JOURNAL OF ELECTRON MICROSCOPY TECHNIQUE 17:200–211 (1991)

Role of the Golgi Apparatus in Cellular Pathology

DOROTHY M. MORRÉ
Department of Foods and Nutrition, Purdue University, West Lafayette, Indiana 47907

KEY WORDS Golgi apparatus, Pathology, Lysosomes, Secretion

ABSTRACT The Golgi apparatus response to pathological disorders is predominantly as an intermediary component of membrane biogenesis where it is involved in processing, sorting and secretion of materials via secretory granules, and in the formation of lysosomes. A common initial response of the Golgi apparatus to any stress is an alteration or cessation of secretory activity. In the transformed cell, the Golgi apparatus is altered both morphologically and biochemically, suggesting a shift from a secretory to a membrane-generating mode of functioning. However, since fewer or less well-developed Golgi apparatus are frequently found in transformed cells, analytical methods of membrane isolation developed for normal tissues may not always yield equivalent results when applied to tumors. Cell surface alterations characteristic of malignant cells may result from modifications occurring at the level of the Golgi apparatus. Some lysosomal dysfunctions may result from underglycosylation of acid hydrolases by the Golgi apparatus. The use of cell-free systems between endoplasmic reticulum and Golgi apparatus or within Golgi apparatus cisterane is providing a new approach to the elucidation of the role of the Golgi apparatus in normal as well as pathological states.

INTRODUCTION

Generally, pathological disorders concerned with the cell surface or cell surface determinants (e.g., cancer), secretion (albuminemia, lipoproteinemias), lysosomes (inheritable storage diseases), or protein or glycolipid glycosylation (viral diseases) involve the Golgi apparatus at at least some stage of disease etiology.

The pathology of the Golgi apparatus reflects its normal pattern of functioning as a cell component of membrane biogenesis (Morré et al., 1979) with a major role in the secretion of materials for export to the cell surface (Fig. 1) (Farquhar and Palade, 1981; also see Beaudoin and Grondin, 1991). It is involved as well in the processing of membrane proteins and glycoproteins (Farquhar, 1985; Kornfeld and Kornfeld, 1985) and in the formation of lysosomes (Creek and Sly, 1984; Farquhar, 1985); where dysfunction may result in a variety of disorders. Analysis is complicated by the organization of the Golgi apparatus as a series of different membrane compartments through which proteins move sequentially on their way either to the plasma membrane or to lysosomes (Pfeffer and Rothman, 1987). The cisternal membranes within the Golgi apparatus show a gradient from rough endoplasmic reticulum-like at the forming face to plasma membrane-like at the mature face (Mollenhauer and Morré, 1991). Although the Golgi apparatus is best characterized as a compartment of the secretory route, it may also act as an intermediary in the endocytic route (Klausner, 1989).

There are perhaps no diseases in which the primary causes have been unequivocally traced to a Golgi apparatus dysfunction. Disorders in which one or more specific glycosyltransferases, normally located exclusively or at least predominantly in the Golgi apparatus, are either overexpressed or underexpressed probably are the best candidates. In most examples, the Golgi apparatus response is through its functional role as an intermediary in membrane flow from the endoplasmic reticulum to the plasma membrane (i.e., expression of viral antigens) in the processing and packaging of lysosomal enzymes (i.e., inheritable storage disorders), or in processing and packaging of secretory materials for export out of the cell (i.e., hyperlipoproteinemia). In these examples, Golgi apparatus involvement in disease etiology is most likely secondary but nonetheless important to the overall expression of the pathologic phenotype. A fundamental problem is that diseases are generally characterized and diagnosed by end product abnormalities (e.g., secretion/storage diseases, lysosomal diseases) rather than by intermediate product alterations that, nonetheless, may be the primary contributing factor to the disease.

PATHOLOGIC ALTERATIONS OF GOLGI APPARATUS FUNCTION

Secretory activity

One of the best studied examples of pathological conditions involving altered secretory activity is the lipoproteinemias associated clinically with atherogenesis and cardiovascular disease. In the liver, the secretory vesicles derived from Golgi apparatus contain particles of very low density lipoproteins (VLDL) and low density lipoproteins (LDL). These particles enter the circulation and consistently have been implicated in atherogenesis (Eisenberg and Levy, 1975). The apoprotein moieties of the lipopoteins are synthesized

Received August 19, 1989; accepted in revised form October 13, 1989.

Address reprint requests to Dorothy M. Morré, Department of Foods and Nutrition, Purdue University, West Lafayette, IN 47907.

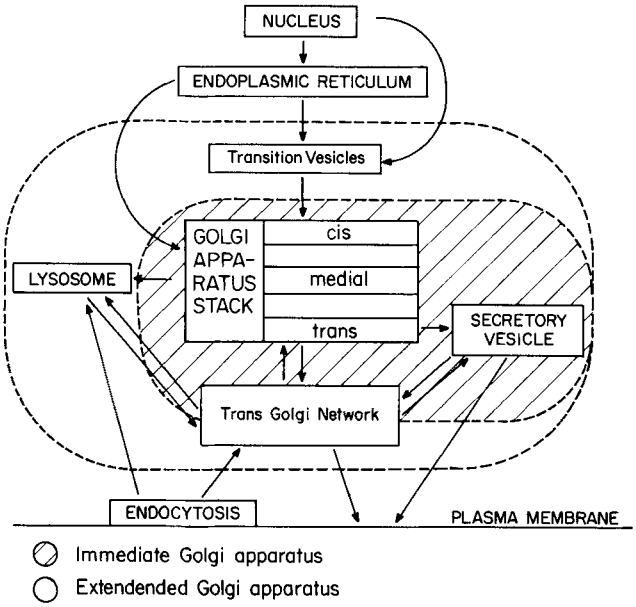

Fig. 1. Diagrammatic representation of the Golgi apparatus and functional relationships to other cell components indicative of the potential contributions of Golgi apparatus dysfunction to disease.

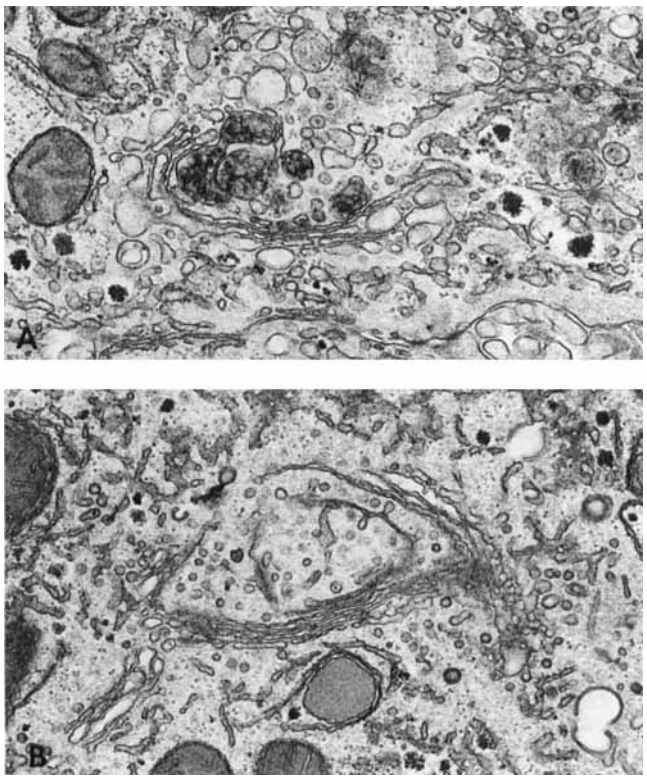

Fig. 2. Electron micrographs of liver from mice given daily doses of T2 toxin. **A:** Section of liver from control mouse showing typical distribution of cellular components; **B:** Initial response of the Golgi apparatus was loss of secretory vesicles within 24 hours and then recovery of secretory activity after 5–7 days of T2 toxin treatment. ×23,000.

on polyribosomes and associated messenger RNA, presumably bound to membranes of the rough endoplasmic reticulum (Schumacher and Adams, 1969). Strongly osmiophilic 30 to 80 nm lipoprotein particles approximating the size range of plasma VLDL appear in smooth endoplasmic reticulum within minutes after refeeding fasted animals (Jones et al., 1967). Next they appear in Golgi apparatus (Hamilton et al., 1967) and are found in the space of Disse within 15 minutes (Hamilton et al., 1967). They proceed from there directly to the circulation (Schumacher and Adams, 1969). Subsequent correlative biochemical, immunochemical, and morphological studies, made possible by the isolation of intact Golgi apparatus from liver, confirmed that the lipoprotein particles of the Golgi apparatus are precursors of plasma VLDL (Mahley et al., 1968) and contain the same major lipoprotein apoproteins as serum VLDL (Alexander et al., 1976).

Administration of a variety of hepatotoxic drugs and/or experimental conditions results in alterations in the lipid or lipoprotein contents within the Golgi apparatus. For example, the Golgi apparatus is transformed into a cluster of dilated vacuoles devoid of coarse electron-dense particles 30 minutes after administration of carbon tetrachloride to rats (Reynolds, 1963). Disrupted or dilated particle-free Golgi apparatus were found in rat livers after administration of a choline-deficient diet (Amick and Stenger, 1964) puromycin (Jones et al., 1967; Treolar et al., 1974) or orotic acid (Jatlow et al., 1965). The increased biochemical activity and morphological prominence of the Golgi apparatus observed with chronic ethanol administration may be an adaptive phenomena resulting from promoted lipoprotein secretion (Lieber, 1985).

Alterations of secretory activity (as determined by the presence or absence of secretory vesicles) is a common initial response of Golgi apparatus to any stress. For example, Mollenhauer et al. (in press), upon inducing toxic stress in mice by administration of trichothecene mycotoxin T-23, found changes in the rough endoplasmic reticulum and smooth endoplasmic reticulum-associated vesicles (Fig. 2). They attributed these changes to inducement of a block of transfer of secretory product by the T-2 between endoplasmic reticulum and Golgi apparatus. Although the Golgi apparatus per se is a relatively resistant cell component, some of its functions involving the synthesis and/or storage of secretory products and its activities in membrane trafficking appear to be quite labile.

Since lipoprotein particles are major carriers not only of triglyceride but also of cholesterol, cholesterol packaging for delivery to the cell surface and to the circulation also is thought to occur in the Golgi apparatus (DeGrella and Simoni, 1982; Glaumann et al., 1975; Hamilton et al., 1967; Mahley et al., 1969; 1970; Mills et al., 1984; Morré et al., 1971). Disruption of the normal transport pathway of cholesterol was observed by Blanchette-Mackie et al. (1988) when they incubated fibroblasts derived from patients with type-C-

Niemann-Pick disease with LDL. There was excessive accumulation of unesterified cholesterol, which was accounted for by premature accumulation of cholesterol in the Golgi apparatus and massive cholesterol storage in lysosomes.

In other extreme pathological conditions, secretion may stop entirely (Ghadillary, 1982), or normal secretion may be reduced as in neoplasia (Redman et al., 1979). Secretion at the level of the Golgi apparatus may be affected by the specificity of a terminal carbohydrate group or sequence of amino acids. Alteration of the terminal sugar sequence may result in the enhanced uptake by the liver of circulating glycoproteins after removal of the terminal sialic acid groups and exposure of galactose groups (Gordon, 1973) and then a subsequent return to a normal rate of uptake upon further removal of the exposed galactose groups.

Membrane flow

A second major function of the Golgi apparatus that occurs in parallel to secretion is delivery of membrane to the cell surface. Here, for example, significant alterations occur with viral disorders and neoplasia.

Viral disorders. Green et al. (1981) were among the first to demonstrate the passage of viral proteins through the Golgi apparatus. Evidence for a flow mechanism to account for the appearance of viral glycoproteins at the cell surface membrane has been reviewed extensively (Morré et al., 1979; Stephens and Compans, 1988). Most enveloped viruses acquire their envelopes by budding through cellular membranes. Enveloped RNA viruses bud most frequently through the plasma membrane (Compans and Choppin, 1971; Compans and Dimmock, 1969; Lenard and Compans, 1974). Other enveloped viruses (i.e., alpha viruses, arena viruses, orthomyxoviruses, paramyxoviruses, retroviruses, and rhabdoviruses) may bud into cytoplasmic endomembrane spaces, e.g., endoplasmic reticulum or Golgi apparatus. Some, like the herpes virus, are assembled within the nucleoplasm and acquire an envelope upon budding at the inner nuclear envelope (Stephens and Compans, 1988).

The protein portions of viral glycoproteins are coded for by the virus. Then they are glycosylated at the Golgi apparatus. In a study of the glycosylation of envelope glycoprotein of vesicular stomatitis virus precursors, Hunt and Summers (1976) used pulse-labeled, virus-infected HeLa cells with radioactive sugar precursors to show the addition of sugar residues (glucosamine and mannose) proximal to the linkage with protein by rough endoplasmic reticulum, the addition of more distal sugars (galactose, sialic acid, fucose, and possibly more glucosamine) in a light density endomembrane fraction now known to be the Golgi apparatus, as well as the accumulation of mature glycoprotein in the plasma membrane.

All coronaviruses, with the exception of TGEV (Laude et al., 1987), contain E1 proteins lacking N-terminal cleavable signal sequences. *O*-Glycosylation of the E1 proteins occurs most likely when the virus particles are transported through peripheral loops of the Golgi apparatus cisternae (Niemann et al., 1982; Tooze et al., 1988). Results obtained with cell fractionation experiments and metabolic labeling of monensin-treated infected 3T3 17C11 cells indicate that at least the first step of *O*-glycosylation occurs in the Golgi apparatus (Niemann et al., 1982).

In contrast to influenza and other viruses which bud from the plasma membrane of the host, nucleocapsids of herpes virus acquire envelopes from the inner leaflet of the nuclear envelope. Antigens become associated not only with the membranes of the nuclear envelope, but with endoplasmic reticulum and plasma membrane as well (Nii et al., 1968), and reach the cell surface via the Golgi apparatus.

The envelope of the best characterized member of the Bundyviridae family, the Uukuniemi virus, contains two glycoproteins, G1 and G2, which along with the N protein accumulate in the Golgi apparatus region of Uukuniemi virus-infected cells (Kuismanen et al., 1984). Subsequently, this region undergoes expansion. Similarly, G1 and G2 accumulate in hamster kidney and chick embryo cells infected with a temperature-sensitive mutant, ts12, of Uukuniemi virus (Gahmberg et al., 1986). The N protein failed to accumulate in the Golgi apparatus region at the restrictive temperature (39°C) although G1 and G2 were retained in the Golgi apparatus and could not be chased to the plasma membrane even after 6 hours' incubation in the presence of cycloheximide at nonpermissive temperatures.

Synthesis and incorporation of the membrane glycoprotein (G protein) vesicular stomatitis virus have been studied extensively in cell-free systems (Morrison and McQuain, 1977; Rothman and Lodish, 1977), as has its intracellular transport (see Wattenberg, this volume). Movement and processing of the G protein has been studied comparing different "donor" and "acceptor" fractions in both cell-free systems and with permeabilized cell preparations. Ativators of mammalian GTP-bindings proteins such as GTPγS and aluminum tetrafluoride in a cell-free system enhanced formation of non-clathrin-coated vesicles that failed to bind to or fuse with recipient Golgi apparatus membranes (Melançon et al., 1987). An additional inhibitory cytosolic component with GTPγS-binding properties was required for inhibition of vesicular transport by GTPγS.

Neoplasia (cancer). The role of the Golgi apparatus in cell transformation and neoplasia is not as well understood as its involvement in the processing of membrane proteins and glycoproteins (Dunphy and Rothman, 1985; Farquhar, 1985; Kornfeld and Kornfeld, 1985) as well as in lysosome formation (Creek and Sly, 1984; Farquhar, 1985). However, several authors have noted the possibility of a relationship between cell transformation and the Golgi apparatus (Morré and Ovtracht, 1977; Reutter and Bauer, 1978; Reutter et al., 1978; Nicolson, 1984; Morré, 1989).

Both morphologic and biochemical investigations have provided evidence for an altered Golgi apparatus in the transformed state. Compared with host liver, a change in the dimensions of Golgi apparatus in hepatomas was noted by McCarthy et al. (1974). Likewise, in a series of 35 Morris hepatomas of differing growth rates, an effect on the lengths or number of cisternae of the Golgi apparatus was largely independent of growth

rate (Hruban et al., 1972, 1979). To varying degrees, hepatomas compared with normal liver also lost the ability to elaborate specific secretory proteins into serum (Redman et al., 1979). Several investigators (Hudgins et al., 1971; Reutter and Bauer, 1978) suggested that the Golgi apparatus of transformed cells may shift from a secretory to a membrane-generating mode of functioning.

Ghadially (1982) noted that most tumors do not contain an abundance of Golgi apparatus compared with their cell of origin. The Golgi apparatus is nearly always poorly developed or difficult to identify in fast-growing anaplastic tumors while relatively well differentiated tumors usually have a well developed Golgi apparatus provided the tissue of origin also has a well developed Golgi apparatus. Furthermore, a correlation exists between the degree of differentiation and the size of the Golgi apparatus; that is, the less differentiated tumors have smaller Golgi apparatus. Finally, some tumors exhibit marked hypertrophy, dilatation, and distortion of the Golgi apparatus. Mostly the Golgi apparatus of tumors seems to acquire a morphology similar to that of Golgi apparatus observed in juvenile or dividing cells (Eisenberg and Levy, 1975).

Aspects of endocytic membrane trafficking in tumor cells have been less well studied. Pancreatic acinar carcinoma cells, when supplied with radiolabeled cationic ferritin, retained the capacity to interiorize and recycle plasma membranes (Kanwar et al., 1983). As determined by electron microscopic autoradiography, the tracer internalized in undifferentiated granule-deficient cells primarily to lysosomes.

The biochemical evidence for a functionally altered Golgi apparatus in transformation frequently has been inferred from the known subcellular localization of gycoconjugate processing enzymes in various parts of the Golgi apparatus rather than from direct measurements done either in situ or with isolated fractions. Often altered glycoproteins and glycolipids in tumorigenesis have *L*-fucose or N-acetylneuraminic acid as terminal sugars (Reutter and Bauer, 1978). Although few good examples are available, many authors have concluded that at least some of the glycoproteins modified in transformation may be involved in alterations in cellular adhesion and communication that contribute to the aberrant social behavior that is characteristic of the transformed phenotype (Nicolson, 1984). Thus, in addition to its likely function as a shipping and receiving center for membrane quanta, the Golgi apparatus may be responsible as well for imparting to the membranes some of the specific characteristics important to their postulated roles in control of growth and cell adhesion (Farquhar, 1985; Farquhar and Palade, 1981; Morré et al., 1979).

In both rodent and human hepatoma cells, transport rates of secretory gycoproteins through the endoplasmic reticulum and Golgi apparatus are variable, but the extent that they are influenced by transformation is unknown (Lodish et al., 1983; Yeo et al., 1985). Overall, the pattern of processing and movement through the Golgi apparatus appears to be similar to that for nontransformed cells and tissues. Thus, in Golgi apparatus, functional alterations are being sought currently in terms of more subtle changes such as alterations in transit times (Bostrom et al., 1986) and in the activities of specific glycosyltransferases (Ikehara and Takahashi, 1983).

Fucosyltransferase, located in the Golgi apparatus, is involved in the formation of both fucoproteins (Reutter and Bauer, 1978) and fucolipids (Bosmann, 1969; Steiner et al., 1973). Alteration of this enzyme, along with sialytransferase in transformed cells, indicates a central role of the Golgi apparatus during tumorigenesis in affecting altered patterns of cell-surface glycosylation. The precise mechanisms whereby the Golgi apparatus may contribute to an altered glycosylation of cell surface glycoproteins and glycolipids presently are not known. The pool size of GDP-L-fucose in Morris hepatoma 7777 was found to be 12.8 nmoles/g wet weight compared with 6.5 nmoles/g wet weight for normal liver. In addition, specific activities of GDP-fucose: glycoprotein fucosyltransferase were increased at least twofold to threefold over that of normal liver in a number of rat hepatomas (Reutter and Bauer, 1978), whereas in these tumors the specific activities of sialyltransferase generally were decreased (Reutter and Bauer, 1978). However, galactosyltransferase-specific activity remained unchanged. CMP-sialic acid:glycoprotein sialyltransferase activity was found to be unchanged or decreased during tumor progression (Creek et al., 1984) while that of galactosyltransferase was unchanged (Elliott et al., 1984) during hepatocarcinogenesis induced in the rat by 2-acetylaminofluorene.

There have been no definitive biochemical studies dealing with Golgi apparatus isolated from transformed cells or tissues. Much difficulty in comparing tumors with normal tissue has arisen from the fact that analytical methods of membrane isolation developed for normal tissues of origin do not yield equivalent results when applied to tumors. Some of the reported differences may, in reality, be the result of contaminating membranes or a failure on the part of the tumor cells to fractionate decisively. Functional changes in membranes are frequently expressed in terms of ultrastructural alterations and vice versa. It is important that only observations of well-fixed and well-preserved material be considered. What may appear as an ultrastructural alteration under certain circumstances may be only a response to fixation or some pathological change resulting from a delay, perhaps, between time of harvest and actual fixation.

Endomembranes play an essential role in oncogene expression in that oncogene products functioning at the cell surface are translated on membrane-associated polyribosomes and delivered to the plasma membrane via the Golgi apparatus and other endomembrane components. An example is the v-*sis* oncogene of Simian sarcoma virus, which has strong sequence homology with platelet-derived growth factor (PDGF) but lacks an obvious stop-transfer sequence or membrane anchor and might be secreted to stimulate growth in an autocrine fashion (Hunter, 1985). Another example is the receptor for epidermal growth factor (EGF), which also is synthesized on polyribosomes of endoplasmic reticulum, glycosylated in Golgi apparatus, and delivered to the cell surface and has homology with the v-*erb*-B on-

cogene of avian erythroblastosis virus. The v-*erb*-B protein appears to be a truncated form of the EGF receptor, which retains the proposed membrane anchor domain but lacks most of the external EGF binding domain (Hayman and Beug, 1984; Schatzman et al., 1986). Doubltess, as new information is generated in this rapidly expanding and important area of cancer research, new understanding of the role of the Golgi apparatus in neoplasia will emerge.

Altered surface in neoplasia/signal transduction. Cell surface alterations are characteristic of malignant cells (Burger, 1973; Emmelot, 1973; Hakomori, 1973, 1975; Herschman, 1972; Rapin and Burger, 1974; Vasiliev and Gelfand, 1968). Both transformation (neoplasia) and malignant behavior (metastasis) generally are considered to involve fundamental alterations in the properties of the cell surface. Scanning electron microscope studies have suggested that the surface of malignant cells is generally more irregular than normal with a relative increase in the number of surface microvilli and cytoplasmic lamellipodia suggestive of a retention in tumors of those features characteristic of rapidly dividing cells. Most likely, membrane alterations expressed at the cell surface arise through biosynthetic or processing modifications and are products of formation of internal endomembranes. Other characteristic alterations of the cell surface of malignant cells include antigenic changes, altered agglutinability by phytohemagglutinins, changed electrokinetic properties, modified contact relationships, deviations in permeability, and/or transport characteristics and enzymatic and compositional changes.

Altered formation of lysosomes

The fact that more than 35 lysosomal storage diseases have been described in humans emphasizes the importance of lysosomal dysfunction in pathology. Most of these result from lysosomal enzyme defects which lead to an accumulation of natural substrates of the enzymes in lysosomes. Modifications of the Golgi apparatus and its functioning are of concern when considering these congenital lysosomal diseases. For example, Seegmiller et al. (1971, 1972) showed that modification of the Golgi apparatus was associated with a chondrodystropic mutation in mice. Although some of these disorders occur due to failure of the cell to synthesize the active form of the relevant enzyme, the defect may be due to an inability to sort and transport an active enzyme from its site of synthesis and subsequent transport through the Golgi apparatus to the lysosome.

Lysosomal enzymes have a common recognition marker that directs the enzymes to the lysosomes and thus prevents their secretion (Hickman and Neufeld, 1972). Sly and Fischer (1982) suggested that the role of the recognition marker was to direct acid hydrolases to the lysosomes and thus may serve as a sorting mechanism for lysosomal enzyme transport to lysosomes. Considerable evidence indicates that phosphomannosyl residues present on high-mannose-type oligosaccharide units of acid hydrolases act as the recognition marker to mediate enzyme uptake by various cell types and target them to the lysosomes (Bach et al., 1979; Distler et al., 1979; Fischer et al., 1980; Hasilik and Neufeld, 1980; Kaplan et al., 1977; Natowicz et al., 1979; Sando and Neufeld, 1977; Ullrich et al., 1978; Von Figura and Klein, 1979).

After enzymes destined for lysosomes are transferred from the endoplasmic reticulum to the Golgi apparatus, two membrane-bound enzymes in the early (probably *cis*) portion of the Golgi apparatus catalyze the phosphorylation of a specific subset of high-mannose oligosaccharide chains at the 6-carbon position of mannose (Pohlman et al., 1982; Goldberg and Kornfeld, 1983). The processing enzymes involved in the addition of the mannose-6-phosphate recognition label have been localized to the Golgi apparatus compartments. The biosynthesis of the phosphomannosyl recognition marker on lysosomal enzymes is by a two-step reaction. First, N-acetylglucosamine-1-phosphate is transferred from UDP-N-acetylglucosamine to mannose residues by UDP-GlcNac:N-acetylglucosaminyl-1-phosphotransferase, which selectively phosphorylates lysosomal enzymes and gives rise to a phosphodiester intermediate (Hasilik et al., 1981; Reitman et al., 1981; Waheed et al., 1982). Then the phosphomannosyl recognition marker is generated by removal of the N-acetylglucosamine by an N-acetyulglucosamine 1-phosphodiester α-N-acetylglucosaminidase (Varki and Kornfeld, 1980, 1981; Waheed et al., 1981). This allows high affinity binding of the recognition marker to the 215 kD mannose-6-phosphate receptors in the Golgi apparatus. Subsequently, there is a low pH-mediated dissociation of the ligands from the receptor, followed by a proteolytic cleavage and a dephosphorylation. Then the receptor recycles back to the Golgi apparatus to pick up another ligand molecule and the lysosomal enzymes are packaged into lysosomes.

Cells of patients with I cell disease (mucolipidosis II) and pseudo-Hurler polydystrophy (mucolipidosis III) characteristically cannot synthesize the phosphomannosyl marker since they lack phosphotransferase activity (Reitman et al., 1981; Hasilik et al., 1981; Varki et al., 1981; Waheed et al., 1982). The inability of their lysosomal enzymes to bind to the mannose-6-phosphate receptors is the major contributor to these and other diseases (Table 1). Although the mannose-6-phosphate pathway is important in targeting enzymes to lysosomes, there is evidence that there are also other mechanisms available for localizing acid hydrolases to lysosomes. Thus far, however, attempts to demonstrate a receptor that binds lysosomal enzymes independent of the recognition marker have been unsuccessful (Kornfeld, 1986).

PATHOLOGIC ALTERATIONS OF GOLGI APPARATUS MORPHOLOGY

There are numberous reports in the literature of alterations in Golgi apparatus morphology under different pathological conditions (Ghadially, 1982). Morphological alterations involved with lipoporteinemias and neoplasia are already summarized under the previous section. Characteristics used to indicate pathological alterations of the Golgi apparatus at the ultrastructural level may include any or all of the following: degree of development (number and size), morphology of the structure as well as the numbers and appearance of

TABLE 1. General classification of lysosomal storage disorders[1]

	References
I. Disorders in which no immunologically detectable enzyme is synthesized. This includes conditions with grossly abnormal structural genes.	Hasilik and Neufeld, 1980; Myerowitz and Neufeld, 1981; Waheed et al., 1982; von Figura et al., 1983a.
II. Disorders in which a catalytically inactive polypeptide is synthesized. The mutation may also affect the stability or transport of the polypeptide.	Proia and Neufeld, 1982; Bach and Neufeld, 1983; Steckel et al., 1983; Reuser et al., 1985; Hoogeveen et al., 1984.
II. Disorders in which a catalytically active enzyme is synthesized that is not segregated into lysosomes.	Reitman et al., 1981; Hasilik et al., 1981; Varki et al., 1981, 1982; Waheed et al., 1982; Hickman and Neufeld, 1972.
IV. Disorders in which a catalytically active enzyme is synthesized that is unstable in prelysosomal or lysosomal compartment.	von Figura et al., 1983b, 1984; Steckel et al., 1982; Waheed et al., 1982; D'Azzo et al., 1982.
V. Disorders in which activator proteins of lipid-degrading hydrolases are missing.	Conzelmann and Sandhoff, 1978; Stevens et al., 1981; Inui et al., 1983; Sandhoff, 1984.
VI. Disorders in which lysosomal enzyme deficiencies result from intoxication with inhibitors of lysosomal enzymes.	Dorling et al., 1980.

[1]Reproduced from Kornfeld, 1986, with copyright permission of the Rockefeller University Press.

secretory vesicles, presence of specific secretory products, and small Golgi apparatus-associated vesicles, numbers of cisternae per stack, cisternal diameters, and width of cisternal lumens.

Number, size, and form of cisternae

The Golgi apparatus usually consists of four to six stacks of lamellae, vacuoles, and vesicles in almost all varieties of cells. In the vicinity of the Golgi apparatus can be seen lysosomes, secretory granules, coated vesicles, multivesicular bodies, and small vesicles.

In the Golgi apparatus of pathological tissues, some of the morphological changes reported to occur include hypertrophy or atrophy, dilatation, or collapse of the elements, changes in its intracellular position as well as quantitative/qualitative differences in the contents of the Golgi apparatus (Ghadially, 1982). The reports of only slight alterations occurring in the Golgi apparatus in pathological tissues are so frequent that it is not possible to cite them all in this chapter; therefore, a few examples which illustrate the significance of such changes will be discussed.

The Golgi apparatus of somatotropic cells in malnourished rats were enlarged, while the secretory granules occupied a lesser volume (César et al., 1987). Golgi apparatus stacks were smaller in diameter in livers of vitamin A-deficient rats (Morré et al., 1981) and characterized by small, often highly fenestrated, saccules (Fig. 3A, B). With vitamin A excess (Fig. 3C), Golgi apparatus membrane surface was increased and more variable, ranging from nearly normal in appearance to much larger than normal. Saccules were larger and many lacked the numerous fenestrations usually present. Also, unusual cisternal configurations were encountered. An increase in Golgi apparatus membranes resulting from vitamin A applications to neoplastic rabbit epithelium was observed previously (Prutkin, 1975). An effect of vitamin A excess on membrane flow through the endoplasmic reticulum-(lysosome-)-Golgi apparatus-plasma membrane export route of rat liver was subsequently confirmed using pulse-chase methodology with [^{35}S]methionine as label (Morré et al. 1988).

Hypertrophy of the Golgi apparatus elements such as the stacks, vesicles, and vacuoles evidenced by either multiple Golgi apparatus occupying larger areas of cytoplasm or an increase in the number of sets of stacks and associated vesicles and vacuoles frequently correlates with increased secretory activity or compensatory hypertrophy due to malfunction in an adjacent cell. An early example is the study of Nakayama et al. (1969), in which hypertrophy of the Golgi apparatus in the ACTH-secreting cells of the adenohypophysis was found in experimentally induced adrenal cortical regeneration in the rat that was restored to normal when adrenal regeneration was completed and the adrenocorticotrophic hormone (ACTH) levels had been restored to normal.

Organization of Golgi apparatus zone

The Golgi apparatus is a multifunctional organelle that acts as a terminal to link to moderate various activities of the cell and directly influences the movement of membrane and products to and from the cell surface as well as to lysosomes. Its zone of influence may extend many microns from the complex itself and includes such ancillatory structures as the trans Golgi network (TGN) (Griffiths and Simons, 1986) (Fig. 1).

Under certain conditions, the Golgi apparatus appears to become easily disorganized. For example, Merisko et al. (1986b) found that when acinar cells of pancreatic lobules were incubated under anoxic conditions which inhibited adenosine triphosphate (ATP) synthesis with resultant blockage of intracellular transport of secretory proteins, transitional elements of the endoplasmic reticulum lost their protrusions and the Golgi apparatus became highly disorganized. Fibrillar aggregates, often containing vesicle-free, small globular cages (a network of basketlike structures) and occasionally vesicle-free, clathrin-like cages, appeared on the *cis* side of the stacks of Golgi apparatus cisternae as well as on the trans side of the Golgi apparatus stacks. There was a striking increase in the population of coated vesicles trans to the Golgi complex and throughout the apical region of the anoxic acinar cells.

In an immunocytochemistry study, Merisko et al.

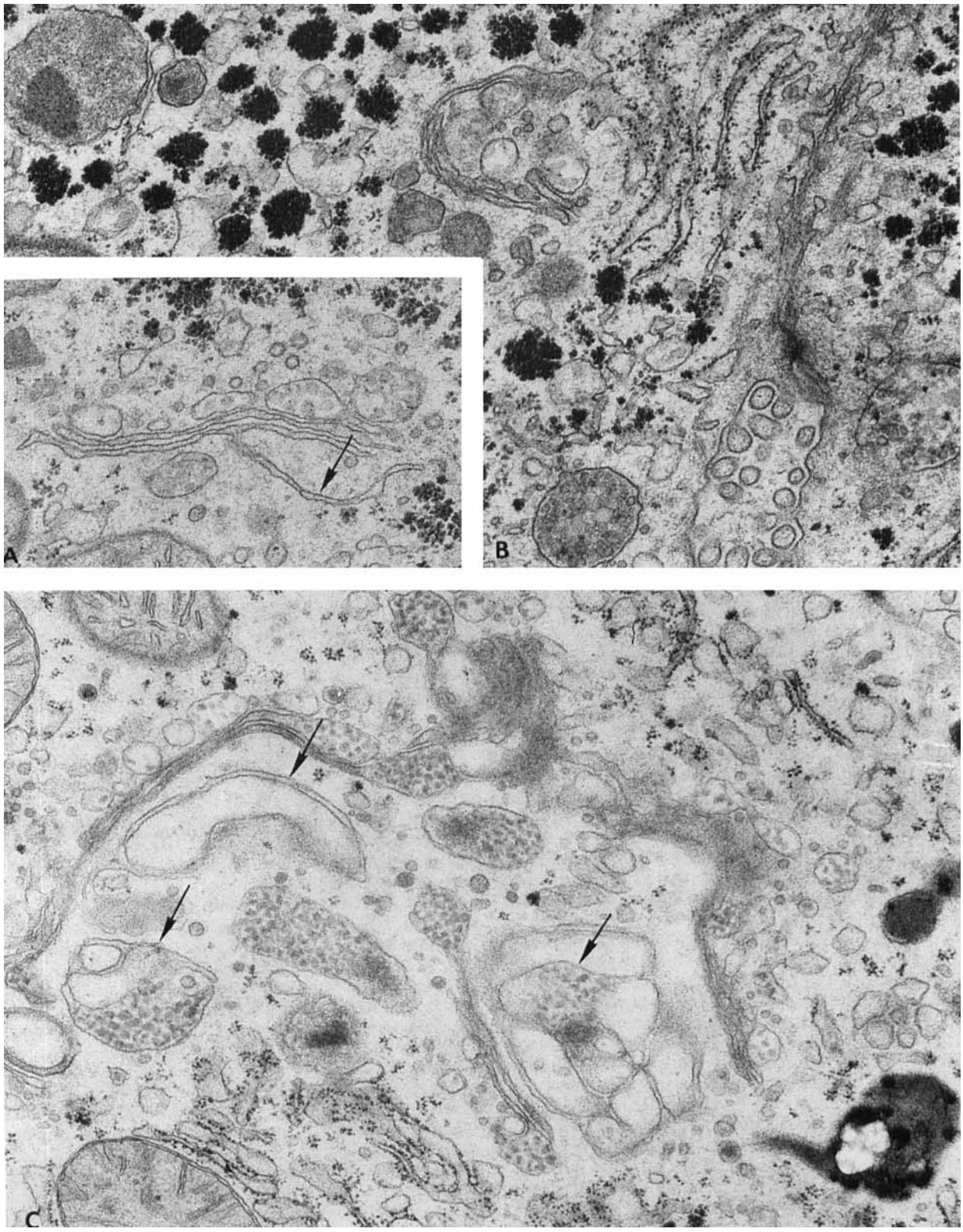

Fig. 3. Electron micrographs of liver of rats fed diets containing deficient (**A,B**) or excess (**C**) amounts of vitamin A with numerous unusual cisternae (arrows). A shows a Golgi apparatus stack (dictyosome) in face view. (Adapted from Morré et al., 1981, with permission of Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, W. Germany)

(1986a) observed a redistribution of clathrin heavy and light chains in anoxic pancreatic acinar cells. They found that coated vesicles increased in number in the cells incubated under N_2. Clathrin light chains were localized among zymogen granules and in small masses at the periphery of the Golgi apparatus. By electron microscopy, antibodies for light and heavy chains reacted with numerous coated vesicles located in clusters on the *trans* side of the Golgi apparatus stacks, while fibrillar aggregates *cis* to the Golgi apparatus stained less intensely and much less uniformly than the coats of the coated vesicle population.

A variety of degenerative changes were seen in atrial cardiocytes from dystrophic compared to nondystrophic mice (Nomura et al., 1987). Development of the Golgi apparatus was impaired, and the relative area occupied by the Golgi apparatus was significantly smaller in the right atrium than in nondystrophic controls. The authors suggested that the synthesis of atrial natriuretic polypeptide is inhibited in drystrophic mice and that its impaired secretion in the heart may account for the water and electrolyte imbalance seen in dystrophic cases.

ER-GA associations and transition vesicles

The recent development of cell-free systems between endoplasmic reticulum and Golgi apparatus as well as within the Golgi apparatus cisternae is providing new insights into the vesicular transport mechanism. The morphological basis for tranfer of membrane materials from endoplasmic reticulum to Golgi apparatus long has been considered to be mediated by small (ca. 60 nm) transition vesicles that bleb off specialized part-rough, part-smooth regions of the endoplasmic reticulum. These vesicles are covered by a nap-like coat material not containing clathrin (Croze et al., 1982; Mollenhauer et al., 1976; Orci et al., 1986) and are thought to coalesce to form new Golgi apparatus cisternae or to fuse with existing Golgi apparatus for delivery of material from the endoplasmic reticulum.

A number of conditions have been used in an attempt to define the underlying mechanism involved in the transfer of materials from the endoplasmic reticulum to the Golgi apparatus. For example, reduced temperature appears to affect post-translational processing and secretion in a number of cell systems. At 10°C, Tartakoff (1986) demonstrated that secretory proteins of the exocrine pancreas accumulated in pre-Golgi apparatus transition vesicles, while at 22°C or higher progress through the Golgi apparatus and into condensing vacuoles occurred. With hepatic cells, secretory proteins were blocked in a pre-Golgi apparatus at 18°C, but these proteins were exocytosed normally at 20°C (Fries and Lindstrom, 1986).

In situ, transitional endoplasmic reticulum of liver incubated over a range of 4°C to 12°C showed little evidence of transition vesicle formation. However, between 16°C and 18°C, transition vesicles were formed and accumulated, presumably due to an inability of the vesicles to fuse with the *cis* Golgi apparatus. Between 18°C and 20°C, quite abruptly the number of transition vesicles declined as the temperature block was relieved (Brand et al., 1985; Fries and Lindstrom, 1986; Saraste et al., 1986; Tartakoff, 1986).

van Deurs et al. (1987) found that delivery of internalized ricin from endosomes to cisternal Golgi elements is a discontinuous temperature-sensitive process. At 37°C, a ricin-horseradish peroxidase conjugate (Ri-HRP) was consistently observed in flattened cisternae of the Golgi apparatus region in 30 to 40% of the Golgi apparatus examined after 30–60 minutes of incubation, whereas at 18°C no Ri-HRP reached the Golgi apparatus region even after 180 minutes of incubation. No labeling of cisternal Golgi elements was detected following incubation with a monovalent transferrin-HRP conjugate or with unconjugated HRP.

BIOCHEMICAL AND CYTOCHEMICAL ALTERATIONS OF GOLGI APPARATUS IN PATHOLOGY

In normal cells and tissues, different functionalities are attributed to different regions of the Golgi apparatus. For example, processing of asparagine-linked oligosaccharides begins at the *cis* face (Kornfeld and Kornfeld, 1985) continues through the middle Golgi apparatus regions (Bumol and Reisfeld, 1982; Nishimoto et al., 1982) and culminates with glycosylation at the *trans* side (Griffiths et al., 1983; Hanover et al., 1983; Quinn et al., 1983; Strous et al., 1983). To what extent these different functionalities are perturbed in different pathological states involving the Golgi apparatus is only beginning to be revealed.

Inflammation induced in rats by subcutaneous injection of turpentine resulted in the release of Galβ-4GlcNac α2-6-sialyltransferase from rat liver Golgi membranes upon sonication followed by incubation at reduced pH (Lammers and Jamieson, 1988). Release of the sialyltransferase was substantially inhibited by pepstatin A, a potent inhibitor of cathepsin D-like proteinases as well as when sonicated Golgi apparatus membranes were incubated with antiserum raised against rat liver lysosomal cathepsin D. The acute-phase behavior of this enzyme might be explained by the possibility that a major portion of sialyltransferase containing the catalytic site is released from a membrane anchor by a cathepsin-like proteinase that is located at the luminal face of the Golgi apparatus.

Bainton et al. (1989), using both trimetaphosphatase histochemistry and an antibody to a Golgi apparatus membrane antigen as markers to study phagocytosis, observed a rapid reorganization of the Golgi apparatus region of macrophages. The Golgi apparatus, which were tightly clustered around the centrioles, dispersed into vesicles and reorganized near the basal surface while there was swelling, fragmentation, and decrease in number of Golgi apparatus cisternae. The membrane antigen was found in the large basal vacuoles as well as associated with the adherent basal surface of the macrophages.

RESPONSE TO DRUGS

Although it is remarkedly resistant to morphological alteration, the Golgi apparatus frequently does respond in one way or another to various inhibitors, effectors, or environmental stimuli. Examples are listed

TABLE 2. Examples of inhibitors, promoters, and modulators of Golgi apparatus structure and/or function[1]

Protein synthesis inhibitors (cycloheximide, puromycin)
RNA synthesis inhibigors (actinomycin D, enucleation)
Respiratory inhibitors (cyanide, DNP)
Antimicrotubular agents (colchicine, Vinca alkaloids)
Antimicrofilament agents (cytochalasins)
Antimetabolites (ethionine, fluoro-phenylalanine
Sugars and glycosides (mannose, ouabain)
Ions and metals (Ca^{++}, Pb)
Hormones; miscellaneous drugs (estrogens, antipyrine)
Environmental factors (temperature, water stress)
Pathogens (viruses, fungi)

[1]Reproduced from Morré et al., 1977, with copyright permission of the Rockefeller University Press.

in Table 2. For example, the extent of the cisternae may increase and one or more additional cisternae may be added when secretion is inhibited. In contrast, when secretion is stimulated, the Golgi apparatus may be reduced by at least one cisterna per stack. Chemical or physical dissembly of microtubules leads to loss of cell polarity and a reversible disorganization of the Golgi apparatus in that the stacks of cisternae are dispersed throughout the cytoplasm (Sandoval et al., 1984; Thyberg and Moskalewski, 1985).

When oubain, which is known to interfere with sodium and potassium transport, was added to cultures of rat and mouse sensory ganglia, some of the Golgi apparatus swelled, and then eventually nearly all of the Golgi apparatus disappeared and in their place large numbers of vacuoles appeared (Whetsell and Bunge, 1969). Also, light ether anesthesia modifies activities of some enzymes involved in the metabolism of the Golgi apparatus (Katona, 1975). For instance, alkaline phosphatase activity was increased significantly, but acid phosphatase was slightly decreased after an initial rise upon exposure to light ether anesthesia. TPPase activity decreased but 10 hours later returned to above control level. Galactosyltransferase was slightly increased while no significant changes were observed in arylsulphatase-A, but the activity of arylsulphatase-B decreased. Earlier, glycosidase (Bosmann and Kessel, 1970) and glycoprotein:glycosyl transferase (Kessel and Bosmann, 1970) were altered in cell lines resistant to certain drugs (Bosmann, 1971). In a more recent study, Martin and Morré (1988) found decreased activity of galactosyltransferase in Golgi apparatus fractions isolated from liver of rats fed excess vitamin A.

CONCLUDING REMARKS

The Golgi apparatus as a multifunctional cell component of membrane biogenesis likely is involved in most pathological disorders. That the Golgi apparatus is modified by many types of injuries is not new. As early as 1914, Cajal observed that the Golgi apparatus is a particularly vulnerable organelle. However, it is important to emphasize that carrying to completion essential metabolic processes within the cell invariably demands interrelationships of a number of cell components such as the mitochondria, endoplasmic reticulum, Golgi apparatus, and others. Frequently, no one component of the cell is singly affected.

REFERENCES

Alexander, C.A., Hamilton, R.L., and Havel, R.J. (1976) Subcellular localization of β-aproprotein of plasma lipoproteins in rat liver. J. Cell Biol., 69:241–263.

Amick, C.J., and Stegner, R. (1964) Ultrastructural alterations in experimental acute hepatic fatty metamorphosis. Lab. Invest., 13: 128–136.

Bach, G., and Neufeld, E.F. (1983) Synthesis and maturation of cross-reactive glycoprotein in fibroblasts deficient in arylsulfatase A activity. Biochem. Biophys. Res. Commun. 112:198–205.

Bach, G., Bargal, R., and Cantz, M. (1979) I-cell disease: deficiency of extracellular hydrolase phosphorylation. Biochem. Biophys. Res. Commun., 91:976–981.

Bainton, D.F., Takemura, R., Stenberg, P.E., and Werb, Z. (1989) Rapid fragmentation and reorganization of Golgi membranes during frustrated phagocytosis of immobile immune complexes by macrophages. Am. J. Pathol., 134:15–26.

Beaudoin, A.R., and Grondin, G. (1991) Secretory pathways in animal cells: with emphasis on pancreatic acinar cells. J. Electron Microsc. Tech., 17:51–69.

Blanchette-Mackie, E.J., Dwyer, N.K., Amende, L.M., Kruth, H.S., Butler, J.D., Sokol, J., Comly, M.E., Vanier, M.T., and August, J.T. (1988) Type-C Niemann-Pick disease low density lipoprotein uptake is associated with premature cholesterol accumulation in the Golgi complex and excessive cholesterol storage in lysosomes. Proc. Natl. Acad. Sci. U.S.A., 85:8022–8026.

Bosmann, H.B. (1969) Glycolipid biosynthesis: Biosynthesis of mannose and fucose-containing glycolipids of HeLa cells. Biochim. Biophys. Acta, 187:122–132.

Bosmann, H.B. (1971) Mechanism of cellular drug resistance. Nature, 233:566–569.

Bosmann, H.B., and Kessel, D. (1970) Altered glycosidase levels in drug-resistant mouse leukemias. Mol. Pharmacol., 6:345–349.

Bostrom, K., Wettesten, M., Boren, J., Bondjuers, G., Wilklund, O., and Olofsson, S.-P. (1986) Pulse-chase studies of the synthesis and intracellular transport of apolipoprotein B-100 in Hep-G-2 cells. J. Biol. Chem., 261:13800–13804.

Brand, M., Jansen, E., and Ploegh, H.L. (1985) Effect of reduced temperature on glycoprotein (Ig, HLA) processing and transport in lymphoid cells. Mol. Immunol., 22:787–794.

Bumol, T.F., and Reisfeld, R.A. (1982) Unique glycoprotein-proteoglycan complex defined by monoclonal antibody on human melanoma cells. Proc. Natl. Acad. Sci. U.S.A., 79:1245–1249.

Burger, M.M. (1973) Surface changes in transformed cells detected by lectins. Fed. Proc., 32:91–101.

César, L.A., Dumm, G., Pucciarelli, H.M., and Dressino, V. (1987) Quantitative ultrastructural study of somatotropic cells in malnourished weanling rats. Acta Anat., 129:200–202.

Compans, R.W., and Choppin, P.W. (1971) In: Comparative Virology. K. Maramon and F. Kurstak, eds. The structure and assembly of influenza and parainfluenza viruses. Academic Press, New York, pp. 407–432.

Compans, R.W., and Dimmock, N.J. (1969) An electron microscopic study of single-cell infection of chick embryo fibroblasts by influenza virus. Virology, 39:499–515.

Conzelmann, E., and Sandhoff, K. (1978) AB variant of infantile G_{M2} gangliosidosis: Deficiency of a factor necessary for stimulation of hexosaminidase A-catalyzed degradation of ganglioside G_{M2} and glycolipid G_{A2}. Proc. Natl. Acad. Sci. U.S.A., 75:3979–3983.

Creek, K.E., and Sly, W. (1984) The role of the phosphomannosyl receptor in the transport of acid hydrolases to lysosomes. In: Lysosomes in Biology and Pathology. J.T. Dingle, R.T. Dean, and W. Sly, eds. Elsevier/North Holand, New York, pp. 63–82.

Creek, K.E., Walter, V.P., Evers, D., Yeo, E., Elliott, W.L., Heinstein, P.F., Morré, D.M., and Morré, D.J. (1984) Sialoglycoconjugate changes during 2-acetylaminofluorene-induced hepatocarcinogenesis in the rat. Biochim. Biophys. Acta, 793:133–144.

Croze, E.M., Morré, D.J., Kartenbeck, J., and Franke, W.W. (1982) Distribution of clathrin and spiny-coated vesicles on membranes within mature Golgi apparatus elements of mouse liver. Eur. J. Cell Biol., 28:130–138.

D'Azzo, A., Hoogeveen, A., Reuser, A.J.J., Robinson, D., and Galjaard, H. (1982) Molecular defect in combined β-galactosidase and neuraminidase deficiency in man. Proc. Natl. Acad. Sci. U.S.A., 79:4535–4539.

DeGrella, R.R., and Simoni, R.D. (1982) Intracellular transport of cholesterol to the plasma membrane. J. Biol. Chem., 257:14256–14262.

Distler, J., Hieber, V., Sahagian, G., Schmictzel, R., and Jourdian, G.W. (1979) Identification of mannose 6-phosphate in glycoproteins that inhibit the assimilation of β-galactosidase by fibroblasts. Proc. Natl. Acad. Sci. U.S.A., 76:4235–4239.

Dorling, P.R., Huxtable, C.R., and Colegate, S.M. (1980) Inhibition of lysosomal α-mannosidase by swainsonine, an indolizidine alkaloid isolated from *Swainsona canescens*. Biochem. J., 191:649–651.

Dunphy, W.G., and Rothman, J.E. (1985) Compartmental organization of the Golgi stack. Cell, 42:13–21.

Eisenberg, S., and Levy, R.I. (1975) Lipropotein metabolism. In: Advances in Lipid Research. R. Paoletti and D. Kritchevesky, eds. New York, Academic Press, vol. 13, pp. 1–89.

Elliott, W.L., Sawick, D.P., Creek, K.E., Walter, V.P., Deutscher, S.L., Quinn, J.F., Yeo, E., Morré, D.M., Heinstein, P.F., Cassady, J.M., and Morré, D.J. (1984) Early biochemical alterations induced by acetylaminofluorene in rat liver. Int. J. Biochem., 16:947–956.

Emmelot, P. (1973) Biochemical properties of normal and neoplastic cell surfaces; A review. Eur. J. Cancer, 9:319–333.

Farquhar, M.G. (1985) Progress in unraveling pathways of Golgi traffic. Ann. Rev. Cell Biol., 1:447–488.

Farquhar, M.G., and Palade, G.E. (1981) The Golgi apparatus (complex)-1954-1981)-from artifact to center stage. J. Cell Biol., 91:77s–103s.

Fischer, H.D., Natowicz, M., Sly, W., and Brethauer, R. (1980) Fibroblast receptor for lysosomal enzymes mediates pinocytosis of multivalent phosphomannan fragment. J. Cell Biol., 84:77–86.

Fries, E., and Lindstrom, I. (1986) The effect of low temperatures on intracellular transport of newly synthesized albumin and haptoglobin in rat hepatocytes. Biochem. J., 237:33–39.

Gahmberg, N., Kuismanen, E., Keränen, S., and Pettersson, R.E. (1986) Uukuniemi virus glycoproteins accumulate in and cause morphological changes of the Golgi complex in the absence of virus maturation. J. Virol., 57:899–906.

Ghadially, F.N. (1982) Golgi complex and secretory granules. In: Ultrastructural Pathology of the Cell and Matrix. Butterworths, London, vol. 2, pp. 265–315.

Glaumann, H., Bergstrand, A., and Ericsson, J.L.E. (1975) Studies on the synthesis and intracellular transport of lipoprotein particles in rat liver. J. Cell Biol., 64:356–377.

Goldberg, D., and Kornfeld, S. (1983) Evidence for extensive subcellular organization of asparagine-linked oligosaccharide processing and lysosomal enzyme phosphorylation. J. Biol. Chem., 258:3159–3165.

Gordon, A.H. (1973) The role of lysosomes in protein catabolism. In: Lysosomes in Biology and Pathology, J.T. Dingle, ed. Amsterdam, North-Holland, pp. 89–137.

Green, J., Griffiths, G., Loward, D., Quinn, P., and Warren, G. (1981) Passage of viral membrane proteins through the Golgi complex. J. Mol. Biol., 152:663–698.

Griffiths, G., Quinn, P., and Warren, G. (1983) Dissection of the Golgi complex. I. Monensin inhibits the transport of viral membrane proteins from medial to trans Golgi cisternae in baby hamster kidney cells infected with Semiliki Forest virus. J. Cell Biol., 96:835–850.

Griffiths, G., and Simons, K. (1986) The *trans* Golgi network. Sorting at the exit site of the Golgi complex. Science 234:438–443.

Hakomori, S. (1973) Glycolipids of tumor cell membrane. Adv. Cancer Res., 18:265–315.

Hakomori, S.I. (1975) Structures and organization of cell surface glycolipids dependency on cell growth and malignant transformation. Biochim. Biophys. Acta, 415:55–89.

Hamilton, R.L., Regan, D.M., and LeQuire, V.S. (1967) Lipid transport in liver. Electron microscopic identification of very low density lipoporteins in perfused rat liver. Lab Invest., 16:305–319.

Hanover, J.A., Elting, J., Mintz, G.R., and Lennarz, W.J. (1982) Temporal aspects of the N- and O-glycosylation of human chorionic gonadotropin. J. Biol. Chem., 257:10172–10177.

Hasilik, A., and Neufeld, E. (1980) Biosynthesis of lysosomal enzymes in fibroblasts. J. Biol. Chem., 255:4937–4945.

Hasilik, A, Waheed, A., and von Figura, K. (1981) Enzymatic phosphorylation of lysosomal enzymes in the presence of UDP-N-acetylglucosamine—Absence of the activity of I-cell fibroblasts. Biochem. Biophys. Res. Commun., 98:761–767.

Hayman, M.J., and Beug, H. (1984) Identification of a form of the avian erythroblastosis virus erb-B gene product at the cell surface. Nature, 309:460–462.

Herschman, H.R. (1972) In: Membrane Molecular Biology, C.F. Fox, A.D. Kieth, eds. Sinauer Assoc., Stamford, Connecticut, p. 471.

Hickman, S., and Neufeld, E.F. (1972) A hypothesis for I-cell disease: Defective hydrolases that do not enter lysosomes. Biochem. Biophys. Res. Commun., 49:992–999.

Hoogeveen, A.T., Graham-Kawashima, H., d'Azzo, A., and Galjaard, H. (1984) Processing of human β-galactosidase in G_{M1}-gangliosidosis and Morquio B Syndrome. J. Biol. Chem., 259:1974–1977.

Hruban, Z. (1979) Ultrastructure of hepatocellular tumors. In: Liver Carcinogenesis. K. Lapis and J.V. Johannessen, eds. McGraw-Hill, New York, pp. 403–431.

Hruban, Z., Mochizuki, Y., Slesers, A., and Morris, H.P. (1972) Endoplasmic reticulum, lipid and glycogen of Morris hepatomas. Lab. Invest., 26:86–99.

Hudgins, R.L., Murray, R.K., Pinteric, L., Morris, H.P., and Schachter, H. (1971) The use of nucleotide-sugar:Glycoprotein glycosyl-transferases to assess Golgi apparatus function in Morris hepatomas. Can. J. Biochem., 49:61–70.

Hunt, L.A., and Summers, D.A. (1976) Glycosylation of vesicular stomatitis virus glycoprotein in virus-infected HeLa cells. J. Virol., 20:646–657.

Hunter, T. (1985) Oncogenes and growth control. TIBS, 10:275–280.

Ikehara, Y., and Takahashi, K. (1983) Glycosyltransferases of the Golgi complex in relation to cell surface changes in rat hepatoma. Gann Monogr. Cancer Res., 19:221–229.

Inui, K., Emmett, M., and Wenger, D.A. (1983) Immunological evidence for deficiency in an activator protein for sulfatide sulfatase in a variant form of metachromatic leukodystrophy. Proc. Natl. Acad. Sci. U.S.A., 80:3074–3077.

Jatlow, P., Adams, W.R., and Handschumacher, R.E. (1965) Pathogenesis or orotic acid-induced fatty change in the rat liver. Light and electron microscopic studies. Am. J. Pathol., 47:125–145.

Jones, A.L., Ruferman, N.B., and Herrera, M.G. (1967) Electron microscopic and biochemical study of lipoprotein synthesis in the isolated perfused rat liver. J. Lipid Res., 8:429–446.

Kanwar, Y.S., Rosenzweig, L.J., Jakubowstri, M.L., and Reddy, J.K. (1983) Plasma membrane retrieval in neoplastic pancreatic acinar cells. Proc. Natl. Acad. Sci. U.S.A., 80:6877–6881.

Kaplan, A., Achord, D.T., and Sly, W.S. (1977) Phosphohexosyl components of a lysosomal enzyme are recognized by pinocytosis receptors on human fibroblasts. Proc. Natl. Acad. Sci. U.S.A., 74:2026–2030.

Katona, E. (1975) Anesthesia and the Golgi apparatus enzyme activity changes in a Golgi-rich fraction of rat liver after a short ether anesthesia. Chem. Biol. Interact., 10:1–9.

Kessel, D., and Bosmann, H.B. (1970) On the characteristics of actinomycin D resistance in L5178Y cells, Cancer Res., 30:2695–2701.

Klausner, R.D. (1989) Sorting and traffic in the central vacuolar system. Cell, 57:703–706.

Kornfeld, S. (1986) Trafficking of lysosomal enzymes in normal and disease states. J. Clin. Invest., 77:1–6.

Kornfeld, R., and Kornfeld, S. (1985) Assembly of asparagine-linked oligosaccharides. Annu. Rev. Biochem., 54:631–664.

Kuismanen, E., Bång, B., Hurme, M., and Petersson, R.E. (1984) Uukumiemi virus maturation: Immunofluorescence microscopy with monoclonal glycoprotein-specific antibodies. J. Virol., 51:137–146.

Lammers, G., and Jamieson, J.C. (1988) The role of a cathepsin D-like activity in the release of Galβl-4GlcNAc α2-6-sialyltransferase from rat liver Golgi membranes during the acute-phase response. Biochem. J., 256:623–631.

Laude, H., Rasschaert, D., and Huet, J.-C. (1987) Sequence and N-terminal processing of the transmembrane protein El of the coronavirus transmissible gastroenteritis virus. J. Gen. Virol., 68:1687–1693.

Lenard, J., and Compans, W. (1974) The membrane structure of lipid-containing viruses. Biochim. Biophys. Acta, 344:51–94.

Lieber, C.S. (1985) Alcohol and the Liver: Metabolism of ethanol, metabolic effects and pathogenesis of injury. Acta Med. Scand [Suppl.], 7032:11–55.

Lodish, H.F., Kong, N., Snider, M., and Strous, J.A.M. (1983) Hepatoma secretory proteins migrate from rough endoplasmic reticulum to Golgi at characteristic rates. Nature (Lond.), 304:80–83.

Mahley, R.W., Bersot, T.P., LeQuire, V.S., Levy, R.I., Windmueller, H.G., and Brown, W.V. (1970) Identity of very low density lipoprotein apoproteins of plasma and liver Golgi apparatus. Science, 168: 380–382.

Mahley, R.W., Gray, M.E., Hamilton, R.L., and LeQuire, V.S. (1968) Lipid transport in liver. II. Electron microscopic and biochemical studies of alterations in lipoprotein transport induced by cortisone in the rabbit. Lab. Invest., 19:358–369.

Mahley, R.W., Hamilton, R.L., and LeQuire, V.S. (1969) Character-

ization of lipoprotein particles isolated from the Golgi apparatus of rat liver. J. Lipid Res., 10:433–439.
Martin, B.R., and Morré, D.M. (1988) Excess vitamin A decreases the specific activity of galactosyltransferase in Golgi apparatus of rat liver. J. Nutr., 118:968–975.
McCarthy, P., Richardson, C.L., Merritt, W.D., Morré, D.J., and Mollenhauer, H.H. (1974) Altered Golgi apparatus architecture in animal and plant tumors. Proc. Ind. Acad. Sci., 84:179–185.
Melançon, P., Glick, B.S., Malhotra, V., Weidman, P.J., Serafini, T., Gleason, M.L., Orci, L. and Rothman, J.E. (1987) Involvement of GTP-binding "G" proteins in transport through the Golgi stack. Cell, 51:1053–1062.
Merisko, E.M., Farquhar, M.G., and Palade, G.E. (1986a) Redistribution of clathrin heavy and light chains in anoxic pancreatic acinar cells. Pancreas, 1:110–123.
Merisko, E.M., Fletcher, M., and Palade, G.E. (1986b) The reorganization of the Golgi complex in anoxic pancreatic acinar cells. Pancreas, 1:95–109.
Mills, J.T., Furlong, S.T., and Dawidowicz, E.A. (1984) Plasma membrane biogenesis in eukaryotic cells: Translocation of newly synthesized lipid. Proc. Natl. Acad. Sci. U.S.A., 81:1385–1388.
Mollenhauer, H.H., Corrier, D.E., and Droleskey, R.E. (1990) An ultrastructural lesion induced by T-2 toxin in mice. Arch. Toxicol. (in press).
Mollenhauer, H.H., Hass, B.S., and Morré, D.J. (1976) Membrane transformations in Golgi apparatus of rat spermatids. A role for thick cisternae and two classes of coated vesicles in acrosome formation. J. Microsc. Biol. Cell (Paris), 27:33–36.
Mollenhauer, H.H., and Morré, D.J. (1991) Perspectives on Golgi apparatus form and function. J. Electron Microsc. Tech., 17:2–14.
Morré, D.J. (1977) Membrane differentiation and the control of secretion: A comparison of plant and animal Golgi apparatus. In: Brinkley, B.R. and Porter, K.R., eds., International Cell Biology 1976–1977. Rockefeller Univ. Press, New York.
Morré, D.J. (1989) Membrane alterations in neoplasia. In: The Pathobiology of Neoplasia. A Sirica, ed. Plenum, New York, pp. 323–344.
Morré, D.J., Kartenbeck, J., and Franke, W.W. (1979) Membrane flow and interconversions among endomembranes. Biochim. Biophys. Acta, 559:71–152.
Morré, D.J., and Ovtracht, L. (1977) Dynamics of Golgi apparatus: Membrane differentiation and membrane flow. Int. Rev. Cytol. [Suppl.], 5:61–188.
Morré, D.J., Keenan, T.W., and Mollenhauer, H.H. (1971) Golgi apparatus function in membrane transformations and product compartmentalization: Studies with cell fractions isolated from rat liver. Adv. Cytopharmacol., 1:159–182.
Morré, D.M., Morré, D.J., and Walter, M. (1981) Vitamin A effects on hepatic Golgi apparatus architecture. Eur. J. Cell Biol., 25:28–35.
Morré, D.M., Morré, D.J., Bowen, S., Reutter, W., and Windel, K. (1988) Vitamin A excess alters membrane flow in rat liver. Eur. J. Cell Biol., 46:307–315.
Morrison, T.G., and McQuain, C. (1977) Assembly of viral membranes: I. Association of vesicular stomatitis virus membrane proteins and membranes in a cell-free system. J. Virol., 21:451–458.
Myerowitz, R., and Neufeld, E.F. (1981) Maturation of α-L-iduronidase in cultured human fibroblasts. J. Biol. Chem., 256: 3044–3048.
Natowicz, M.R., Chi, M.M.Y., Lowry, O.H., and Sly, W.S. (1979) Enzymatic identification of mannose 6-phosphate on the recognition marker for receptor-mediated pinocytosis of β-gaucuronidase by human fibroblasts. Proc. Natl. Acad. Sci. U.S.A., 76:4322–4326.
Nakayama, I., Nickerson, P.A., and Skelton, F.R. (1969) An ultrastructural study of the adrenocorticotrophic hormone-secreting cell in the rat adenohypophysis during adrenal cortical regeneration. Lab. Invest., 21:169–175.
Niemann, H., Boxchek, C.B., Evans, D., Rosing, M., Tamura, T., and Klenk, H.-D. (1982) Post-translational glycosylation of coronavirus glycoprotein El: Inhibition by monensin. EMBO J., 1:1499–1504.
Nicolson, G.L. (1984) Cell surface molecules and tumor metastasis. Exp. Cell Res., 150:3–22.
Nii, S., Morgan, C., Rose, H.M., and Hsu, K.C. (1968) Electron microscopy of Herpes Simplex virus: IV. Studies with ferritin-conjugated antibodies. J. Virol., 2:1172–1184.
Nishimoto, S.K., Kajiwara, T., Ledger, W., and Tanzer, M.L. (1982) Effects of the ionophore monensin on type II collagen and proteoglycan synthesis and secretion by cultured chondrocytes. J. Biol. Chem., 257:11712–11716.
Nomura, T., Mizukawa, K., and Otsuka, N. (1987) Myocardial lesions and the alteration of atrial granularity in dystrophic mice. Arch. Histol. Jpn., 50:335–346.
Orci, L., Glick, B.S., and Rothman, J.E. (1986) A new type of coated vesicular carrier that appears not to contain clathrin: its possible role in protein transport within the Golgi stack. Cell, 46:171–184.
Pfeffer, S.R., and Rothman, J.E. (1987) Biosynthetic protein transport and sorting by the endoplasmic reticulum and Golgi. Annu. Rev. Biochem., 56:829–852.
Pohlman, R.A., Waheed, A., Hasilik A., and von Figura, K. (1982) Synthesis of phosphorylated recognition marker in lysosomal enzymes is located in the cis pat of Golgi apparatus. J. Biol. Chem., 257:5323–5325.
Proia, R.L., and Neufeld, E.F. (1982) Synthesis of β-hexosaminidase in cell-free translation and in intact fibroblasts: An insoluble precursor α chain in a rare form of Tay-Sachs disease. Proc. Natl. Acad. Sci. U.S.A., 79:6360–6364.
Prutkin, L. (1975) Mucous metaplasia and gap junctions in the vitamin A acid-treated skin tumor, keratoacanthoma. Cancer Res., 35: 364–369.
Quinn, P., Griffiths, G., and Warren, G. (1983) Dissection of the Golgi complex. II. Density separation of specific Golgi functions in virally infected cells treated with monensin. J. Cell Biol., 96:851–856.
Rapin, A.M.C., and Burger, M.M. (1974) Tumor cell surfaces: general alterations detected agglutins. Adv. Cancer Res., 20:1–91.
Redman, C.M., Yu, S., Bannerjee, D., and Morris, H.P. (1979) In vitro synthesis and secretion of albumin by Morris hepatoma 5123C and 7800. Cancer Res., 39:101–111.
Reitman, M.L., Varki, A., and Kornfeld, S. (1981) Fibroblasts from patients with I-cell disease and Pseudo-Hurler polydystrophy are deficient in uridine 5'-diphosphate-N-acetylglucosamine: Glycoprotein N-acetylglucosaminylphosphotransferase activity. J. Clin. Invest., 67:1574–1579.
Reuser, A.J.J., Kroos, M., Oude Elferink, R.P.J., and Tager, J.M. (1985) Defects in synthesis, phosphorylation, and maturation of acid α-glucosidase in glycogenosis type II. J. Biol. Chem., 260:8336–8341.
Reutter, W., and Bauer, C. (1978) Terminal sugars in glycoconjugates: Metabolism of free and protein-bound L-fucose, N-acetylneuraminic acid and D-galactose in liver and Morris hepatomas. In: Morris Hepatomas. Mechanisms of Regulation. H.P. Morris and W.E. Criss, eds. Plenum, New York, pp. 405–437.
Reutter, W., Tauber, R., Vischer, P., Harms, E., Grunholz, H. J. and Bauer, C. (1978) Turnover of proteins and glycoproteins of plasma membrane in liver, regenerating liver and Morris hepatoma. In: Protein Turnover and Lysosome Function, H.L. Segal and D.J. Doyle, eds., Academic Press, New York, pp. 779–790.
Reynolds, E.S. (1963) Liver parenchymal cell injury. I. Initial alterations of the cell following poisoning with carbon tetrachloride. J. Cell Biol., 19:139–157.
Rothman, J.E., and Lodish, H.F. (1977) Synchronized transmembrane insertion and glycosylation of a nascent membrane protein. Nature, 269:775–780.
Sandhoff, K. (1984) In: Molecular Basis of Lysosomal Storage Disorders. J.A. Barranger and R.O. Brady eds. Academic Press, New York, pp. 19–49.
Sando, G.N., and Neufeld, E.F. (1977) Recognition and receptor-mediated uptake of a lysosomal enzyme, α-L-iduronidase, by cultured human fibroblasts. Cell, 12:619–627.
Sandoval, I.V., Bonifacino, J.S., Klausner, R.D., Henkart, M., and Wehland, J. (1984) Role of microtubules in the organization of the Golgi apparatus. J. Cell Biol., 99:113s–118s.
Saraste, J., Palade, G.E., and Farquhar, M.G. (1986) Temperature-sensitive steps in transport of secretory proteins through the Golgi complex in exocrine pancreatic cells. Proc. Natl. Acad. Sci. U.S.A., 83:6425–6429.
Schatzman, R.C., Evan, G.I., Privalsky, M.L., and Bishop, J.M. (1986) Orientation of the v-erb-B gene product in the plasma membrane. Mol. Cell Biol., 6:1329–1333.
Schumaker, V.N., and Adams, G.H. (1969) Circulating lipoproteins. Annu. Rev. Biochem., 38:113–136.
Seegmiller, R., Ferguson, C.C., and Sheldon, H. (1972) Studies on cartilage. VI. A genetically determined defect in tracheal cartilage. J. Ultrastruct. Res., 38:288–301.
Seegmiller, R., Fraser, F.C., and Sheldon, H. (1971) A new chondrodystrophic mutant in mice. Electron microscopy of normal and abnormal chondrogenesis. J. Cell Biol., 48:580–593.
Sly, W.S., and Fischer, H.D. (1982) The phosphomannosyl recognition

system for intracellular and intercellular transport of lysosomal enzymes. J. Cell Biochem., 18:67–85.

Steckel, F., Gieselmann, V., Waheed, A., Hasilik, A., von Figura, K., Elferink, R.O., Kalsbeek, R., and Tager, J. (1982) Biosynthesis of acid α-glucosidase in late-onset forms of glycogenosis type II (Pompe's disease). FEBS Lett., 150:69–76.

Steckel, F., Hasilik, A., and von Figura, K. (1983) Biosynthesis and maturation of arylsulfatase B in normal and mutant cultured human fibroblasts. J. Biol. Chem., 258:14322–14326.

Steiner, S., Brennan, P.J., and Melnick, J.L. (1973) Fucosylglycolipid metabolism in oncoRNA virus-transformed cell lines. Nature, 245: 19–21.

Stephens, E.B., and Compans, R.W. (1988) Assembly of animal viruses at cellular membranes. Annu. Rev. Microbiol., 42:489–516.

Stevens, R.L., Fluharty, A.L., Kihara, H., Kaback, M.M., Shapiro, L.J., Marsh, B., Sandhoff, K., and Fischer, G. (1981) Cerebroside sulfatase activator deficiency induced metachromatic leukodystrophy. Am. J. Hum. Genet., 88:900–906.

Strous, G.J., Van Kerkhog, P., Willemsen, R., Gueze, H.J., and Berger, E.G. (1983) Transport and topology of galactosyltransferase in endomembranes of HeLa cells. J. Cell Biol., 97:723–727.

Tartakoff, A.M. (1986) Temperature and energy dependence of secretory protein transport in the exocrine pancreas. EMBO J., 5:1477–1482.

Thyberg, J., and Moskalewski, S. (1985) Microtubules and the organization of the Golgi complex. Exp. Cell Res., 159:1–16.

Tooze, J., Tooze, S.A., and Warren, G. (1988) Site of the addition of N-acetyl-galactosamine to the El glycoprotein of mouse hepatitis virus. J. Cell Biol., 106:1475–1487.

Treolar, M., Sturgess, J.M., and Moscarello, M.A. (1974) An effect of puromycin on galactosyltransferase of Golgi-rich fractions from rat liver. J. Biol. Chem., 249:6628–6632.

Ullrich, K., Mersmann, G., Weber, E., and von Figura, K. (1978) Evidence for lysosomal enzyme recognition by human fibroblasts via a phosphorylated carbohydrate moiety. Biochem. J., 170:643–650.

van Deurs, B., Petersen, O.W., Olsnes, S., and Sandvig, K. (1987) Delivery of internalized ricin from endosomes to cisternal Golgi elements is a discontinuous temperature-sensitive process. Exp. Cell Res., 171:137–152.

Varki, A.S., and Kornfeld, S. (1980) Identification of a rat liver α-N-acetylglucosaminyl phosphodiesterase capable of removing "blocking" α-N-acetylglucosamine residues from phosphorylated high mannose oligosaccharides of lysosomal enzymes. J. Biol. Chem., 255:8398–8401.

Varki, A.S., and Kornfeld (1981) Purification and characterization of rat liver α-N-acetylglucosaminyl phosphodiesterase. J. Biol. Chem., 256:9937–9943.

Varki, A., Reitman, M.L., and Kornfeld, S. (1981) Identification of a varient of mucolipidosis III (pseudo-Hurler polydystrophy): A catalytically active *N*-acetylglucosaminyl-phosphotransferase that fails to phosphorylate lysosomal enzymes. Proc. Natl. Acad. Sci. U.S.A., 78:7773–7777.

Varki, A., Reitman, M., Vannier, A., Kornfeld, S., Grubb, J.H., and Sly, W.S. (1982) Demonstration of the heterozygous state for I-cell *disease and pseudo-Hurler polydystrophy by assay of N-acetylglu*cosaminylphosphotransferases. Am. J. Hum. Genet., 34:717–729.

Vasiliev, J.M., and Gelfand, I.M. (1968) Surface changes disturbing intracellular homeostasis as a factor inducing cell growth and division. Curr. Mod. Biol., 2:43–55.

von Figura, K., and Klein, U. (1979) Isolation and characterization of phosphorylated oligosaccharides from α-N-acetylglucosaminidase that are recognized by cell-surface receptors. Eur. J. Biochem., 94: 347–354.

von Figura, K., Hasilik, A., and Steckel, F. (1984) In: Molecular Basis of *Lysosomal Storage Disorders. J.A. Barranger, and R.O. Brady*, eds. Academic Press, New York, pp. 133–146.

von Figura, K., Steckel, F., and Hasilik, A. (1983a) Juvenile and adult metachromatic leukodystrophy: partial restoration of arylsulfatase A (cerebroside sulfatase) activity by inhibitors of thiol proteinases. Proc. Natl. Acad. Sci. U.S.A., 80:6066–6070.

von Figura, K., Hasilik, A., Steckel, F., and Van de Kemp, J. (1983b) Biosynthesis and maturation of α-N-acetylglucosaminidase in normal and Sanfilippo B-fibroblasts. Am. J. Hum. Genet., 36:93–100.

Waheed, A., Hasilik, A., Cantz, M., and von Figura, K. (1982) Phosphorylation of lysosomal enzymes in fibroblasts: Marked deficiency of N-acetylglucosamine-1-phosphotransferase in fibroblasts of patients with mucolipidosis III. Hoppe-Seyler's Z. Physiol. Chem., 363: 169–178.

Waheed, A., Hasilik, A., and von Figura, K. (1981) Processing of the phosphorylated recognition marker in lysosomal enzymes. Characterization and partial purification of a microsomal α-N-acetylglucosaminyl phosphodiesterase. J. Biol. Chem., 256:5717–5721.

Whetsell, W.O. Jr., and Bunge, R.P. (1969) Reversible alterations in the Golgi complex of cultured neurons treated with an inhibitor of active Na and K transport. J. Cell Biol., 42:490–500.

Yeo, K., Parent, J.B., Yeo, T.-K., and Olden, K. (1985) Variability in transport rates of secretory glycoproteins through the endoplasmic reticulum and Golgi in human hepatoma cells. J. Biol. Chem., 260: 7896–7902.