A. Introduction

As reviewed in Chap. 3, this volume, glucagon-like peptide-1 (GLP-1) is the designation given to the sequence in proglucagon corresponding to residues Nos. 72–108 (Bell et al. 1983a, 1983b). In proglucagon, this sequence is flanked by pairs of basic amino acid residues, i.e., typical processing cleavage sites, and shows an almost 50% homology with glucagon itself; hence its designation. Early immunochemical studies indicated that the proteolytic processing of proglucagon would, indeed, lead to the formation of this peptide, but mainly in the intestinal mucosa, whereas in the pancreas this sequence was contained in the “major proglucagon fragment” as predicted by Patzelt (Mojsø et al. 1986; Ørskov et al. 1986; Patzelt and Schlitz 1984). Synthetic replicas of this sequence, which were soon made available after the structure of proglucagon had been deduced (Bell et al. 1983b), were reported to exhibit weak insulinotropic activity (Schmidt et al. 1985), but most investigators found the peptide inactive (Ørskov 1992). Physiological and pathophysiological studies had clearly shown that the distal intestinal mucosa, in which the glucagon gene is being expressed in the so-called L cells (Mojsø et al. 1986; Novak et al. 1987), contained an insulinotropic hormone distinct from gastric inhibitory polypeptide (GIP) (Ebert 1990; Lauritzen et al. 1980; Moody et al. 1970; Novak et al. 1987). Therefore, a search for alternative products of intestinal expression of the glucagon gene was carried out, and it turned out that intestinal extracts contained a peptide with GLP-1-like immunoreactivity which was potently insulinotropic (Holst et al. 1986, 1987). Upon structural analysis, this peptide was found to correspond to a truncated form of GLP-1 (Holst et al. 1986, 1987). Further chemical analysis showed that the structure corresponded to proglucagon 78–107 amide (Ørskov et al. 1989a). A synthetic replica of this peptide turned out to be the most potent insulinotropic peptide hitherto isolated (Ørskov 1992). The glycine-extended peptide, proglucagon 78–108, a probable processing intermediate, was equally insulinotropic (Mojsø et al. 1987). This discovery, that alternative processing of the glucagon precursor gave rise to novel biologically active products, prompted further investigations of proglucagon processing in humans, and today a complete picture of proglucagon processing in human gut and pancreas can be assembled (Buhl et al. 1988; Holst et al. 1994a; Ørskov et al. 1996).
This was possible by combining, on one hand, gel permeation chromatography of unfractionated extracts using processing-independent radioimmunoassays for the various regions of proglucagon and, on the other hand, isolation and chemical structural analysis of each of the products identified. Using this approach the possibility that some products might escape detection was minimized.

Thus, in humans (Fig. 1) the pancreatic processing of proglucagon (henceforth designated PG) leads to the formation of (a) glicentin-related pancreatic peptide corresponding to PG 1-30, originally isolated from porcine pancreas (Moody et al. 1981; Thim and Moody 1982); so far this peptide has not been associated with any known biological activity; (b) glucagon itself, occupying positions 33-61 in PG; (c) a hexapeptide (sometimes designated intervening peptide-1) corresponding to PG 64-69 (Holst et al. 1994a; Yanaihara et al. 1985; Kadowaki et al. 1985); and (d) the major proglucagon fragment (MPGF) corresponding to PG 72-158 (Holst et al. 1994a). A small fraction of MPGF may be further processed to PG 72-107, i.e., full-length GLP-1 (Holst et al. 1994a). In humans almost all of this peptide occurs in its amidated form, less than 5% remaining glycine-extended (= PG 72-108) (Ørskov et al. 1994). In agreement with the formation of small amounts of GLP-1, human pancre-