About 27 years ago, Goldstein isolated a protein which he identified as a lymphocyte differentiation promoting factor, and which he called ubiquitin (Goldstein and Dayhoff, 1975) as he thought it was probably ubiquitous to living cells. A few years later, the non-histone protein component of the nuclear protein A24 was identified as ubiquitin (Hunt *et al*., 1977) and A24 was found to be a covalent adduct of ubiquitin and histone H2A. The ubiquitin is conjugated to H2A by formation of an isopeptide bond between a lysine side-chain ε-amino group and the carboxyl terminus of ubiquitin (Goldknopf *et al*., 1977). So this appeared to be a new role for ubiquitin, and established that ubiquitin could be conjugated to other proteins.

While protein synthesis was well understood, the breakdown of proteins back to amino acids in the cell was only poorly understood. However it was realised that proteins were continually synthesised and degraded in cells, and that some proteins turned over more rapidly than others. The lysosome system of mammalian cells was known to degrade intracellular proteins but this didn't give the clue about how could protein degradation occur in rabbit reticulocytes (the precursors of erythrocytes) since this cells lack lysosomes. Therefore, rabbit reticulocytes became a useful cell model to study non-lysosomal intracellular proteolysis. A soluble (cytosolic) proteolytic system in reticulocytes was found, surprisingly, to be ATP-dependent (Etlinger and Goldberg, 1977) Fractionation of reticulocyte "lysate" (cytosol) generated two fractions (I and II) which were required for at least some of the ATP-dependent proteolysis of some test proteins. The active factor in Fraction I called APF-I was purified, and was found to be covalently conjugated to proteins in the presence of ATP and Fraction II (Ciechanover *et al*., 1980). APF-I was then shown to be identical to ubiquitin (Wilkinson *et al*., 1980).