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MINIREVIEW

Proposed Uniform Nomenclature for the Proteins and Protein Domains of the Bacterial Phosphoenolpyruvate:Sugar Phosphotransferase System

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The phosphoenolpyruvate:sugar phosphotransferase system (PTS) consists of two general energy-coupling proteins, enzyme I and HPr, as well as the sugar-specific permeases, commonly referred to as the enzyme II complex (15, 19, 24, 26). The system catalyzes the concomitant transport and phosphorylation of its sugar substrates in a process termed group translocation (16, 25). The PTS permeases found in a variety of bacteria may consist of one, two, three, or four distinct polypeptide chains and, in certain instances, some of these sugar-specific proteins are fused to protein domains which serve the general energy-coupling function(s) of enzyme I and/or HPr (8, 31, 34) (see Fig. 1 and 2 for schematic depictions). Evidence suggesting that the entire enzyme II complex is required for concomitant sugar transport and phosphorylation but that enzyme I and HPr merely function to phosphorylate this complex has been presented (4, 9). The enzyme II complex should therefore be considered the functional unit designated permease in this paper.

Recent sequence comparison studies have shown that most of the PTS permeases are homologous, i.e., derived from a common ancestral protein (13, 21, 28, 33). These group translocators, comprising the major group of the enzyme II complexes, generally have similar molecular weights of about 68,000, corresponding to about 635 total amino acyl residues (31). Most of them consist either of a single polypeptide chain, commonly termed enzyme II, or of two proteins, commonly called an enzyme II-III pair or an enzyme IIB-IIA pair (15, 31). In a few cases, these permeases consist of three or four proteins (6, 14, 22). Regardless of the number of polypeptide chains in each of these permeases, there are always at least three well-recognized functional domains: a hydrophobic transmembrane domain which binds and transports the sugar substrate (10), a hydrophilic enzyme III-like domain which possesses the first phosphorylation site (always a histidyl residue [31]), and a second hydrophilic protein or protein domain which possesses the second phosphorylation site (either a cysteyl residue, as for the major group of homologous PTS permeases [1, 18, 22] [see Fig. 3], or a histidyl residue, as for a splinter group of three distinct sequenced PTS permeases which catalyze the transport and phosphorylation of mannose in *Escherichia coli*, fructose [to yield fructose 6-phosphate] in *Bacillus subtilis*, and sorbose in *Klebsiella pneumoniae* [5, 12a, 14]). These three permeases of the splinter group lack sufficient sequence similarity with the major group of PTS permeases to establish homology with them, but they are clearly homologous to each other.

At the present time, well over 12 PTS permeases have been completely sequenced. While the permeases within the major group are homologous, sequence comparisons have revealed that during their evolution, the various hydrophilic and hydrophobic domains have become either fused to each other in different orders and combinations or spliced from each other to become distinct polypeptide chains (2, 13, 22, 31, 34). The various possibilities are illustrated in Fig. 1 and 2. In some cases, sequence similarities among permeases are insufficient to establish homology, either for all or for part of a particular permease complex. Regardless of whether a PTS permease consists of one, two, three, or four polypeptide chains, the entire complex must probably be present in association with the membrane to efficiently transport sugar (4, 5, 9). It therefore seems that the proteins which constitute a PTS permease function as an enzyme unit, the enzyme II complex, and that the number of polypeptide chains as well as the order of the domains within any one protein constituent of a PTS permease is largely immaterial to the function of that permease.

At present there is no uniform nomenclature for the proteins and protein domains of the PTS. Thus, the term enzyme II is currently used for the protein constituent of the PTS that spans the membrane, forms a transmembrane channel (29), and provides the sugar binding site (10). However, as illustrated in Fig. 2, recent studies have established that the enzyme II protein may contain as part of its polypeptide chain none (II^{Man} and II^{Cel}), one (II^{Glc} and II^{Scr}), or two (II^{Mtl} and II^{Nag}) of the hydrophilic, sugar-specific energy-coupling domains. When one or both of the latter domains is lacking from enzyme II and the protein has a single cytoplasmic polypeptide chain, that cytoplasmic protein is referred to as enzyme III. Enzyme III (also sometimes called factor III or enzyme IIA) may consist of a single domain (III^{Glc}, III^{Lac}, and III^{Gut} in Fig. 2) or of two fused domains (III^{Man} in Fig. 2). When the two hydrophilic domains are present in distinct water-soluble proteins, those proteins are referred to as enzyme III and enzyme IV (III^{Cel} and IV^{Cel} in Fig. 2) or are given names based on the genes encoding them (e.g., LevD and LevE of the *B. subtilis* fructose permease [forming fructose 6-phosphate] shown in Fig. 2). To make matters even more confusing to the uninitiated, the integral membrane enzyme II may consist of two distinct polypeptide chains (the II-P^{Man} and II-M^{Man} proteins of the mannose permease of *E. coli* and the LevF and LevG proteins of the fructose permease [fructose 6-phosphate forming] of *B. subtilis*) (Fig. 2). Finally, in one case, that of the nonhomologous glucitol enzyme II, a hydrophilic domain, probably that bearing the second phosphorylation site, separates the two portions of the membrane-embedded moiety (designated C and C′ in Fig. 2).

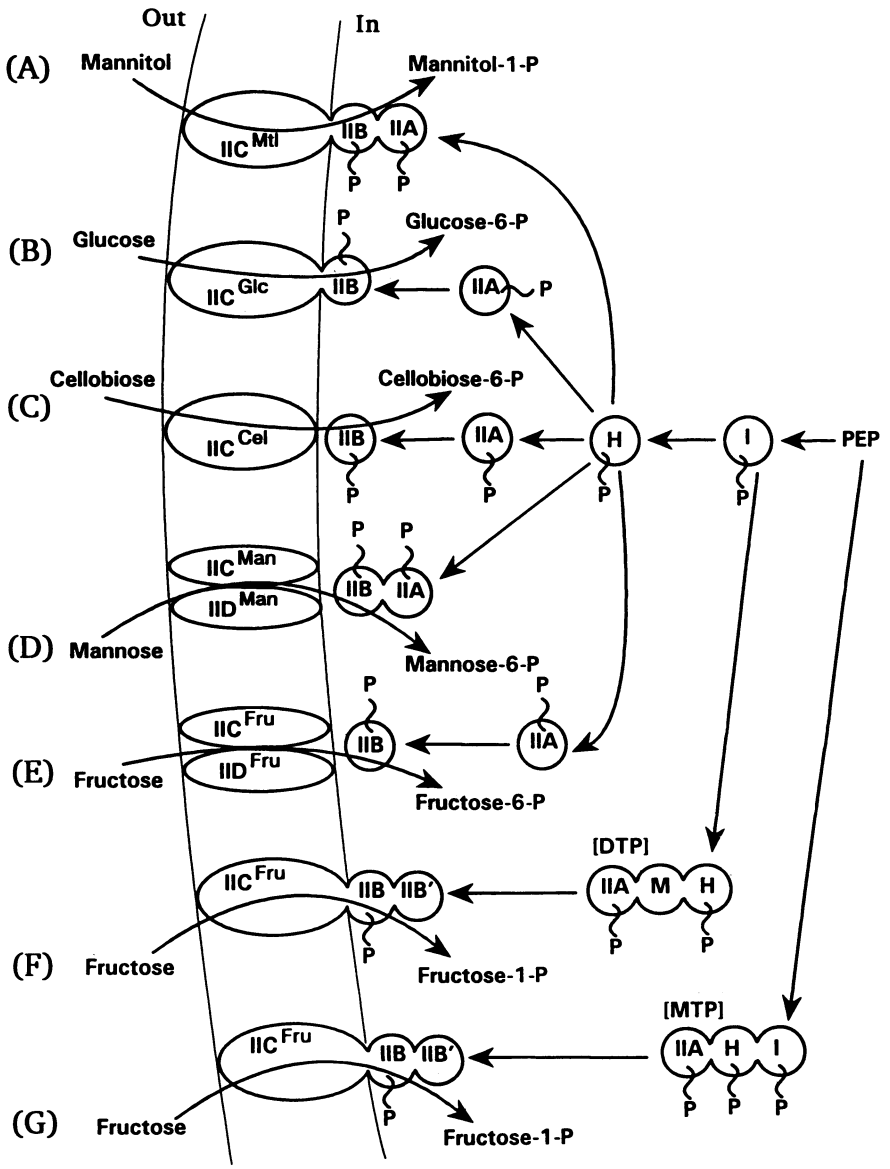

FIG. 1. Schematic depiction of representative PTS permeases and their energy-coupling proteins found in enteric bacteria (A to D and F), *B. subtilis* (E), and *R. capsulatus* (G). Only proteins of the PTS and their functional domains are depicted. DTP (previously referred to as III^{Fru} or FPr) is the diphosphoryl transfer protein of *S. typhimurium* (F) which bears the enzyme IIA domain (IIA), a central domain (M), and an HPr-like domain (H) in a single polypeptide chain. MTP is the multiphosphoryl transfer protein of *R. capsulatus* (G) which contains the functional and structural equivalents of enzyme IIA (IIA), HPr (H), and enzyme I (I) in a single polypeptide chain (34). The fructose IIB'BC proteins of both *E. coli* and *R. capsulatus* (F and G, respectively) have duplicated B domains, but only the second B domain (not the first B' domain) is believed to be functional in phosphoryl transfer. The domain order within the various polypeptide chains is not indicated in this figure but is provided in Table 1 and Fig. 2. All abbreviations are as defined in Table 1 and the text, except that species designations have been omitted for simplicity. P, phosphate; PEP, phosphoenolpyruvate.

In this article, we review the functions, structures, and evolutionary relationships of the protein domains of all sequenced PTS permeases and, on the basis of these considerations, propose a uniform nomenclature which serves to specify the domains in a PTS protein as well as to designate the order of homologous domains within that protein. This nomenclature, which takes into account all biochemical, genetic, and molecular biological information currently available, corrects, extends, and refines that originally suggested by Kundig and Roseman (12) and based solely on the biochemical data available in 1970. The following rules serve to define this proposal. (i) Each PTS permease is referred to as enzyme II or an enzyme II complex (designated as II). When sequence data are not available for such a protein or when one wishes to refer to the entire permease in general terms, no further refinement of the designation is needed. (ii) The specific domains of the various sequenced permeases are referred to by letter (after "II") as follows: the hydrophilic domain bearing the first phosphorylation site is termed A; the hydrophilic domain bearing the second phosphorylation site is termed B; the principally hydrophobic domain presumed to bear the transmembrane channel (29) and sugar binding site (10) is termed C; and the homologous, partially hydrophobic proteins of

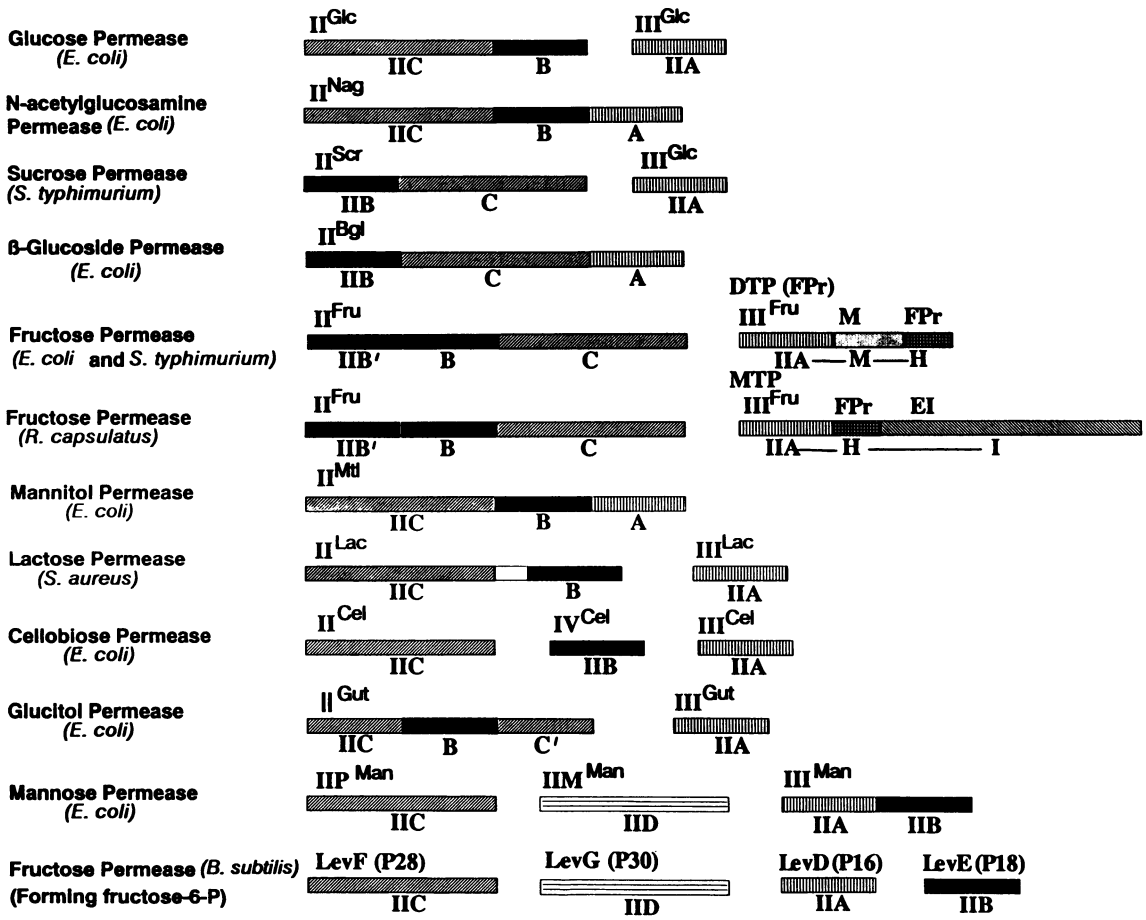

FIG. 2. Schematic depiction of representative PTS permeases showing the different known permutations of the constituent proteins and domains. The different portions or domains of the various proteins are indicated as follows: ▨, hydrophobic transmembrane domain (IIC); ▥, the domain bearing the first phosphorylation site (IIA); ■, the domain bearing the second phosphorylation site (IIB); ▦, an HPr-like domain (H); ▤, a partially hydrophobic transmembrane domain of unknown function (IID); ▩, a nonhomologous domain of unknown function; ▧, an enzyme I-like domain (I). All permeases shown exhibit convincing regions of homology, except for the last three, and the last two are homologous to each other. The designations for these proteins which are most frequently in current use are indicated above the bars representing these proteins, while the proposed uniform domain nomenclature is given below the bars. Information about most of the permeases shown can be found in references 13 and 31, with the following exceptions: the fructose permease of enteric bacteria (8, 20), the fructose permease of *R. capsulatus* (33, 34), the cellobiose permease of *E. coli* (17, 22), and the fructose permease (forming fructose 6-phosphate) of *B. subtilis* (14). The B′ domains in the fructose enzyme II complexes of *E. coli* and *R. capsulatus* are discussed in the legend to Fig. 1. The C′ domain in glucitol enzyme II refers to the second half of the hydrophobic (IIC) domain. DTP and MTP are as defined in the legend to Fig. 1.

the splinter group PTS permeases are termed D. This last class of proteins, currently referred to as the IIM protein of the *E. coli* mannose system (6) or the LevG protein of the fructose permease (fructose 6-phosphate forming) of *B. subtilis* (14), has not been studied in detail, and although it is known to be an essential constituent of the permeases, its specific function is unknown. Like the IIC protein, this class of proteins may consist of more than a single domain and may participate in channel formation. (iii) The order of the protein domains in a given PTS protein (N terminus to C terminus) is designated by the order of the letters which represent the protein domains. (iv) Following the designation for a particular protein, the sugar specificity is indicated by a three-letter superscript abbreviation of that sugar, while the bacterial species from which the protein was derived can be indicated by a subsequent three-letter superscript abbreviation of the name of that species. When ambiguity arises in the designation of the sugar specificity of two or more enzymes II with overlapping specificities, alternative sugar substrates (e.g., II^{Man} versus II^{Glc}) or a designation indicating the range of sugar substrates (e.g., II^{Bgl} for β-glucoside enzyme II) should be used. The three-letter species designation is derived from the first letter of the genus name, capitalized, followed by the first two letters of the species name (e.g., Sty for *Salmonella typhimurium* and Sth for *Streptococcus thermophilus*). (v) Enzyme I and HPr or enzyme I-like and HPr-like domains are designated I and H, respectively. (vi) A domain of structure and function unrelated to or not known to be related to the homologous domains exhibiting an essential PTS permease function is designated by an alternative letter. For the designation of novel domains and/or proteins of the PTS or for correction of errors in the current system, the authors have agreed to serve as a "clearing house" for the approval of new designations.

The protein and domain designations of all of the currently

TABLE 1. Domain structures of sequenced PTS permeases[a]

Cluster	Sugar	Organism	Domain structures of permease proteins
1	Sucrose (Scr)	*Salmonella typhimurium*	$IIBC^{Scr,Sty} + IIA^{Glc,Sty}$
	Sucrose (Scr)	*Bacillus subtilis*	$IIBC^{Scr,Bsu} + IICBA^{Glc,Bsu}$
	Sucrose (Scr)	*Streptococcus mutans*	$IIBCA^{Scr,Smu}$
	β-Glucoside (Bgl)	*Escherichia coli*	$IIBCA^{Bgl,Eco}$
2	Glucose (Glc)	*Escherichia coli*	$IICB^{Glc,Eco} + IIA^{Glc,Eco}$
	Glucose (Glc)	*Bacillus subtilis*	$IICBA^{Glc,Bsu}$
	N-Acetylglucosamine (Nag)	*Escherichia coli*	$IICBA^{Nag,Eco}$
3	Fructose (Fru)	*Escherichia coli* and *Salmonella typhimurium*	$IIB'BC^{Fru,Eco} + IIAMH^{Fru,Sty}$
	Fructose (Fru)	*Rhodobacter capsulatus*	$IIB'BC^{Fru,Rca} + IIAHI^{Fru,Rca}$
	Mannitol (Mtl)	*Escherichia coli*	$IICBA^{Mtl,Eco}$
	Mannitol (Mtl)	*Staphylococcus carnosus*	$IICB^{Mtl,Sca} + IIA^{Mtl,Sca}$
4	Lactose (Lac)	*Staphylococcus aureus*	$IICB^{Lac,Sau} + IIA^{Lac,Sau}$
	Cellobiose (Cel)	*Escherichia coli*	$IIC^{Cel,Eco} + IIB^{Cel,Eco} + IIA^{Cel,Eco}$
5	Glucitol (Gut)[b]	*Escherichia coli*	$IICBC'^{Gut,Eco} + IIA^{Gut,Eco}$
6	Mannose (Man)	*Escherichia coli*	$IIC^{Man,Eco} + IID^{Man,Eco} + IIAB^{Man,Eco}$
	Fructose (Fru)[c]	*Bacillus subtilis*	$IIC^{Fru,Bsu} + IID^{Fru,Bsu} + IIB^{Fru,Bsu} + IIA^{Fru,Bsu}$
	Sorbose (Sor)	*Klebsiella pneumoniae*	$IIC^{Sor,Kpn} + IID^{Sor,Kpn} + IIB^{Sor,Kpn} + IIA^{Sor,Kpn}$

[a] The newly proposed nomenclature is used to designate the PTS proteins as well as the order of homologous domains within each of the distinct polypeptide chains. For a clarification of the structural features of these proteins and of their designations, see Fig. 1 and 2.

[b] The B domain in the $IICBC'^{Gut}$ protein appears to be flanked by the two halves of the C domain (here designated C and C') (35, 36).

[c] This system phosphorylates fructose at the 6-position rather than the 1-position and therefore resembles the mannose system of *E. coli* catabolically as well as structurally. It also exhibits sequence similarity to the sorbose system of *K. pneumoniae* (12a).

sequenced PTS permeases are provided in Table 1. On the basis of sequence similarities, members of the major group of homologous PTS permeases fall into four groups, regardless of the domain analyzed. Figure 3 shows a phylogenetic tree for those parts of the hydrophobic transmembrane domains (IIC domains) which show the greatest degree of sequence identity among the various homologous PTS permeases (21, 28, 33). The sucrose and β-glucoside permeases form a cluster (cluster 1) of closely related permeases (Fig. 3). In all of these permeases, the domain bearing the second phosphorylation site (B) precedes the hydrophobic transmembrane domain (C), and these two domains constitute a single polypeptide chain (Fig. 2). In some of these permeases (the sucrose permeases of *S. typhimurium* and *B. subtilis*),

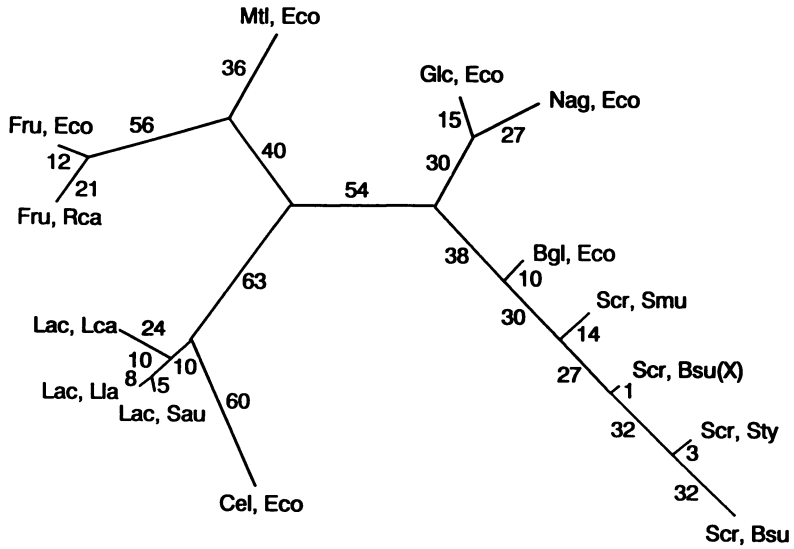

FIG. 3. Phylogenetic tree of the hydrophobic segments of several homologous PTS permeases. The segments analyzed correspond to the second halves of the IIC domains of the PTS permeases, i.e., those regions showing the greatest degree of sequence identity (33). Relative distances are provided adjacent to the branches. The three-letter abbreviations for sugars and species are as provided in Table 1. Lca and Lla denote *Lactobacillus casei* and *Lactococcus lactis*, respectively. The programs of Doolittle and Feng (3) and Feng and Doolittle (7) were used to calculate evolutionary distances.

the A domain is a distinct protein, but in others (the sucrose permease of *Streptococcus mutans* and the β-glucoside permease of *E. coli*), the A domain is fused to the C terminus of the C domain (Table 1) (28). In the former two cases, the A domain is actually the enzyme III^{Glc} protein or domain (21, 28) and is consequently designated IIA^{Glc}. The sucrose permease of *S. typhimurium* is thus designated $IIBC^{Scr,Sty}$ + $IIA^{Glc,Sty}$, and the *E. coli* permease specific for β-glucosides is designated $IIBCA^{Bgl,Eco}$ (Table 1).

In the glucose and *N*-acetylglucosamine permeases, which constitute the second cluster, the C domain precedes the B domain (Fig. 3) (28). Only in the glucose permease of *E. coli* is the A domain a distinct polypeptide chain. Therefore, this permease is designated $IICB^{Glc,Eco}$ + $IIA^{Glc,Eco}$, whereas the *N*-acetylglucosamine permease of *E. coli* is designated $IICBA^{Nag,Eco}$ (Table 1 and Fig. 2).

The mannitol and (fructose 1-phosphate-forming) fructose permeases constitute the third permease cluster (Fig. 3). The sequenced (fructose 1-phosphate-forming) fructose permeases are structurally more complex than the other PTS permeases, as they bear an internal duplication of the B domain (the B and B′ domains shown in Fig. 1 and 2, both of which precede the C domain), and the second protein, bearing the A domain, has this A domain fused to other energy-coupling protein domains (8, 33, 34). The latter domains in the fructose permease of *S. typhimurium* include a C-terminal HPr-like domain (here designated H) and a central domain which does not show sequence similarity with any other sequenced PTS protein domain (here designated M). The corresponding protein from *Rhodobacter capsulatus* lacks the M domain, but it possesses both the H (HPr) domain and an I (enzyme I) domain (34). In the mannitol permease of *E. coli*, the C domain precedes the B and A domains, which together constitute a single polypeptide chain, but in the mannitol permeases of bacilli and staphylococci, the A domains form distinct polypeptide chains. Designations for these proteins are provided in Table 1 and Fig. 2.

The lactose and cellobiose permeases constitute the fourth permease cluster (Fig. 3) (22, 28). While the domain structure of the three sequenced lactose permeases resembles that of the glucose permease of *E. coli*, that of the *E. coli* cellobiose permease is unique in comparison with presently sequenced PTS permeases in that each of the three known domains constitutes a distinct polypeptide chain (17, 22). Thus, the latter permease is designated IIA^{Cel} + IIB^{Cel} + IIC^{Cel}.

The remaining PTS permeases listed in Table 1 do not exhibit sufficient sequence similarity with the major group of PTS permeases to establish homology. The glucitol permease, which alone constitutes cluster 5, is unique in that what is probably the B domain is sandwiched between two hydrophobic domains, termed C and C′ in Fig. 2, each half the size of the usual C domain (36). However, in many respects this permease resembles the others (30, 35).

The remaining three permeases (the splinter group) constitute cluster 6. In these homologous cluster 6 permeases, there are two integral membrane proteins rather than one; one is largely embedded in the membrane, and the other probably traverses the membrane only twice (6, 12a, 14). The former protein is superficially analogous in structure to the IIC domain of other PTS permeases and is therefore designated IIC, while the partially hydrophilic transmembrane protein, which does not possess a recognizable counterpart in the major group of homologous PTS permeases, is designated IID. In the mannose permease of *E. coli*, the two hydrophilic domains, both known to be phosphorylated on histidyl residues (5), are joined to each other in a single protein (IIAB), but in the other two permeases which constitute this cluster, these two domains are associated with two distinct polypeptide chains (IIA and IIB; Fig. 2 and Table 1). Close examination of the various PTS proteins reveals that when two domains are linked to each other in a single polypeptide chain, alanine-proline (AP)-rich linkers (5, 13, 34), glutamine (Q)-rich linkers (32), or other types of less well-characterized linkers serve to connect the domains.

The results summarized in Fig. 2 and Table 1 and the considerations presented previously (2, 13, 28, 31) establish that during the evolution of the PTS proteins, gene fusion, splicing, shuffling, duplication, and possibly deletion have occurred. It is probable that additional combinations of the known homologous PTS protein domains will be found together with each other and with other functionally distinct domains; thus, while the proposed system of nomenclature should be capable of describing all foreseeable related PTS proteins, the extent of structural variety should not be considered to be fixed and final. It will increase as our knowledge of PTS protein structure and function becomes more extensive.

Some of the classes of non-PTS permeases, such as the strongly hydrophobic solute:cation symporters and solute facilitators, have not undergone such genetic rearrangements or alterations during their evolution (11), suggesting that a specific domain sequence may be required for their function. However, other explanations can be entertained. For example, the genetic regions encoding interdomain linkers of specific amino acyl composition may prove to be excellent sites of genetic recombination, and these regions may have been derived from mobile genetic elements (34). Some evidence suggests that the hydrophobic domains of these two classes of permeases (facilitators and group translocators) are related (23, 33). Consequently, it has been postulated (27, 29) that the PTS permeases represent channel-type facilitators onto which the energy-coupling domains or proteins have been superimposed to effect a group translocation mechanism. Such a possibility was originally suggested by Mitchell in 1973 (16). Further experimentation will be required to test this important hypothesis.

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