The pancreas is a unique organ comprising both endocrine and exocrine tissues. The endocrine tissue is only 1–2% of the volume in the adult pancreas and is scattered as islets of Langerhans throughout the exocrine pancreas. The question of what advantage is conferred by having scattered islands of endocrine cells was posed by Henderson in 1969 (25). He hypothesized that the high local levels of islet hormones were necessary for the proper maintenance and functioning of the acinar tissue and that the hormones were carried via an insulo-acinar portal system. Such a portal system was based on earlier data on the microcirculation patterns as described by Wharton (80) and Thiel (77). In the past 15 years our understanding of the anatomy and functional implications of the microvasculature of the pancreas has greatly increased. This chapter will review our current understanding of these areas as well as the regulation of blood flow within the pancreas.

The pancreas is part of the splanchnic circulation; blood is supplied by the celiac and superior mesenteric arteries and drains into the portal vein. The regional variation of the pancreas, based on embryonic derivation from different anlage, includes separate vascularization, ductal drainage, and varied composition of islets (57). Thus the head of the pancreas, which has pancreatic polypeptide-rich and glucagon-poor islets, is supplied by the superior mesenteric artery, while the body and tail, which have glucagon-rich and pancreatic polypeptide-poor islets, are supplied by the celiac via the splenic artery. The interlobular arteries and veins run in parallel and in close proximity to the major ducts. The intralobular artery runs straight through the center of a lobule with branches to islets, acini, and ductules; in some species the intralobular vein is more peripheral and not parallel to the artery (53,55), while in the rat the intralobular vessels are parallel to each other (5).

Large lymphatic vessels run between the lobules within the mesentery. No ramification of these vessels is seen within the lobule nor within the islets (7,19). Amy-
lase, lipase, and insulin have been inconsistently detected in thoracic duct lymph in normal individuals (7,10,50) but could be accounted for by the high permeability of the pancreatic capillaries.

PERMEABILITY

The permeability of the pancreatic capillaries has been described as highly permeable and comparable to those of the small intestine (22,41). Pancreatic capillaries were permeable to horseradish peroxidase in less than 5 minutes but were more restrictive to larger molecules with minimal permeability to hemoglobin and none to ferritin, albumin, and immunoglobulin G. However, it may not be valid to lump all the pancreatic capillaries together since capillaries within the islets and those within the exocrine differ in a number of characteristics. In another study, horseradish peroxidase was seen to pass into the islet pericapillary interstitial space within 45 seconds (45), implying that islet capillaries may be even more permeable than the rest of the pancreatic capillaries. Morphologically islet capillaries have a greater diameter than exocrine ones (5,7,27) and tenfold more fenestrations per μm of endothelium (27). In fact there was an abrupt transition in the capillaries at the edge of an islet, with significantly more fenestrations facing the endocrine cells than facing the exocrine cells (27) (our unpublished data). Thus, the microvessels of the pancreas are highly permeable with the islet capillaries being even more so. The high permeability of both the islet and pancreatic capillaries play a role in the integration of the endocrine and exocrine tissues.

REGULATION OF BLOOD FLOW

Much of the early work on the pancreatic blood flow used whole mounts of pancreas that had been intravenously infused with vital dyes, India ink, or the like. The islets were found to be more vascular than the exocrine tissue and to be filled first with infusion. Islets were found to have a direct arteriolar blood flow; the exocrine tissue had different patterns depending on the species. These various patterns will be discussed later. Recently intravital dye infusion, using a fluorescent dextran that outlined the endothelial walls, was able to characterize the dynamic state of the blood flow in the pancreas (63). In basal conditions no selective flow regulation occurred within an islet, that is there was a constant velocity without intermittent changes. These findings were in contrast to earlier work that had suggested intermittent blood flow caused by precapillary sphincters (50). The question of sphincters has not been clearly resolved.

A perfusion of the islets 8–20 times greater in intensity than that of the acinar tissue was found using nonradioactive microspheres to quantify blood flow (30,31,43,44,51). Jansson measured in the rat a pancreatic blood flow of 0.60 ml/min/g pancreas, whereas that of the islets was 0.069 ml/min/whole pancreas (31). Thus the islets, which are 1–2% of the pancreatic volume, receive approximately 10% of the pancreatic blood flow (31,43,44,51). An average islet is completely perfused every 3 seconds. The rate of flow/unit islet volume was linear for increasing islet size until the islet diameter was greater than 165 μm in diameter; above this size the perfusion decreased (44). Lifson et al. found that the largest 20% of the islets, those greater than 140 μm accounted for 72% of the islet volume and 64% of the islet blood flow. Conversely the smallest 40% of islets (77 to 25 μm diameter) accounted for only 4.5% of the volume and 8% of the islet blood flow. Thus the overall function of the islet organ is dominated by the small number of large islets (5,44).

Jansson and coworkers have used the same technique to expand our understanding of the regulation of pancreatic and islet blood flow. They found that elevated glucose concentration increased the islet blood flow in islets from all regions of the pancreas (31,32). This increase was preferential for the islets, and there was little change in the pancreatic blood flow. Further studies lead to their finding that the glucose-sensitive control mechanism for the blood flow was extrapancreatic. Intracarotid infusion of D-glucose, but not L-glucose, 3-O-methylglucose, or saline, caused rapid increases in serum insulin concentrations and islet blood flow (33). These increases could be abolished by vagotomy or atropine, leading to the conclusion that glucose-induced increases in islet blood flow were due to a neurally mediated redistribution of flow within the pancreas (29). Their evidence suggested a vagal cholinergic influence. Several additional agents have been suggested to regulate the blood flow: norepinephrine (64), vasoactive peptides from either the islet nerves, e.g., VIP (42), or from islet endocrine cells, e.g., calcitonin-related gene product (CRGP) (6,59). The regulation of blood flow through the islet may be yet another way to regulate hormone secretion; this possibility needs further study.

THE MICROVASCULATURE OF THE PANCREAS

The microvasculature of the pancreas can be divided into that of the islet, of the acini, and of the ducts. Such a separation is only a convenience for discussion because the microvasculature is actually interconnected. The microvasculature of the islet, described as glomerular-like, has been studied in many species (dog, rat, cat, rabbit, guinea pig, mouse, horse, pig, human, and monkey) (2,8,17,26,77) with ink- or dye-infused whole mounts or with scanning electron microscopy of corrosion casts. The microvasculature of the rat has been studied the most extensively and can serve as a paradigm.
FIG. 1. The microvasculature of the small (less than 160 μm diameter) islet of Langerhans. A: A scanning electron micrograph of a methymethacrylate corrosion cast. The same islet had been viewed at numerous angles and tilts to verify the continuity of the various vessels. Arterioles (A) and venules (V) can be identified and distinguished by the different imprints of the endothelial nuclei (arrowheads) seen in the casts. In this islet an arteriole passes by and gives off at least two smaller arterioles (a), which branch into numerous capillaries forming a glomerular-like network. Numerous efferent capillaries (e) arise from this glomerulus, pass around the islet, and coalesce at 50–100 μm distance to form collecting venules. These efferent vessels are the basis of the insulo-acinar portal system. Magnification bar = 20 μm. B: Diagram based on corrosion casts and reconstructions of India ink-infused, immunostained islets. Fewer capillaries than actually present are shown. The arterioles enter the islet through a gap in the non-B cell mantle and directly enter the B-cell core where they branch into numerous capillaries. After traversing the core, the capillaries pass along and through the mantle, and then coalesce into collecting venules just outside the islet or after passing through exocrine tissue. (Reproduced from ref. 5 by permission of the American Diabetes Association.)
Corrosion casts, made from infusing unpolymerized plastic through the aorta, then polymerizing the plastic and digesting away the tissue, have afforded 3-dimensional views of the islets within the pancreas. Islets are not randomly nor evenly distributed throughout the pancreas. Islets could be classed by size with each class having a preferential location within the vascular tree (2,5). Small islets (60–160 μm diameter) are usually toward the tip of a lobule, enmeshed in exocrine tissue, and not close in association with large branches of either blood vessels or ducts. Intermediate islets (160–260 μm diameter) are found along secondary vessels. Large islets (260–
grade and retrograde perfusion, Lifson et al. found in the rat and rabbit the arterial supplies to the endocrine and exocrine tissues in parallel, with 10–20% going to islets but 80–90% going directly to acini. In the rabbit all or nearly all of the blood upon leaving the islet was said to then go to the acinar tissue, via an insulo-acinar portal system (43). In most infusion studies, islets filled first even when there was incomplete filling of the pancreatic vasculature. This finding led to the conclusion that all blood first passed through the islets before reaching the exocrine tissue. However, even with parallel circulations one would expect islet vasculature to fill first for two reasons: 1) the arterial pressure would be higher at the end of the short islet afferent arteriole than at the longer exocrine one (2) and 2) the larger diameter of islet capillaries should confer a lower flow resistance than the smaller exocrine capillaries.

While it is often dangerous to generalize across species, such generalizations can be helpful in developing concepts. Even so each species needs to be reexamined with corrosion casts and with attention to islet size and location; only then will it be clear how much variation actually exists between species. With these caveats let us describe an overall pattern that seems consistent for most species: The more numerous small islets, which are embedded in the exocrine tissue, have efferent capillaries extending into the exocrine tissue, forming an insulo-acinar portal system; the fewer in number large islets, which are not usually closely related to exocrine tissue, drain directly into venules. All mammalian species probably have direct arteriolar flow to both islets and acini, direct venous drainage from large islets, and an insulo-acinar portal system mainly from small islets; it is also probable that species vary in the proportions of these options.

FUNCTIONAL IMPLICATIONS OF THE MICROVASCULATURE OF THE PANCREAS

The anatomy of the microvasculature of the pancreas illustrates how well the endocrine and exocrine components of the pancreas are integrated. In addition these morphological data are useful in defining constraints that limit the potential interactions suggested by physiological data. The two important levels of interactions within the pancreas are the intraislet and the islet-acinar.

INTRAISLET INTERACTIONS

Many interactions within the islet have been postulated; these interactions were based on the complex organization of the endocrine cells and on physiological data. The mammalian islet has a nonrandom distribution of endocrine cells usually with a core of B-cells surrounded by a discontinuous mantle of non-B- (glucagon-producing A-, somatostatin-producing D-, and pancreatic poly-
peptide-producing PP-) cells (13,58). Human and other primates have a more complex pattern but can be considered composites of several mantle-core subunits or being lobulated with mantle-core lobules (13,21,56). Presently the one exception to this pattern is in the horse, which is reported to have a core of A-cells (16,17); however, this exception has not been reevaluated in 20 years. Experiments using exogenous islet hormones with either isolated islets or perfused pancreas preparation have provided data that islet hormones can influence the other islet cells in feedback loops (49,67). These studies have led to the concept of paracrine interactions regulating islet secretion.

Fujita provided the anatomic basis for the concept that the A- and D-cells could and did regulate B-cell secretion (16,17). Using both ink-infused samples of horse pancreas and corrosion casts of monkey pancreas, he described the arteriole entering the islet at the level of the A-cells before breaking into the islet capillaries. In the horse and monkey the A-cells were described as centrally located in the islet with an arteriole penetrating further in the islet core than in the rat and rabbit, which have A-cells as a peripheral mantle of cells. Fujita suggested that the microcirculation of the islet was designed so that blood laden with glucagon and somatostatin could be conveyed to the downstream B-cell and regulate it. This hypothesis was valuable in stimulating ideas and experiments, but more recent work has provided compelling evidence for a different set of intraislet interactions. A study we did combining the three-dimensional organization of the microvasculature of the islets afforded by corrosion casts and serial reconstructions of immunostained ink-infused rat pancreas showed that while the arteriole does break into capillaries close to the mantle of non-B-cells, the arteriole enters directly into the B-cell core passing into the islet through one of the gaps or discontinuities of the non B-cell mantle (5) (Fig. 3). Such a microvascular pattern confers a directionality of blood flow from the point of arteriolar entry through the B-cell core to the peripheral non-B-cell mantle. This pattern favors high concentrations of blood-borne insulin influencing the downstream A- and D-cells. The converse, that of the A- and D-cells influencing insulin secretion, was less likely. Stagner and Samols have since added physiological data that supports the directionality of islet blood flow from B- to non-B-cell. In fact their series of passive neutralization experiments using both anterograde and retrograde perfusions in dog, rat, monkey, and man support a B to A to D pattern (72–74). In fact they have shown that a relatively small increase in glucagon secretion can cause a sevenfold increase in somatostatin secretion (72). The functional implications of this directional blood flow can be understood with variations of insulin secretion. When glucose stimulates insulin secretion, the insulin will locally suppress glucagon release. This is a more attractive explanation than having the A-cells directly sense glucose (79). In diabetes when insulin secretion is minimal, glucagon secretion would no longer be suppressed and would thereby increase, which in turn would stimulate an increase in somatostatin secretion; increased glucagon is often seen in diabetes (68).

The term paracrine has been often used to describe all local effects. However, paracrine can be limited to the effects of simple diffusion through the interstitium, with the blood-borne mediated effects described as endocrine or portal. With this narrower definition of paracrine, there has been little strong evidence for paracrine interactions within the islet. Without an intact microvasculature isolated islets do not provide valid data on this issue. In fact valid data are hard to gather since little is known about the interstitial fluid flow. One can presume that it would be in the same direction as the blood flow and that diffusion inward to the islet core would be severely limited. If this were so, then in large islets there should be a central core of B-cells that would be essentially isolated by their distance from the non-B cells and thus from all but systematically circulating islet hormones. On the other hand the peripheral B-cells may be under local or paracrine influence of hormones secreted by adjacent or nearby non-B-cells. In contrast in small islets essentially all the B-cells might be close enough to the non-B cells to be influenced by them; thus all the B-cells could be considered peripheral ones. Some differences between peripheral and central B-cells have been reported. Central B-cells of large islets have been reported to have smaller nuclei than either the peripheral B-cells of large islets or any B-cells in small islets (23). In addition central B-cells degranulate before peripheral ones when a rat is stimulated in vivo with either glucose or glibenclamide (75). These findings may reflect the paracrine protection of

**FIG. 3.** An example of a large islet seen in sectioned tissue following India Ink infusion and staining by immunofluorescence to show the non-B-cells; such sections were used in the reconstructions of the islets. Blood vessels filled with India ink appear as black spaces of irregular contour, and an arteriole (arrow) is seen entering the islet at a discontinuity of the non-B-cell mantle. Magnification bar = 50 μm. (Reproduced from ref. 5 by permission of the American Diabetes Association.)
the central B-cells and the paracrine influence of non-B-cell hormones on peripheral B-cells. In addition there is convincing evidence that there are heterogenous populations of B-cells when they are studied as single cells in vitro (28,60,66,69), but no correlation between these in vitro and in vivo differences has yet been made.

INSULO-ACINAR INTERACTIONS

The hypothesis that islets of Langerhans were scattered throughout the exocrine pancreas in order to regulate the exocrine functions is well supported by both anatomical and physiological data. In fact this arrangement may also help coordinate the hormonal and enzymatic components of food digestion and utilization. The basis of this arrangement is the extension of efferent capillaries from the islet into the acinar tissue. Thus as blood passes through the islets it becomes enriched with high concentrations of islet hormones. These hormones can then diffuse through highly permeable capillaries into the acinar tissue. This type of vascular arrangement has been called a continuous portal system since there are no intervening larger vessels (26).

However, the concept that all the blood to the pancreas first passes through the islets is not supported by the anatomical evidence. Let us consider the rat, a laboratory animal often used in the physiological studies as well as having been most extensively studied anatomically. The microsphere studies have shown that a disproportionately large fraction of the pancreatic blood flows through the islets but even with glucose stimulation this fraction is only 22% (31). Therefore at least 78% of the acinar blood flow is direct arteriolar flow and not part of an insulo-acinar portal system. One must then consider that 60–70% of the islet volume, that is the large islets, does not influence the acinar tissue much since there is direct venous drainage from these islets. Then the remaining 40% of islet volume, that is the islets of less than 140 μm diameter, account for no more than 8% of the pancreatic blood flow. Thus in the rat, the insular-acinar portal system probably transports less than one-tenth of the pancreatic blood flow, but its contribution to the overall function of the exocrine pancreas is notable.

The local effects of islet hormones on acinar tissue could act via leakage of interstitial fluid directly from islets or be vascuarily mediated via the insulo-acinar portal system. One barrier to the free flow of islet interstitial fluid into the surrounding acinar tissue is the islet capsule. The capsule is a layer of fibroblasts and the collagen fibers laid down by these cells; it surrounds an islet and separates the islet from the acinar tissue. However sometimes the capsule is incomplete and then only the basement membranes of the exocrine and endocrine cells are between these cells. Stagner and Samols have elegantly shown that most of islet-acinar effects were vascularly mediated (68). They measured the insulin concentration in acinar interstitial fluid in rat pancreas that was perfused anterogradely or retrogradely at normal and elevated glucose levels. With perfusions of both directions the vascular concentration of insulin increased in response to glucose, but its concentration in the interstitial fluid only increased with anterograde perfusion, thus ruling out an indiscriminate leakage from the islet at the initial step. However, if the lymphatic vessels do only pass by rather than through lobules (19), then one could expect that acinar interstitial fluid would drain toward these vessels and that a gradient of islet hormones would extend further than the islet effluent capillary network.

Morphological differences between acinar cells that are near islets (peri-insular) and distant from islets (tele-insular) have been recognized for many years. The peri-insular acinar cells rim the islet in a halo 50–100 μm diameter; these cells are larger, with larger nuclei and with more zymogen granules than tele-insular acinar cells (40). Most often these differences have been attributed to the local high insulin levels since halos were more prominent in hyperinsulinemic obese (ob/ob) mice (24) and were said to disappear after alloxan destruction of beta cells. However, peri-insular halos were prominent after treatment with another beta cell toxin, streptozotocin, so the other islet hormones may also be involved, possibly by their inhibition of enzyme secretion (47). Biochemical differences in peri-insular and tele-insular acini have also been reported (47). The amylase to chymotrypsinogen ratio is lower for peri-insular acini; this has been confirmed with immunogold staining (61). In addition individual zymogen granules from one animal differ markedly for those same enzymes (52), but it is still unresolved if this granule heterogeneity is present within the same cell, the same acinus, or even the same lobule (1).

Strong suggestions of islet influence on exocrine pancreas have been drawn from studies of human diabetes. In type 1 (IDDM) autopsied pancreas are often atrophied with increased fibrosis and fatty infiltration (62). In addition high incidence of pancreatic dysfunction has been observed in IDDM (15). The preservation of exocrine function has been shown to be proportional to the residual B-cell secretion as measured by C-peptide levels (15).

The physiological evidence for an insulo-acinar system has been reviewed by Williams and Goldfine (82). Some experiments have infused exogenous hormones into the pancreas such that all the pancreatic blood flow would have elevated concentrations instead of the 8% that would be carrying islet-enriched blood; such experiments can only show potential interactions rather than actual interactions. Even when endogenous islet secretion in vascally intact pancreas is studied, the interpretations of the actions of each islet hormone are complicated. These complications are further illustrated by the discrepancy often found for effects in vascally per-
fused pancreas and isolated acini. This discrepancy may be due to loss of receptors on acini during isolation or to intraislet vascularity mediated interactions.

*Insulin* has clearly been shown to enhance the function of the acinar tissue, and its absence in diabetes has been shown to impair exocrine function. Saito et al. showed the effect of insulin on exocrine tissue using the perfused rat pancreas (65). When endogenous insulin was stimulated by infusion of glucose, pancreatic secretion in response to CCK was potentiated (200%). Sugars that did not stimulate insulin release did not have this effect. Neither insulin nor high glucose stimulated amylase secretion directly, but both potentiated the effects of secretagogues for the exocrine tissue (18,65). Passive neutralization experiments using anti-insulin serum in the perfused rat pancreas resulted in a marked reduction of stimulated amylase and lipase secretion (78). These data were interpreted as showing the direct effect of insulin on the exocrine tissue, but the effects may be more complicated. With insulin bound to its antibody, its suppression of glucagon would also be removed. With the resulting glucagon stimulation, somatostatin would also be stimulated and could then directly inhibit exocrine function. The reduction of pancreatic secretion could then be due to both the loss of enhancement by insulin and the inhibition by somatostatin. In vitro experiments have shown direct effects of insulin on enhancement of acinar function; insulin added to acini in vitro increased glucose transport and increased protein synthesis (37,81). Other evidence of direct effects are that insulin receptors are on the basolateral membranes of acinar cells (3,39). Insulin, on a transcriptional level, has been shown to regulate amylase mRNA in rats (38) and one amylase isoform in mice (11).

*Somatostatin* seems also to have direct effects on acinar tissue. When infused in vivo, somatostatin inhibits stimulated pancreatic secretion in dogs, man, and rats (4,9,14,70,76). Exocrine tissue is extremely sensitive to low levels of somatostatin, but there are some species differences. Specific somatostatin receptors have been identified on acinar cells (18). In fact in a single pass perfusion of the canine pancreas 80% of the infused somatostatin was cleared by the pancreas whereas only 10–20% of infused insulin or glucagon was cleared (35).

The effect of glucagon is not so well defined. In vivo glucagon in dogs and rats inhibited CCK or secretin-stimulated pancreatic secretion (12,36), but in vitro glucagon has been reported to stimulate secretion (36,48). A contaminant was suggested as the stimulatory agent (82), but another explanation may be possible. Intraislet increases of glucagon promote very large increases of somatostatin secretion (72), and the acinar tissue is extremely sensitive to somatostatin; perhaps the in vivo inhibition attributed to glucagon is only indirect via the somatostatin increase.

The effect of *pancreatic polypeptide* is also confusing. Intravenous infusion of pancreatic polypeptide inhibits pancreatic secretion during the interdigestive stage and after CCK stimulation (46,71). In addition passive neutralization experiments with the infusion of anti-pancreatic polypeptide serum caused an increase in both interdigestive and postprandial pancreatic secretion (71). However in vitro experiments have shown no inhibition of stimulated secretion and in fact no binding of radiolabelled PP to acini (34). These data suggest that PP may affect the acinar tissue only indirectly. It is not known where PP is in the intraislet perfusion order but it may be that PP cells are similarly situated as A-cells, in which case the effect of PP could be via an enhanced somatostatin secretion that inhibits the pancreatic secretion. There are however other data suggesting a positive effect of PP on the acinar tissue. PP in culture is reported to stimulate acinar cell DNA synthesis (20). Even stronger data are found at autopsy of type 1 (IDDM) diabetics. The pancreas of IDDM patients is generally markedly atrophied, but the PP-rich lobe (the ventral lobe) of the pancreas was found to be normal in weight even with marked atrophy of the dorsal lobe (62). These findings suggest that a trophic or protective factor (possibly PP) is secreted from the islets in this lobe.

The integration of the morphological and the physiological data on the insulo-acinar portal system is consistent with a heterogeneous pancreas. Such a heterogeneity has been recently suggested (1). There may be temporal differences in responses (1), but in addition significant differences could occur from the small portion of the acinar tissue in the peri-insular regions exposed to high levels of islet hormones. The different proportions of enzymes in the peri-insular acini and the insulin-potentiated responses to CCK and other secretagogues by these acini could contribute to the nonparallel enzyme secretion that has been observed.

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**REFERENCES**


54. Ohtani O, Kikut A, Ohkusa A, Taguchi T, Murakami T. Microvascular studies as the microvascular corrosion casting/


