present model), associated with increased intracellular protein and water, may be the basis for the "ballooning" of the hepatocytes that is commonly observed in alcoholic liver disease.

To determine the subcellular distribution of the increase in liver protein, mitochondria, microsomes, and cytosol were prepared. Recovery of each fraction was assessed by appropriate markers (*4*). Protein increased in all three fractions, but the total increase in mitochondrial and microsomal proteins accounted for less than half of the total increase in liver protein (Fig. 2). The major protein increase occurred in the 100,000*g* supernatant, or cytosolic fraction. Thus, in addition to the known increase in organelle protein (*5*), there is an even greater increase in soluble protein.

To determine whether the increase in soluble protein could be due, at least in part, to hepatic accumulation of proteins that are primarily exported from the liver into the plasma, albumin and transferrin where chosen as typical examples of export proteins. The concentration of these proteins was measured in deoxycholate extracts of the liver by immunoprecipitation with specific rabbit antiserums (*6*). The amount of plasma albumin that remained in the liver after perfusion with saline was calculated by tracing extrahepatic albumin with intravenously injected rat albumin labeled with ^{14}C, and dividing the radioactivity in the liver extracts by the specific activity of the plasma albumin. This value was similar in ethanol-fed rats (0.87 ± 0.08 mg per gram of liver) and in controls (0.86 ± 0.08; 8 pairs). The concentration of intrahepatic albumin increased in ethanol-fed rats (2.27 ± 0.24 mg per gram of liver; 10.12 ± 0.95 μg per milligram of liver protein) compared to controls (1.77 ± 0.24 and 7.75 ± 0.70, respectively; $P < .01$). Hepatic transferrin concentration also increased in the ethanol-fed rats (0.40 ± 0.02 mg per gram of liver and 2.15 ± 0.13 μg per milligram of liver protein compared to 0.34 ± 0.01 and 1.91 ± 0.13, respectively, in the controls; $P < .01$). Plasma concentrations of these proteins were similar in both groups of animals. The increases in hepatic albumin and transferrin concentrations indicate that intrahepatic deposition of export proteins could contribute to the increase in soluble protein. By contrast, the concentration of a nonexport protein of the cytosol, ferritin, when measured by radial immunodiffusion (*7*) in a "heat supernatant" of liver homogenate (*8*), showed a significant decrease in the animals treated with ethanol (0.33 ± 0.03 mg per gram of liver and 1.77 ± 0.16 μg per milligram of protein compared to 0.40 ± 0.02 and 2.24 ± 0.11, respectively, in the controls; $P < .02$).

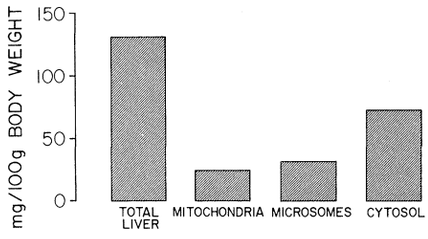

Fig. 2. Distribution among subcellular fractions of the increase in liver protein induced by ethanol feeding. The increase in mitochondrial protein is not significant. All other increases are significant ($P < .01$).

Accumulation of export proteins in the liver could be due either to increased production or to decreased transport into the blood. Albumin and transferrin production decreased after acute administration of ethanol, whereas albumin production was unaffected by long-term feeding of ethanol (*9*). Since it has been postulated that the microtubular system plays a role in the export of proteins by the liver (*10*), colchicine binding, which is a characteristic property of microtubular protein, was measured (*11*). Colchicine binding, which depends on the equilibrium between soluble and insoluble microtubular protein, reflects the functional state of the microtubular system. Cytosolic proteins from the livers of rats that were fed ethanol bound significantly less colchicine (22.23 ± 1.45 nmole per gram of protein; 1.57 ± 0.13 nmole per gram of liver) than those of controls (27.00 ± 1.85 and 2.12 ± 0.14, respectively; 10 pairs; $P < .01$), resulting in an absolute decrease in the hepatic capacity to bind colchicine (18.94 ± 1.98 nmole per total liver compared to 23.30 ± 2.12 in controls; $P < .01$). This suggests a decreased amount or an altered functional state of microtubular protein in the livers of ethanol-fed rats. This finding is consistent with the hypothesis that the feeding of ethanol may decrease the ability of the liver to export proteins. In any event, the alteration of this fundamental hepatic function and the hitherto unrecognized accumulation of proteins in the liver reveal a potentially important new site of the hepatotoxic action of ethanol.

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Exocrine Pancreas: Evidence for Topographic Partition of Secretory Function

Abstract. *The pattern of amylase, lipase, and chymotrypsinogen content found in pancreatic exocrine tissue surrounding the islets of Langerhans (periinsular halos) differs from that of the rest, or teleinsular part, of the pancreas. Such a topographic partition of secretory function may play a role in the regulation of pancreatic juice composition.*

The pancreatic islets of Langerhans were first described more than a century ago (*1*), their endocrine function was established 25 years later (*2*), and their two main hormones, insulin and glucagon, were isolated in 1921 and 1948, respectively (*3*). While much data have accumulated about their structure and function, it is still not clear why the endocrine pancreatic cells are disseminated in discrete clusters within the exocrine gland in most higher vertebrates (*4*).

There is structural and functional evidence that intimates physiological links between the endocrine and exocrine cells of the pancreas, both of which are thought to

Table 1. The concentrations of amylase (A), lipase (L), and chymotrypsinogen (Ch), relative to each other, and the teleinsular/periinsular ratios of such relative concentrations. Mean values (± standard error of the mean) in the three groups of animals are shown together with the number of individual determinations in each group (in parentheses). Mean ratios significantly different from unity are indicated by the following symbols: *$P < .005$; †$P < .05$; ‡$P < .02$.

Hydrolases	Location	Normal rats	Diabetic rats	Spiny mice
	Relative concentrations of hydrolases in teleinsular and periinsular tissues			
A/L	Teleinsular	2.49 ± 0.34(9)	0.12 ± 0.04(10)	0.81 ± 0.07(12)
	Periinsular	1.21 ± 0.17(6)	0.09 ± 0.03(10)	0.66 ± 0.04(12)
A/Ch	Teleinsular	10.43 ± 0.81(9)	0.60 ± 0.18(10)	2.91 ± 0.17(12)
	Periinsular	8.26 ± 0.73(6)	0.39 ± 0.11(10)	1.94 ± 0.12(12)
L/Ch	Teleinsular	4.83 ± 0.52(9)	4.46 ± 0.84(10)	3.79 ± 0.33(12)
	Periinsular	7.39 ± 1.18(6)	4.47 ± 1.01(10)	3.03 ± 0.23(12)
	Teleinsular/periinsular ratio of relative concentrations			
A/L		1.784 ± 0.162*(6)	1.566 ± 0.230†(10)	1.255 ± 0.100†(12)
A/Ch		1.158 ± 0.088(6)	1.362 ± 0.072*(10)	1.530 ± 0.086*(12)
L/Ch		0.712 ± 0.062‡(6)	1.076 ± 0.131(10)	1.278 ± 0.090‡(12)

be derived from the ductular epithelium (*5, 6*). For instance, the exocrine tissue has almost no direct arterial supply; most of the arterioles go to the islets where they break into capillaries. The exocrine capillary network is supplied through the efferent capillaries emerging from the islets (*7*). Functionally, the endocrine and exocrine cells not only display simultaneous response to nervous (*8, 9*) or extrapancreatic hormonal stimulation (*10*), but they may also exert a mutual and direct control of their secretory activity. That is, insular hormones modify exocrine function (*11, 12*), and exocrine factors may alter islet cells' responsiveness to certain secretagogues (*13*).

Another provocative feature of pancreatic organization is the presence around the islets of acini, which can be distinguished from the teleinsular exocrine tissue by tinctorial criteria. Such periinsular halos were described as early as 1899 (*14*), and are composed of large acinar cells packed with zymogen granules (*8, 15, 16*). Our data presented here indicate that such an anatomical segregation coincides with a functional heterogeneity of the exocrine tissue.

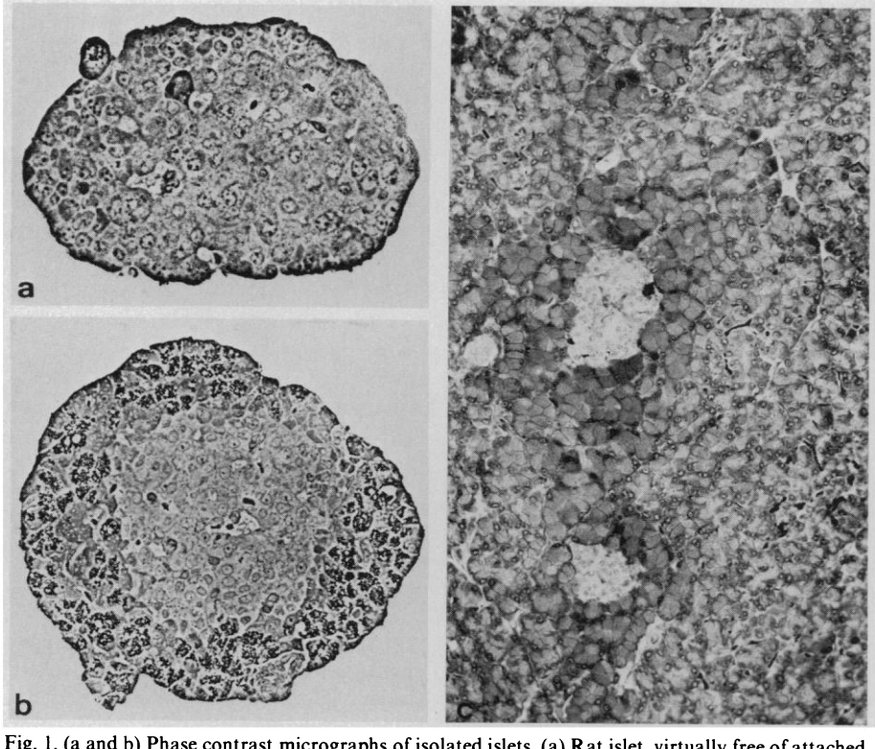

Fig. 1. (a and b) Phase contrast micrographs of isolated islets. (a) Rat islet, virtually free of attached exocrine tissue (× 300); (b) spiny mouse islet: an irregular layer of exocrine cells completely surrounds the islet (× 200). (c) Light micrograph of the pancreas of a streptozotocin-diabetic rat. Aldehyde fuchsin stain. The islets contain no granulated B cell. The acinar cells forming the periinsular halo appear larger and darker than the teleinsular acinar cells (× 120).

Our study was prompted by the following observations. First, when islets are isolated by the technique of Lacy and Kostianovsky (*17*), and exposed to collagenase at 37°C, it is possible to obtain islets completely free of surrounding acini (Fig. 1a). In the spiny mouse (*Acomys cahirinus*), however, the halo remains firmly attached to the islets during the islet isolation procedure (Fig. 1b). The above method allows easy separation of periinsular and teleinsular exocrine tissue, respectively. Second, while studying rats made diabetic with streptozotocin, we noticed that they exhibited particularly striking periinsular halos, when compared with intact control rats (Fig. 1c). We decided, therefore, to measure the concentration of hydrolases in periinsular and teleinsular exocrine tissue from spiny mice and from normal and diabetic rats.

Pancreases were excised from normal, fully fed rats (approximately 250 g), from rats made diabetic by intravenous injection of streptozotocin (40 to 60 mg per kilogram of body weight) and examined 1 week later ($N = 5$) and 30 weeks later ($N = 5$), and from spiny mice (40 g; 7 weeks old) obtained from a colony bred at the Institut de Biochimie Clinique (University of Geneva) (*18*). The pancreas from each animal was treated with collagenase (10 to 13 mg per pancreas) (*17*). In order to obtain rat islets with attached periinsular exocrine tissue, the collagenase digestion was halted before completion. One sample of 200 to 300 islets with surrounding acini and two samples of teleinsular acinar fragments were collected after being so identified by observation under a binocular dissecting microscope, homogenized in distilled water (1.0 ml), and stored at −20°C until assayed. Amylase activity was measured at 30°C, with potato starch as the substrate and colorimetry with 3,5-dinitrosalicylic acid (*19*), lipase was measured with tributyrin as the substrate (*20*), and chymotrypsinogen was assayed according to the technique described by Vandermeers-Piret *et al.* (*21*). All results were expressed in activity units, defined as micromoles of the product assayed liberated per minute and per milliliter of tissue homogenate (*22*). As a rule, the concentration of the hydrolases in the homogenates of both teleinsular and periinsular exocrine tissue remained well within the limits of fidelity for the enzyme assays.

In order to correct for the inherent variations in the amount of exocrine tissue present in each homogenate, the concentration of hydrolases relative one to another was calculated for each sample (Table 1, upper panel). Three major findings emerged from these calculations. (i) Diabe-

tes is associated with a preferential reduction of the amylase content relative to that of lipase and chymotrypsinogen, in both teleinsular and periinsular exocrine tissue (*12*). (ii) The relative concentration of amylase in spiny mice, which are known to present an abnormal pattern of insulin release (*23*), occupies an intermediate position in between that of normal and diabetic rats. (iii) In certain instances, the relative concentration of hydrolases, within the same group of animals, appears to differ in teleinsular and periinsular tissue. The last-mentioned finding was substantiated by computing the ratio of teleinsular to periinsular values for the relative amounts of hydrolases in each animal (Table 1, lower panel). Among the nine computed ratios (Table 1), seven differed significantly from unity ($P < .05$ or less). For instance, the concentration of amylase relative to that of lipase was invariably higher in the teleinsular than in the periinsular exocrine tissue, whether in tissue from spiny mice, normal rats, or diabetic rats. Highly significant differences ($P < .005$) were found at least once in each group of animals.

Our data indicate that in both normal and diabetic rats, as well as in spiny mice, the pattern of hydrolase content is significantly different in teleinsular from that of periinsular exocrine pancreatic tissue. This difference was detected despite the limited cross contamination which may have affected our sampling of periinsular and teleinsular tissues. We cannot rule out the possibility that more marked differences between periinsular and teleinsular tissues could be found for other exportable enzymes, which might be preferentially synthesized in one of these two compartments of the exocrine pancreas. In the framework of present knowledge, we can only surmise the significance of such a topographic partition of secretory function in the exocrine pancreas.

In considering the influence of islets hormones on surrounding exocrine tissue function, emphasis is often given to the possible role of insulin (*16*). Landing (*24*), however, found the same proportion of periinsular halos in the pancreases of normal and diabetic children. Moreover, we observed that the histological identification of the halos was more obvious in rats made diabetic with streptozotocin and in spiny mice, known for their abnormal pattern of insulin release, than in normal rats. Consideration should be given, therefore, to the possible role of the secretory product of the other islet cell types.

A hypothetical implication of our findings is that the secretory partition of the exocrine pancreas would be responsible for modulations in the composition of pancreatic juice under different experimental conditions. Recent studies indicate that preferential and rapid release of certain hydrolases can be evoked by intragastroduodenal administration of certain nutrients (*25*) or by intravenous injection of chymodenin, a peptide extracted from the hog duodenum (*26*). These observations seem incompatible with the commonly held view that pancreatic enzyme secretion is an en masse discharge of secretory granules (*27*) in which the different enzymes are packaged together (*21, 28*). The existence of a functional compartmentalization of the exocrine pancreas could reconcile these two series of observations. Thus, the periinsular acini may differ from the teleinsular tissue in the level of their secretory activity (*16*), their response to various secretagogues (*8*), and, as shown above, their relative content in different hydrolases.

Our findings indicate that the precise concentration of each hydrolase in pancreatic juice and its adaptation to environmental factors such as the type of food ingested may be governed, at least in part, by a coordinated participation of hormones emerging not only from the gastrointestinal mucosa, but also from the islets of Langerhans and affecting topographically distinct areas of the exocrine pancreas.

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