Chapter 2
The Comparative Anatomy of Islets

R. Scott Heller

Abstract In the past 20 years, numerous publications on a variety of mammalian and non-mammalian species have appeared in the literature to supplement the excellent comparative work performed in the 70s and 80s by the Falkmer, Epple, and Youson groups. What emerges is that islets are much more complex than once thought and show a lot of similarities in rodents and higher primates. The diversity of lifestyles, metabolic demands, and diets has most likely influenced the great diversity in both structure and cell-type content of islets in lower vertebrate species. In this chapter, I try to provide an overview of the evolution from endocrine cell types in invertebrates to the higher mammals and focus on what has been reported in the literature and some of our own experiences and also include a description of other hormones reported to be found in islets.

Keywords Comparative · Hormones · Islets · Species · Structure

2.1 Introduction

During the past 30 years or so, we have seen emergence of data on islet architecture and cell type expand from just a few species into a broad diversity across many phyla. In three model organisms in which developmental biology studies of the pancreas have been conducted (*Oryzias latipes*, *Xenopus laevis*, and chicken), three buds materialize from the gut tube; two from its ventral side and one from the dorsal [1–3]. In mouse, while initially three buds exist that come from the gut tube (where there is contact between the endoderm and the endothelium), the pancreas only develops from two of these buds, one dorsal and one ventral [4]. This aspect of dorsal and ventral pancreas development of the pancreas has never been examined in species earlier in evolution that teleost fish. The differences in the development

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Table 2.1 Other peptides found in islets

Peptide	Cell type	Species	References
CART	δ	Rat	[75]
		Sheep	[76]
	δ	Ice rat	[54]
CCK	α, β, δ	Spiny dogfish	[77]
	β	Rat	[78]
	β	Ice rat	[54]
CGRP	δ	Rat	[79]
IGF	δ, PP	Lizards	[38]
	α, PP	Frogs, birds	[38]
PYY	PP	Cat, dog, pig	[80]
	PP, α	Mouse, rat	[80]
	α, β, δ	Rat	[81]
		Bullfrog, eel	[33]
	α	Sea bream	[82]
		Brazilian sparrow	[83]
	α, PP	Ice rat	[54]
	PP	Spiny mouse	[84]
Secretin	Unique	Frogs	[36, 85]
TRH	α, β	Rat	[86]
		Rat, guinea pig	[87]

The references cited are mostly based on immunoreactivity.

of the dorsal and ventral pancreas, which later fuse to form one organ in higher verterbrates, also likely explains the different composition of islets in head (ventral derived) or tail (dorsal derived).

The islets of Langerhans have generally been described as round clusters composed mainly of insulin (β-cells) and glucagon (α-cells) and minor populations of somatostatin (δ-cells) and pancreatic polypeptide cells (PP) generally in the mantle or rim of the islets. As the chapter and species evolve you will see there are many exceptions to this generalization. Recent times have shown that in most species during development and the early postnatal period, a unique 5th endocrine cell type, the ϵ-cell, which produces the hormone ghrelin, is found [5–7]. Other endocrine hormones found in the islets are also discussed (Table 2.1). One must remember that almost all of this knowledge has been gained by using immunocytochemical methods based on antisera raised primarily against rodent or human hormones and that differences in the structures of the hormones between different species may be the reason why some hormones are found in some species and not in others. Finally, I have taken a phylogenetic approach to the presentation of the different species discussed (Fig. 2.1).

2.2 Invertebrates

A substantial amount of literature exists on hormones of the pancreatic family in a number of different invertebrates like the silk worm, tobacco hornworm, and

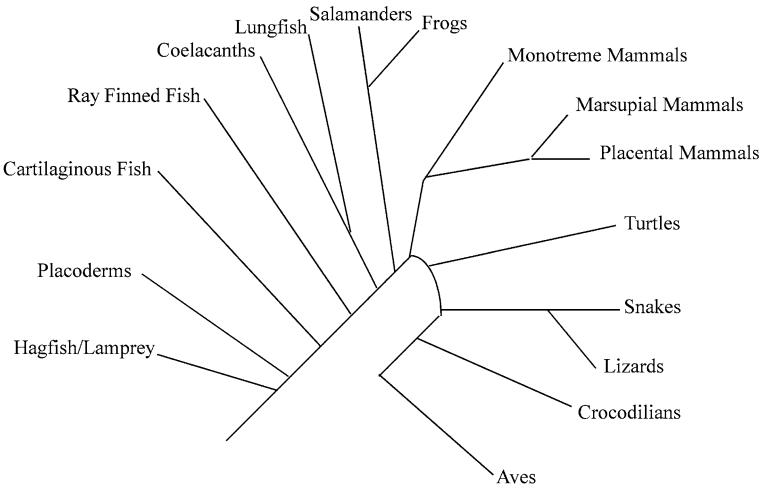

Fig. 2.1 Phylogenetic Tree of Vertebrates. The base of the phylogenetic tree represents the ancestral lineage, and the ends of the branches signify the descendents of that ancestor. When you move from the base to the ends, you are moving from the past to the present. When a lineage divides (speciation), it is demonstrated as branching on a phylogeny. When a speciation episode occurs, a single ancestral lineage gives rise to two or more daughter lineages. The figure was adapted from the Understanding Evolution website from the University of California Museum of Paleontology. http://evolution.berkeley.edu.

dipteran blowfly, in which hormones belonging to the insulin, glucagon, PP (started out as NPY), and somatostatin families have been demonstrated to exist [8]. In addition, a large amount of work on insulin peptides in the phylum mollusca has also been performed [9]. Here I focus on the Drosophilia, where some very important recent molecular studies have been performed that give a great insight into the evolution of the insulin- and glucagon-like peptides.

Pancreatic islets are not found in any invertebrate species but surprisingly many regulatory peptides are found in the midgut of Drosophila, and Ilp3, the equivalent of the Drosophila insulin gene, is found surprisingly in the muscle and not the endocrine cells [10] (Fig. 2.2). The major source of insulin-like peptides (there are seven in Drosophila) is a group of neurons in the pars intercerebralis of the brain [11]. Like insulin from islets, the insulin-like peptides in Drosophila are crucial for the regulation of glucose (actually trehalose, a disaccharide of two glucose molecules) levels in the hemolymph and energy metabolism [12]. Ablation of the insulin producing neurons generates growth deficient and diabetic phenotypes. Interestingly, it has been demonstrated that the insulin producing neurons make direct projections to communicate with the corpora cardiaca (CC) cells located at the heart, which produce glucagon-like peptides. Thus information from insulin-producing cells to communicate with α-cells was established quite early [12].

The insect corpora cardiaca (CC) are clusters of endocrine cells in the ring gland. One of the principal peptides produced is adipokinetic hormone (AKH), which is surprisingly similar to mammalian glucagon, is found in dense core vesicles, is

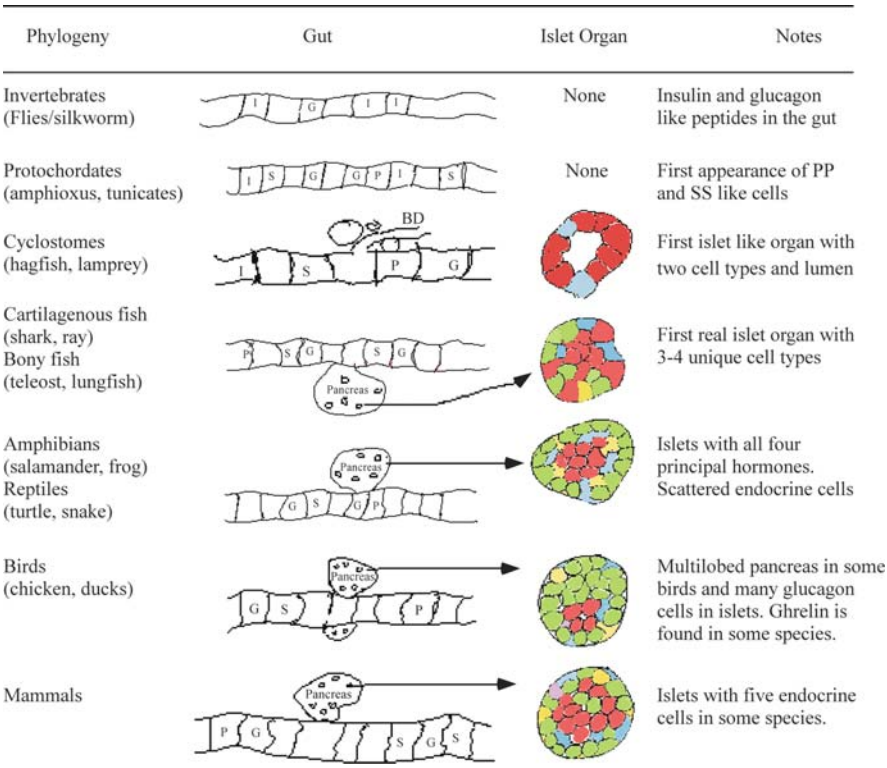

Fig. 2.2 Evolution of the Islet organ from invertebrates to mammals. Considerable species variation occurs in all classes but the scheme is meant to be semi-representative. Family member cell types that still remain in the gut are represented by single letters. I = insulin, G = glucagon peptides, SS = somatostatin peptides, P = PP family peptides. The cyclostomes are the first species where islet like clusters have migrated out of the gut tube into a separate cluster (islet) surrounding the common bile duct. It is with the cartilaginous and bony fish that the first real pancreas is formed with islets containing three and sometimes four hormones. These islets can lie within large islets (Brockmann bodies) or multiple islets within an exocrine pancreas. Reptiles and Amphibia are the first species with islets containing all four of the major hormones. Some species of Aves have multilobed pancreata and the islets tend to contain a lot of glucagon cells and this is the first appearance of ghrelin cells in some species. Mammals have a diverse range of structures but are generally round and contain four or five islet hormones. Insulin (*red*), Glucagon (*green*), Somatostatin (*blue*), Pancreatic Polypeptide (*yellow*), Ghrelin (*purple*). BD = bile duct

synthesized as a preprohormone, and has actions on the insect fat body to increase glycogenolysis and lipolysis, similar actions to mammalian glucagon [13, 14]. Injection of AKH in insects is sufficient to increase glucose in the hemolymph [13, 14]. A recent study demonstrated that ablation of the CC in Drosophila disrupts glucose homeostasis and that overexpression of the AKH gene reverses the effects on hemolymph glucose, thus demonstrating that a glucagon-like peptide is critical to regulation of glucose levels even in invertebrates [15]. In addition,

like in mammalian islets, the CC cells are in direct contact with the vasculature. Interestingly, the CC cells arise during development from delamination from epithelia that give rise to the gut [16]. Kim et al. speculate that CC and neuroendocrine regulatory cells that are important for metabolism may have come from an ancient energy sensing cell and that β-cells may have actually come from ancient α-cells. This is a very interesting and intriguing idea but will require more research to prove the hypothesis.

If we look back to the stem of vertebrate evolution and examine the primitive chordates: urochordates (tunicates) and cephalochordates (Branchiostoma-Amphioxus), we find that peptides related to somatostatin, glucagon, and PP like (primitive NPY) are localized in the tunicate brain, while insulin uniquely moved to the gastrointestinal tract (GI) mucosa [17, 18]. Thus it appears that insulin is the first hormone to have left the nervous system for the gut. Amphioxus is the earliest species for which all four of the main endocrine cell types are found in the GI tract, but not yet organized into an islet organ [19] (Fig. 2.2).

2.2.1 Agnatha-Cyclostomes – First Appearance of an Islet Organ

The Hagfish is a very ancient fish and it has been demonstrated to have an islet organ, which consists of only insulin and somatostatin cells. It is located as a bulge in the intestine near to the exit of the common bile duct (Figs. 2.2 and 2.3). Scattered insulin cells are also found associated with the bile duct as is also found in higher vertebrates [20]. No glucagon, PP or ghrelin (Heller and Christensen, unpublished data) cells have been identified in the structure [19]. The lamprey, a bottom dwelling ocean relative of the hagfish, also has a distinct islet organ, which was described by August Epple as Follicles of Langerhans due to its curious structure and that it was embedded in the submucosa of the intestine and features a duct-like lumen [19]. It is comprised of insulin and somatostatin immunoreactive cells. Interestingly, it appears that many of the somatostatin cells from the gut have now migrated into the islet organ [21]. One very interesting difference between the lamprey and hagfish is that removal of the islet organ in lamprey but not hagfish induced hyperglycaemia [19, 22].

2.2.2 Chondrichthyes (Jawed Fish)

Chondrichthyes is a large class consisting of rays, sharks, and skates. Here we see a large evolution in the islet organ as well as the appearance of some exocrine tissue associated with the islet tissue. Whether the islet organ in these ancient fish is derived from the dorsal or ventral pancreas or both is unknown. The glucagon cells have now migrated out of the GI tract and into the islet organ and are grouped together with insulin and somatostatin (Fig. 2.3) [23]. The first appearance of the PP cells is found and some species such as the elephant fish have abundant PP cells [15].

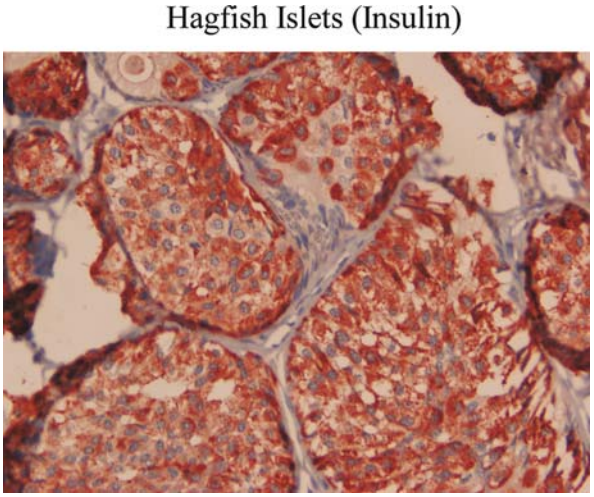

Fig. 2.3 The islets from the hagfish. The section was stained for insulin using the perxoidase staining protocol by Erna Pedersen (Hagedorn Research Institute). Insulin is in *red*. Image is taken at 200*x* magnification

The pancreas of the shark *Scyliorhinus stellaris* has large islets observed around small ducts. In addition, single islet cells or small groups of endocrine cells can also be observed to be incorporated into acini [24]. Ghrelin has not been identified or examined for. Now, for the first time, we see an islet organ with juxtaposed exocrine and endocrine tissue with the four main pancreatic cell types observed in most but not all Chondrichthyes. Interestingly, many glucagon, PP family, and somatostatin cells remain in the gut, a feature that remains with most higher vertebrates as these peptide families play important roles in GI physiology.

2.2.3 Osteichthyes (Lungfish and Teleost Fish)

Lungfish are unique when compared to the vast literature on the teleost fish. The anatomy of the pancreatic region is quite distinctive with a number of scattered encapsulated islets completely surrounded in the dorsal foregut wall. The stomach and intestine wrap around the organ and the spleen is also in close association [25, 26]. For the first time we see islets that are encapsulated by a collagenous-type connective tissue to exclude them from the exocrine tissue [8]. Glucagon, insulin, and somatostatin immunoreactive cells are localized in the islets but few or no PP cells are found [27, 28] (Fig. 2.2).

The teleost are bony fish of the rayfin subclass and have been widely studied. Detailed developmental studies in zebrafish have demonstrated that the dorsal pancreas gives rise to the principal islet body often referred to as the Brockmann body (mainly found in the most advanced teleosts), while the ventral bud leads to

the exocrine pancreas and associated smaller islets, also seen on other fish [29]. Islet structures vary broadly in this class of fish with some members having many islet structures scattered as clumps throughout the abdominal cavity with associated exocrine tissue [30]. Generally, the islet organ is located in the mesentery that connects the stomach, intestine, liver and gallbladder. Teleost fish tend to have islets that very much resemble mammalian islets with the insulin cells in the core surrounded by a mantle of glucagon, somatostatin, and PP cells but not all teleost islets contain all four cell types [31]. Ghrelin cells have been detected in the pancreas of the catfish [32]. Eels have been shown to have numerous peptide YY (PYY) cells in the islets (Table 2.1) [36].

2.2.4 Amphibia

Amphibia, which includes the urodeles (salamanders, newts) and anurans (frogs, toads) vary greatly in their islet structures. In some urodeles, the islets are not encapsulated, appear poorly innervated, and the cell types are more randomly distributed, while in others the islets appear as in most other tetrapods [34]. The literature on newts and salamanders is limited but what has been reported shows that all four of the main cell types are found but are most often in clusters that do not show a distinct distribution, with insulin cells in the core surrounded by the other cell types. It has been reported that the endocrine cells in the mudpuppy appear as groups of cells that are unencapsulated [35]. Ghrelin has not yet been described in urodeles.

Frogs and toads have been more intensely studied and are the first species with five or even six unique cell types in the islets. In addition, Amphibia are the earliest vertebrates to show the classical islet structure of the β-cells in the centre surrounded by the other cell types (Fig. 2.2). While the appearance of the islet structures in frogs is quite close to that of mammals, the cell composition is very different. In some frogs, there are equal numbers of insulin, glucagon, and PP cells and fewer somatostatin cells (Fig. 2.4). Interestingly, like hagfish, frog β-cells appear to lack Zn^{2+}. Also, like mammals, the splenic or tail portion of the pancreas often has larger islets. In addition to the four main cell types, single or small groups of secretin cells have been described in the Red Bellied frog [36]. While, *Xenopus* appear to have ghrelin cells in the islets, bullfrogs have the mRNA but not the immunoreactive peptide [37]. Insulin-like growth factor-1 (IGF-1) has also been observed to colocalize with either PP or glucagon (Table 2.1) [38]. PYY immunoreactive cells have also been described in the bullfrog pancreas [39] (Table 2.1).

2.2.5 Reptilia (Turtles, Crocodiles, Lizards, Snakes)

While these animals were the first to make a complete transition from an aquatic to a terrestrial way of life and represent the animals that evolved into birds and mammals, very little is known about their islets compared to fish and amphibians.

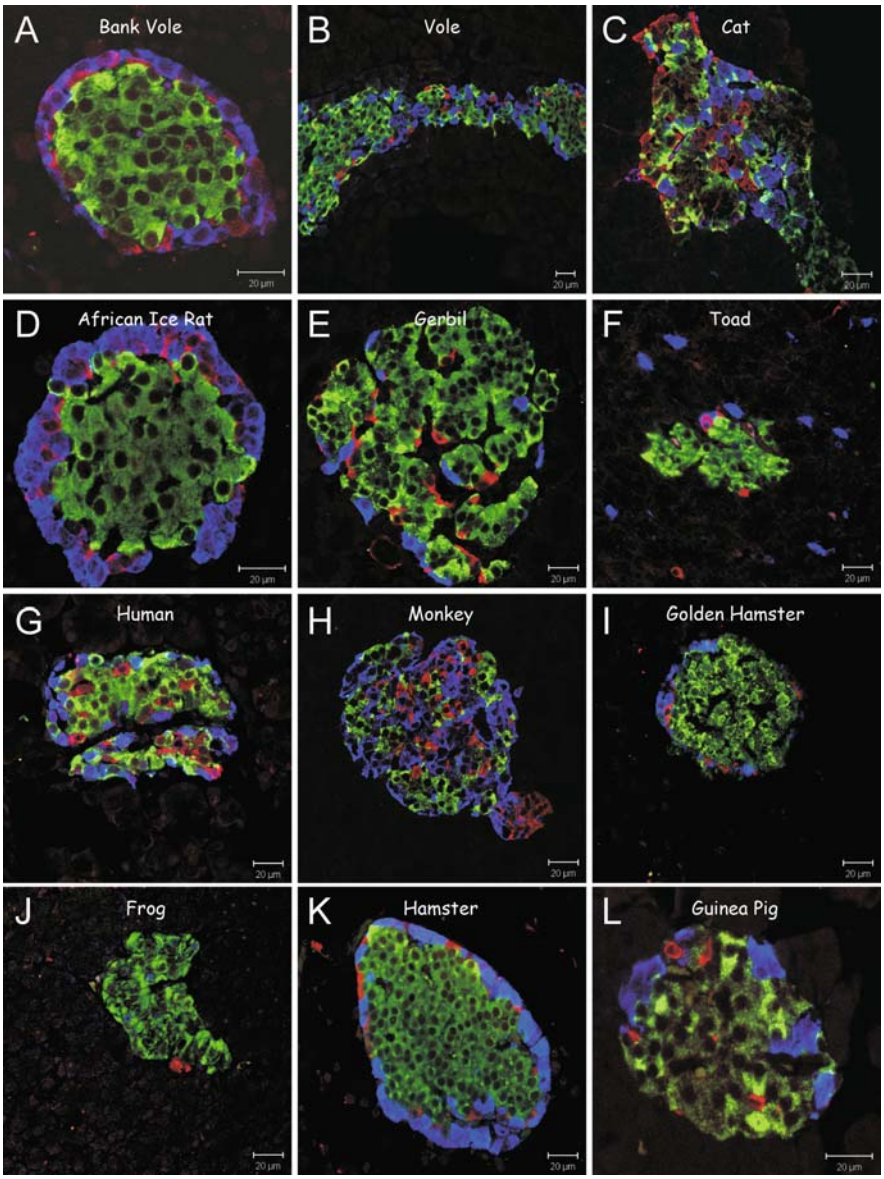

Fig. 2.4 The Comparative anatomy of islets in 12 different species. Bank Vole (**A**), Vole (**B**), Cat (**C**), African Ice Rat (**D**), Gerbil (**E**), *Bufo*(toad) (**F**), Human (**G**), Monkey (**H**), Golden Hamster (**I**), Xenopus (frog) (**J**), Hamster (**K**), Guinea Pig (**L**). Sections were stained for insulin (*green*), somatostatin (*red*) and glucagon (*blue*) and scanned with a Zeiss LSM 510 confocal microscope. Scale bar = 20 μM

Reptiles in general have a distinct pancreas with exocrine tissue and islets. Perhaps not surprisingly, the Crocodilia and Squamata (lizards) are more similar than the turtles. They exhibit a compact pancreas with all four of the established pancreatic hormone cell types. In crocodiles, the insulin cells make up about 50% of the islets while in lizards, the glucagon cells are in abundance with a ratio of 4–5 for every insulin cell. Lizard islets also tend to be large and located in the tail of the pancreas [40, 41]. Interestingly, alligators have been reported to have a large number of somatostatin cells [15]. IGF-1 was shown to colocalize with either somatostatin or PP in lizards (*Lacerta viridis*, *Scincus officinalis*) (Table 2.1) [39] and ghrelin has not been described in these species.

Chelonia (turtles) are the oldest in the class of reptiles and show a large diversity. A recent study in *Melanochelys trijuga* demonstrated that numerous scattered glucagon cells appear in the exocrine pancreas. In addition, small insulin islets of 3–20 cells are found, but when the cells are found together they form islets with β-cells in the centre and α-cells on the periphery and that the α-cells out number the β-cells [42]. In *Chrysemys picta*, it has been described that the duodenal (head) part of the pancreas contains scattered SS and PP cells that are distant from islets made of only glucagon and insulin cells, and that the PP cells are found in an inverse relationship to the glucagon cells. Interestingly, in this species insulin cells are still found in the gut, which is an evolutionary reverse predating the amphibians [43]. Not a lot of literature exists about other hormones in the islets but ghrelin cells have been identified in the pancreas of the red-eared slider turtle [44] and IGF-1 in snakes (*Psamophis leniolatum*, *Coluber ravergieri*) in the glucagon or somatostatin cells [38] (Table 2.1).

The endocrine pancreas in a few snakes have been reported and it appears that in general, glucagon and somatostatin cells are found in the mantle, but also there are scattered somatostatin cells intermingled with the other endocrine cell types. Interestingly, in *Natrix*, there are more α-cells than β-cells but not in *Vipera*, where both appear to have about equal numbers of δ and β-cells, which is also quite different from mammals. Surprisingly, the authors did not find PP or gastrin/CCK family peptides in the islets [45].

2.2.6 Aves

The avian pancreas has evolved as a multilobed and distinct pancreatic organ in the few species that have been studied. Almost all the data comes from chickens, ducks, quail, and pigeons and all of these show quite a lot of similarity and are more closely related to what we observed in the Chelonia compared to the Crocodilia class. Early on it was observed that Aves have what is referred to as A and B islets, which consist of primarily glucagon or insulin cells with somatostatin cells as well as mixed islets [46]. More recently, these observations have been confirmed in the Japanese quail where it was observed that in the β-cell islets, the somatostatin cells were in the periphery while in the α-cell islets they were scattered throughout the islet [47]. Similar data were observed in the domestic duck, where A and mixed

islets were more concentrated in the splenic lobe, and decreased in number in the other lobes [48]. Two exceptions to these species appear to be the Australian eagle and the Houbara bustard, which were reported not to have A and B islets but only islets of the mixed type, and no reciprocal relationship between PP and glucagon was observed [49, 50]. More exceptions may well be observed as more species are studied, but one consistent finding is that birds tend to have large numbers of α-cells.

As we move further up the evolutionary scale, more and more different peptides have been localized in the islets. IGF-1 has been reported to colocalize with either SS or PP [38]. Using specific non-cross-reacting antisera, PYY-specific cells have been observed in the chicken exocrine pancreas with rare cells in islets, which is also similar to what was observed in turtles [51]. Adrenomedullin has been described to be localized with the PP cells in chickens [52]. Ghrelin cells are found in adult domestic chickens (Nils Wierup, personal communication) but nothing is known in other Aves species (Table 2.1).

2.2.7 Mammals

Many more mammals have been investigated than lower vertebrate species and extensive literature is available. There are currently 5,400 species of mammals distributed in about 1,200 genera, 153 families, and 29 orders. This includes species from the Monotremes (echidnas and the platypus), Theriiformes (live-bearing mammals), marsupials, Anagalida (lagomorphs, rodents, and elephant shrews), Grandorder Ferae (carnivorans, pangolins), Grandorder Archonta (bats, primates, colugos, and tree shrews), Grandorder Ungulata, Mirorder Eparctocyona [condylarths, whales, and artiodactyls (even-toed ungulates)], Mirorder Altungulata: perissodactyls (odd-toed ungulates), elephants, manatees, and hyraxes (Fig. 2.1). Many of these have never been examined but I will describe what has been reported.

By the time the mammals evolved, the basic structure of the pancreas, with multiple lobes and encapsulated islets was really set. It is in mammals that we now have strong evidence that the islets are producing much more than the five main islet hormones (insulin, glucagon, somatostatin, pancreatic polypeptide, and ghrelin) and this includes a wide and diverse group of peptides and proteins, including islet amyloid polypeptide (IAPP), cholecystokinin (CCK), peptide YY (PYY), thyrotropin releasing hormone (TRH), GABA, and cocaine amphetamine regulated transcript (CART) (Table 2.1).

2.2.7.1 Rodents

Forty per cent of all mammals are rodents and this includes mice, rats, chipmunks, squirrels, gophers, hamsters, porcupines, beavers, guinea pigs, gerbils, degus, chinchillas, prairie dogs, and groundhogs. Out of all of these animals, the islet architecture and content has only been examined in mice, rats, hamsters, gerbils, and guinea pigs. In general, rodents such as mice, rats, and hamsters have fairly round

islets with glucagon, somatostatin, and PP cells in the mantle and β-cells in the center [53] (Figs. 2.2 and 2.4). We have recently examined the African Ice Rat (*Otomys sloggetti robertsi*) and observed that these animals have nearly equal numbers of α and β-cells and the islets generally have two layers of glucagon cells surrounding the β-cells [54]. In addition, we have fresh studies on several desert gerbils and have described their islet morphology [55]. In gerbils of the Meriones family, we observed that like rats and mice, the β-cells are in the centre of the islets and are surrounded by a ring of α-, δ- and PP cells. We often observed colocalization of PYY with PP as well and this is seen in a number of mammalian species (Table 2.1). Cocaine amphetamine related transcript (CART) and CCK are also often colocalized with mostly δ-cells and β-cells, respectively (Table 2.1). Hamsters and guinea pigs also tend to have all the glucagon, somatostatin, and PP cells in the mantle, the core being only insulin cells (Fig. 2.4). We have recently examined two species of voles and found that in one the islets showed very similar morphology to other rodents, while the other had larger more elongated islets (Fig. 2.4).

2.2.7.2 Carnivora

Of the approximately 260 species, which includes dogs, foxes, bears, weasels, pandas, elephant seals, and cats, we only really have data on the domestic cat and dog and a few rare animals. The dog β-cells generally occupy the central portion of the islets but are also found as single cells in the exocrine pancreas [53], while the α-cells are generally in the periphery but also found centrally in some islets. The δ-cells are generally mixed in the islets while PP cells appear as single cells or groups [43, 56]. The endocrine pancreas of the Cape fur seal showed very similar morphology to what is observed in other carnivorous species like the dog and cat and this shows a central core of β-cells surrounded by glucagon, somatostatin, and PP cells. Like what we have seen in cats, they also observed scattered endocrine cells in the exocrine pancreas [57]. The red fox, *Vulpes vulpes*, was described to have small islets with insulin in the centre surrounded by glucagon and somatostatin immunoreactive cells. The authors were unable to detect PP cells [58]. Our experience with the examination of the domestic cat shows that these animals have very unusual islets with every shape you can imagine but not round islets, and the endocrine cells can also be arranged in different sorts of clusters mixed together with groups of α-, β- or δ- cells clustered together (Fig. 2.4). Whether this is a common occurrence in other cats is not known.

2.2.7.3 Artiodactyls (Even-Toed Ungulates)

The most widely studied even-toed ungulate is the pig. The minipig has been used in both type 1 and type 2 studies of diabetes [59, 60]. The islets of the minipig have been described to have three types of islets: small with low numbers of β-cells, large islets with β-cells in the core, and large islets with β-cells in the periphery [53]. Interestingly, the left lobe of the pancreas was described to be high in α-cells and devoid of PP cells, while the δ-cells are mostly at the periphery of the

islets or between acinar cells [53]. There has been one description in the literature on the morphology of the camel pancreas. In this paper it was observed that the insulin immunoreactive cells were found in the central and peripheral parts of the islets of Langerhans, as well as some solitary β-cells in the exocrine pancreas outside the islets. Glucagon immunoreactive cells were located in the periphery of the islets and were approximately 23% of the total islet cells while insulin immunoreactive cells were 67% [61]. Little is known about other peptides in these species and the expression of, but not colocalization of CART was recently described in sheep (Table 2.1).

2.2.7.4 Marsupials

The presence of the marsupium (distinctive pouch) is what characterizes this unique class of mammals. A few species have been examined. The fat-tailed dunnart, *Sminthopsis crassicaudata*, was shown to have all four of the major immunoreactive hormones clustered into islets as well as numerous PP cells scattered in the exocrine pancreas [62]. The same group has also looked at the Australian brush tailed possum, *Trichosurus vulpecula* [63]. They found that like the dunnart, the β-cells are in the middle of the islets, with the α-, δ-, and PP cells in the periphery, with numerous PP cells found in the exocrine pancreas. In the possum, *Trichosurus vulpecula*, it was described by another group that insulin cells were found in islets not only centrally but also in the periphery of islets, and in some islets the glucagon cells were the dominant cell type, found both centrally and in the mantle [64]. PP cells were quite rare with usually only 1 or 2 per islet, while somatostatin cells were mainly in the periphery. These data are similar to what was also observed in the opossum, *Didelphis virginiana* [65]. A common feature in marsupials appears to be scattered PP cells in the exocrine pancreas. A recent study of the Tammar wallaby, *Macropus eugenii*, showed that ghrelin cells were found in the developing pancreas up to day 10 but were not present 150 days after birth [66]. These data are the same as found in mice [5, Heller unpublished data].

2.2.7.5 Archonta – Bats, Primates, Tree Shrews

Archonta is the superorder which contains the bats, tree shrews, colugos, and primates (humans). A very interesting study was conducted on the fruit bat, *Rousettus aegyptiacus*[67]. They found that the endocrine tissue makes up about 9% of the pancreas, which is close to double of what is found in all other species studied so far, and this probably relates to the fact that these animals must absorb large amounts of glucose in very short periods of time. The endocrine cells were distributed in islets throughout the gland and also occurred as discrete cells in the exocrine ducts. The four major endocrine cell types were irregularly scattered throughout the islets with insulin (47.4%) cells located throughout the islet and in between the glucagon cells (28.6%). Somatostatin cells made up 7.8% and pancreatic polypeptide (PP) cells 16.2%, which is much higher than normal in other mammals. Interestingly, using pancreatic vascular casts of the common tree shrew (*Tupaia glis*) it was found

that the α- and δ-cells appeared to occupy the core whereas the β-cells were found at the periphery of the islets of Langerhans. This is quite unusual for a higher vertebrate [68].

The primates, which include monkeys, apes, and humans, have been widely studied morphologically. In general, there is a lot of similarity between monkeys and humans, with an intermingling of the major cell types (Fig. 2.4). In monkeys, it is not uncommon to see central groups of glucagon cells and large clusters of insulin cells that occupy specific sides including the mantle of the islet [69]. The somatostatin cells are generally intermixed while the PP and ghrelin cells are in the periphery of the islets [7].

2.3 Conclusion

In conclusion, the islets of Langerhans have evolved from quite simple organs [70] in the ancient fish to very complex organs in higher vertebrates, producing many hormones, neurotransmitters, and other signaling molecules. Many of the variations of the standard map of the islet that we observe are likely to be related to the diet and environment of the animals, while the need to maintain blood glucose and regulate metabolism within a tight physiological range is an evolutionary pressure that is rarely altered. I think that as new immunocytochemical techniques such as whole-mount immunoctyochemistry [71, 72] and optical projection tomography [73, 74] become more widespread in islet research, we should see an expanded knowledge of how these important cellular clusters are localized, shaped, and function in different species and perhaps even reveal greater differences or more similarities than what has been appreciated from 2-dimensional analysis.

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