and also to illustrate the fact that there appears to be a good deal of specificity in the matching of a given sugar to a given amino acid residue, we chose to list the single glycosylamino acid derivatives.

A number of derivatives, 27 to be exact, are involved in cross-links, and as such undoubtedly contribute special structural integrity to the proteins in which they occur. Many of these cross-links involve two different amino acids, and we have in those cases attempted to list the derivative under the amino acid that is activated in the cross-link formation. For example, the cross-link N^{ϵ}-(γ-glutamyl)lysine is formed through the activation of glutamine and subsequent transamidation in which the primary amine of lysine displaces ammonia to form the new "isopeptide" bond. This derivative is therefore listed under the activated parent amino acid, glutamine.

Although the majority of the derivatives involve modification of the side chains of the amino acids, a substantial number also involve the free α-amino and α-carboxyl group at each end of the polypeptide chain, mostly as N^{α}-acetyl (or N^{α}-formyl) derivatives at the NH_2-terminal end and amides at the COOH-terminal end. Derivatives of a special type that belong in this group are the aminoacyl-protein derivatives identified in a footnote to Table 2. These amino acids are transferred from the corresponding aminoacyl-tRNA derivative directly to an acceptor protein in the absence of ribosomes, and the evidence shows that it is the α-amino group of the NH_2-terminal group of the acceptor protein that is aminoacylated in each case (*13, 14*). A mammalian enzyme transfers arginine to acceptor proteins with NH_2-terminal aspartic acid, glutamic acid, and to a lesser extent cysteine (*13*), and a bacterial enzyme transfers either leucine or phenylalanine to acceptor proteins with NH_2-terminal lysine, arginine, and to a lesser extent histidine. A similar reaction involving the COOH-terminal end of the protein tubulin has recently been reported. In this case, tyrosine is added to the COOH terminus of the protein in the presence of adenosine triphosphate (ATP) (*15*). These processing steps should be classified as "silent" modifications. The product containing a new NH_2-terminal or COOH-terminal amino acid would be indistinguishable from an unmodified polypeptide chain, and only the knowledge of the nucleotide sequence of the mRNA carrying the genetic code for that protein would reveal that an extra amino acid had been added to the encoded sequence. Table 2 actually contains two definite examples of "silent" modifications, namely, the spontaneous conversion of the primary amino acids asparagine and glutamine to two other primary amino acids, aspartic acid and glutamic acid, and again only a comparison of mRNA sequence and amino acid sequence would unequivocally establish whether a given aspartic acid or glutamic acid residue in a protein was a result of direct, genetically determined incorporation of that amino acid or a result of deamidation of the corresponding amide. The deamidation reaction involved in this conversion is probably not enzyme-catalyzed; but since it is clear that the relative stability of the amides under physiological conditions is determined by the nature of the neighboring amino acids in the polypeptide chain (*16*), we consider the asparagine-aspar-

tate and glutamine-glutamate conversions as real and significant in vivo modification steps.

A brief mention should be made of the 12 derivatives listed in brackets in Table 2. Some of these derivatives have been inferred to be present in proteins without any direct evidence for their actual existence. Thus, β-hydroxytrosine and β-hydroxyphenylalanine are assumed to exist as the precursors of the corresponding glycosylated derivatives; the residue that, after reaction with nitromethane and acid hydrolysis, yields aspartic acid and that incorporates ^3H from NaB^3H_4 to give [3-^{3}H]alanine is assumed to be dehydroalanine; acid- and alkali-resistant *O*-methyl groups are assumed to represent *O*-methyl ethers of serine and threonine; dihydroxyphenylalanine is assumed to occur naturally since we know it can be produced through the action of tyrosinase on protein-bound tyrosine; and dihydroxyproline, which has been identified in acid hydrolyzates of "proteinacious material" of diatom cell walls, is assumed to come from a protein rather than from peptidoglycan-like substances. Another group of derivatives included in Table 2 in brackets (cysteine persulfide, α-ketobutyryl protein, O^4-phosphonoaspartic acid, π-phosphonohistidine, τ-phosphonohistidine, and N^ϵ-phosphonolysine) represents a large class of compounds that we find difficult to classify since they either are unstable,

Table 2. Amino acids and amino acid derivatives in proteins. The following symbols are used to identify certain classes of derivatives: [ ] indicates derivatives, the existence of which is based on indirect evidence; italics indicate glycosylamino acids. The selection of the references in the table is rather arbitrary and does not properly acknowledge the individuals who discovered the different derivatives; an attempt was made to include the most recent research articles and reviews rather than the original reports. An attempt has been made to follow the nomenclature rules recommended by the IUPAC Commission on the Nomenclature of Organic Chemistry and the IUPAC-IUB Commission of Biochemical Nomenclature. Abbreviation, ADP, adenosine diphosphate.

Primary amino acids	Secondary (derived) amino acids
Alanine	*N*-Acetylalanine (*19*); *N*-methylalanine (*32*)
Arginine	N^ω-Methylarginine (*33*); N^ω,N^ω-dimethylarginine (*34*); N^ω,$N^{\omega'}$-dimethylarginine (*35*); ADP-ribosylarginine (*36*); citrulline (*37*), ornithine (*38*); arginyl-protein*(*13*)
Asparagine	Aspartic acid (*16, 39*); N^4-(N-*acetylglucosaminyl)asparagine* (*10, 40*); N^ϵ(β-aspartyl)lysine† (*41*)
Aspartic acid	Aspartic α-amide (*42*); *N*-acetylaspartic acid (*43*); [O^4-phosphonoaspartic acid] (*44*)
Cysteine	Cystine†, [*S*-mercaptocysteine] (*45*); S-*galactosylcysteine* (*46*); S-*glucosylcysteine* (*47*); *S*-cysteinyl-heme (*48*); 8α-(*S*-cysteinyl) flavin thiohemiacetal (*49*); [dehydroalanine]‡ (*50*)
Glutamic acid	Glutamic α-amide (*42*); γ-carboxyglutamic acid (*51*); γ-methylglutamic acid (*52*)
Glutamine	Glutamic acid (*16*); glutaminamide (*53*); pyroglutamic acid (*54*); N^ϵ-(γ-glutamyl)lysine† (*55*)
Glycine	Glycinamide (*56*); *N*-acetylglycine (*19*); *N*-formylglycine (*57*); N-*glucuronylglycine* (*58*)
Histidine	Histidinamide (*59*); π-methylhistidine (*60*); [π-phosphonohistidine] (*61*); [τ-phosphonohistidine] (*61*); 4-iodohistidine (*62*); 8α-(π-histidyl)flavin (*49*); 8α-(τ-histidyl)flavin (*49*)
Isoleucine	
Leucine	Leucyl-protein (*14*)
Lysine	N^ϵ-Methyllysine (*33, 34*); N^ϵ-dimethyllysine (*33*); N^ϵ-trimethyllysine (*33, 34*); [N^ϵ-phosphonolysine] (*61*); N^ϵ-acetyllysine (*63*); N^ϵ-(phosphopyridoxyl)lysine (*64*); N^ϵ-lipoyllysine (*65*); N^ϵ-biotinyllysine (*66*); N^α-murein-lysine (*67*); allysine (*68*); dehydrolysinonorleucine† (*68*); lysinonorleucine† (*68*); allysine aldol† (*68*); dehydroallysine aldol† (*68*); dehydromerodesmosine† (*68*); merodesmosine† (*68*); dihydrodesmosines† (*68*); desmosines† (*68*); tetrahydrodesmosines† (*68*); "compound 285" † (*68*); (allysine aldol)histidine† (*69*)
	δ-Hydroxylysine (Hyl); the following compounds are derivatives of Hyl and the δ has been omitted: N^ϵ-trimethylhydroxylysine (*70*); O$^\delta$-*(β-D-galactosyl)hydroxylysine* (*71*); hydroxyallysine (*68*); (dehydrohydroxylysino)norleucine† (*68*); hydroxylysinonorleucine† (*68, 72*); (dehydrohydroxylysino)hydroxynorleucine† (*68*); (hydroxylysino)hydroxynorleucine† (*68*); syndesine† (*68*); dehydrohydroxymerodesmosine† (*68*); (dehydrohistidino)hydroxymerodesmosine† (*73*); (hydroxyallysinealdol)histidine† (*74*)
Methionine	Methioninamide (*42, 75*); *N*-acetylmethionine (*76*); *N*-formylmethionine (*77*)
Phenylalanine	Phenylalaninamide (*78*); [β-hydroxyphenylalanine] (*79*); O$^\beta$-*glycosyl-β-hydroxyphenylalanine* (*79*); phenylalanyl-protein* (*14*)
Proline	Prolinamide (*80*); [3,4-dihydroxyproline] (*81*); 4-hydroxyproline (4Hyp) (*4, 82*); 3-hydroxyproline (3Hyp) (*4, 82*); O^4-*arabinosylhydroxyproline* (*83*); O^4-*galactosylhydroxyproline* (*84*)
Serine	Pyruvate (*85*); *N*-acetylserine (*19, 30*); O^β-phosphonoserine (*86*); O^β(ADP-ribosyl-phosphono)serine (*87*); [O^β-methylserine] (*88*); O^β-(4′-phosphonopantetheine)serine (*89*); O$^\beta$-*xylosylserine* (*90*); O$^\beta$-*mannosylserine* (*91*); O$^\beta$-*(N-acetylgalactosaminyl)serine* (*92*); O$^\beta$-*galactosylserine* (*93*)
Threonine	[α-Ketobutyrate] (*94*); *N*-acetylthreonine (*95*); O^β-phosphonothreonine (*86, 96*); [O^β-methylthreonine] (*88*); O$^\beta$-*fucosylthreonine* (*97*); O$^\beta$-*mannosylthreonine* (*98*); O$^\beta$-*(N-acetylgalactosaminyl)threonine* (*92*); O$^\beta$-*galactosylthreonine* (*93*)
Tryptophan	
Tyrosine	Tyrosinamide (*99*); tyrosine O^4-sulfate (*100*); 3-iodotyrosine (*62*); 3,5-diiodotyrosine (*62*); 3-chlorotyrosine (*101–103*); 3,5-dichlorotyrosine (*103*); 3-bromotyrosine (*102, 103*); 3,5-dibromotyrosine (*102, 103*); 5-bromo-3-chlorotyrosine (*103*); 3,5,3′-triiodothyronine† (*104*); 3,5,3′,5′-tetraiodothyronine† (*104*); 3,3′-bityrosine† (*105*); 3,3′;5′,3″-tertyrosine† (*105*); O^4-adenylyltyrosine (*106*); O^4-uridylyltyrosine (*107*); [β-hydroxytyrosine] (*79*); O$^\beta$-*glycosyl-β-hydroxytyrosine* (*79*); [dihydroxyphenylalanine] (*108*); proteinyltyrosine* (*15*)
Valine	Valinamide (*42*); *N*-acetylvaline (*109*)

*These designations, aminoacyl-protein or proteinyl-amino acid, are used to list derivatives produced by the direct transfer of the aminoacyl moiety of aminoacyl-tRNA or of free amino acids to acceptor proteins. Since several amino acids are derivated in these reactions, the derivatives have been listed under the amino acid that is transferred. †These derivatives constitute protein cross-links. ‡ The in vivo precursor of dehydroalanine is unknown. Since dehydroalanine is known to be a product of alkali treatment of cystine in vitro, it has been tabulated as a derivative of cysteine.

transient derivatives or are formed only as intermediates in the catalytic action of specific enzymes. We have deliberately omitted a large number of derivatives that have been established to occur only as such transient intermediates in enzyme catalysis (for example, several thiol esters and hemiacetals, Schiff bases of lysine amino groups, and acylated serine residues), and perhaps some members of this last group of six derivatives should have been omitted as well. The reason for including them is to emphasize that this area of ambiguity does exist, and to suggest that some derivatives that are shown to be formed as transient intermediates in enzyme-substrate interactions in some cases also could be the result of true posttranslational modification in other systems.

Where and When Does the Chemical Modification Take Place?

A good deal of information on these points is available on individual proteins and in individual cells and organisms, and it is beyond the scope of this article to attempt to review all the individual cases. Considering all the derivatives in Table 2, it is clear that the posttranslational modifications can occur at any stage of protein synthesis from the level of free aminoacyl-tRNA (the products of step 1 in Table 1) to the level of completed proteins released from the synthetic machinery of the mRNA-ribosome complex and in the process of being transported to its ultimate compartment. Thus, in prokaryotes methionyl-tRNA (Met-tRNA^{fMet}) is converted to formylmethionyl-tRNA (fMet-tRNA^{fMet}) prior to its incorporation as the NH_2-terminal amino acid in the polypeptide chain (*17*), and it also appears that pyroglutamic acid (pyrrolidone carboxylic acid) (*18*) and perhaps even some *N*-acetylamino acids (*19*) are formed at this level. There is good evidence that some modification reactions take place in the nascent polypeptide chain still attached to the polysomes; hydroxylation of lysine and proline (*4*), the removal of the formyl group from the coat protein of a prokaryotic RNA virus (*20*), some disulfide bond formation (*21*), some N^{α}-acetylation (*22*), and some glycosylation reactions (*10*) are examples of this.

The majority of the modification reactions appear to occur after the completion of the polypeptide chain and its release either to the cytosol, or to the membrane system of the endoplasmic reticulum and the Golgi complex, to storage granules or, indeed, during and after transport to distinct organelles or to extracellular space. Illustrations of the variety of sites involved in protein processing can readily be given; the evidence is generally based on finding the appropriate enzyme in a given compartment. Thus, the presence of protein kinases in cytosol, in various membranes, and in the nucleus (*23*) and of protein methylases in cytosol and in the nucleus (*24*) suggests that those processing steps occur in these compartments. A large number of processing enzymes are associated with the endoplasmic reticulum and the Golgi complex, and it has been concluded that most of the protein glycosylation, halogenation, disulfide bond formation, and probably also some acylations take place at these sites. Peptide bond cleavage occurs in secretory granules and also extensively in extracellular space, and it also appears that a majority of the complex cross-links derived from lysine and hydroxylysine, the isopeptide cross-links [N^{ϵ}-(γ-glutamyl)lysine and N^{ϵ}-(β-asparty l)lysine] and the iodotyrosine ether cross-links are formed in extracellular compartments after secretion of the precursor proteins. While most of the reactions involved in protein processing appear to be enzyme-catalyzed, it is perhaps of some importance to note that some (for example, asparagine to aspartic acid, glutamine to glutamic acid, cross-linked derivatives formed from oxidatively deaminated lysine and hydroxylysine) can occur spontaneously without the involvement of specific catalysts. Thus, when we consider all the reactions involved in the posttranslational modification of all the proteins of a given organism, it is obvious that the total process is extremely complex both in terms of biochemistry and cell biology.

What Determines the Specificity of the Processing Reactions?

It is well established that the posttranslational modification reactions are restricted to one or several specific amino acid residues of each kind, and never involves all of them. Consequently, the reactions must be guided by some recognition process by which specific residues are selected for modification. Perhaps the best way to approach this question at this time is to propose some broad principles that may have general validity even if they do not provide much detailed information. First of all, it must be correct to state categorically that the specificity of the chemical modification reactions involving aminoacyl-tRNA is determined by the tRNA and not by the amino acid attached to it. In the case of the formation of *N*-formyl-Met-tRNA in *Escherichia coli*, for example, a single enzyme catalyzes the formation of two distinct Met-tRNA products, Met-tRNA^{Met} and Met-tRNA^{fMet}, differing only in the structure of the tRNA moiety. Only one of these derivatives, Met-tRNA^{fMet}, is an acceptor for the formyl group and can be converted to the desired *N*-formyl-Met-tRNA^{fMet} product (*25*). Additional support for this point can be derived from the recent finding that artificially produced N^{ϵ}-acetyllysyl-tRNA^{Lys} was incorporated into hemoglobin almost as efficiently as was the natural unmodified lysyl-tRNA^{Lys} (*26*). On the basis of current knowledge, it further appears safe to state that the specificity of any modification of the nascent polypeptide chain that takes place before a substantial amount of three-dimensional structure has been formed must be determined by the amino acid sequence around the susceptible residues, and further that modification of completed and folded polypeptide chains also should be determined primarily by the amino acid sequence, but with the possible additional restriction that the appropriate sequence must be available on the surface of the protein molecule (*27*).

A good deal of accumulated evidence supports the proposition that the amino acid sequence is the main specificity determinant in the in vivo modification of proteins. Thus, it has been deduced that in order for an asparagine residue to be glycosylated, it must be in a sequence -Asn-X-Thr(Ser)- (*10*), that protein kinases will phosphorylate serine or threonine only when they exist in a sequence -Arg-X-Y-(Z)-Ser-(Thr)- (*28*), and that hydroxylases require the sequences -X-Pro-Gly- or -X-Lys-Gly to catalyze the hydroxylation of proline or lysine (*4*). Unfortunately, there are exceptions to these specificity rules both in terms of proper sequences that are not modified and improper sequences that appear to act as substrates, and the present models are obviously not sophisticated enough to explain the full range of specificities observed.

A general puzzle associated with the specificity aspect of protein processing is the observation that in a given protein population only a fraction of the molecules of one kind are modified. Thus, bovine pancreatic ribonuclease is secreted as a mixture of nonglycosylated and glycosylated forms (*29*), one of the *Escherichia coli* ribosomal proteins is a mixture of N^{α}-acetylated and nonacetylated forms (*30*), and histone acetylation is al-

so known to occur unequally on a given population of histones (*31*). We can broaden our current models by considering compartmentization of different modification enzymes, but it would appear that this merely amounts to asking the same question about specificity in another way: what specificity determinants direct a given protein to a given compartment during the processing steps? Some of the main difficulties in arriving at coherent and specific answers to the questions about specificity at this time are related to the paucity of information and the fact that we compare data from many different species. Part of the complete answer may be that different forms have developed different, specific recognition signals along with their special processing reactions.

Why Do Proteins Undergo Posttranslational Modification?

Some of the modification reactions that have been established to date have fairly obvious explanations. The derivatives in which a coenzyme is covalently linked to an enzyme would appear to fit in this category, and if we accept the general premise that cross-links represent an important means of stabilizing a given protein structure, then the evolution of the various kinds of cross-links also has a reasonable rationale. It is known that thyroglobulin, a glycoprotein whose molecular weight is 670,000, is processed by iodination and ether formation and then completely degraded to release the modified amino acid thyroxin as the desired end product, and we can rationalize this complicated and expensive means of synthesizing a small hormone as a natural evolutionary way to ensure a fine control of the rapid production and release of this physiologically active compound. There are some exciting possibilities that the oligosaccharides of glycoproteins together with sugar-specific lectins may represent the key to important intercellular and intermolecular communication processes. We know that phosphorylation-dephosphorylation reactions and some acetylation and methylation reactions represent on-off switches for the activity of many enzymes and regulatory proteins, and we can consider the malonic acid moiety of γ-carboxyglutamate as a unique chelating structure; at the same time we know that there are stable phosphoproteins, stable acyl proteins and methyl proteins, and we also know of many metal-binding proteins without γ-carboxyglutamate; therefore, it is clear that many of the answers at present are tentative and incomplete. For a number of the modification steps (N^{α}-acetylations and many methylation and halogenation steps, for example) we do not even have tentative answers.

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The Natural Resources Program at the United Nations University

Walter Shearer-Izumi

The new United Nations University, which began its initial operations in September 1975, now includes programs on the alleviation of world hunger, on human and social development, and on the use and management of natural resources. From its temporary headquarters in the Toho Seimei Building in Tokyo, the university, under the direction of Rector James M. Hester, former president of New York University, is beginning to fulfill its mandate to organize top scientific and scholarly collaboration to help identify and alleviate pressing global problems of human survival, development, and welfare. This new university does not have a campus, students, or degree courses, but rather it was founded on a unique concept whereby it operates from the central planning and coordinating center in Tokyo through networks of institutions and scholars all over the world.

In order to achieve its goals, the U.N. University organizes associated institutions and scholars to (i) identify critical international problems, (ii) to undertake internationally coordinated research and advanced training, (iii) to strengthen research and advanced training resources in developing countries, (iv) to disseminate the research results both to scholars and decision-makers, and (v) to encourage mission-oriented multidisciplinary research and advanced training. While the U.N. University is sponsored by the United Nations and the U.N. Educational, Scientific and Cultural Organization (Unesco), the university is not an intergovernmental organization, but an autonomous academic institution with financial independence and guaranteed academic freedom in the choice of subject matter, participating institutions, and individuals.

Among the three program areas of the university, the natural resources program is the newest, having just begun in February 1977 under the direction of Vice-Rector Walther Manshard, former director of the Institute of Geography at the University of Freiburg, Federal Republic of Germany. This is the U.N. University's response to the serious resource supply and management problems felt by people all over the world. As with the other program areas, all decisions on program priorities and implementation are made after extensive meetings and consultations with scientists and experts in order to draw upon their knowledge and experience, and after consultation with other organizations of the U.N. family, such as Unesco,

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