ANIMAL MODEL OF HUMAN DISEASE

# *Spontaneous Diabetes Mellitus–Islet Amyloid Complex in Adult Cats*

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## Human Disease

Type 2 (non-insulin-dependent) diabetes mellitus constitutes up to 90% of all cases of diabetes mellitus in humans. In contrast to Type 1 (insulin-dependent) diabetes mellitus, where evidence supports an absolute insulin deficiency related to insulitis and islet cell destruction by a combination of viral and immunologic mechanisms, the intra-islet deposition of amyloid is a common islet alteration in human Type 2 diabetes (Figure 1).[1-3] The relationship of islet amyloid to diabetes mellitus is still incompletely understood, but recent immunohistochemical and immunochemical evidence indicates that islet amyloid is an insulin-related product.[4,5] However, further clarification is needed for determination of the etiopathogenic relationship of islet amyloid and diabetes mellitus.

The diabetes mellitus–islet amyloid complex which occurs spontaneously in adult cats has many documented similarities to Type 2 diabetes mellitus in humans, and provides a model with which we can further investigate the sequential morphologic and biochemical alterations that occur in islets of individuals with this form of diabetes mellitus associated with aging.

## Biologic Features

Diabetes mellitus occurs predominantly in aged cats, with the highest incidence in those 8 years of age or older.[6] More than 90% of diabetic cats are over 6 years of age. There is no evidence of any breed predilection in cats. Although a greater incidence in males has been suspected on the basis of case reports, there appears to be no statistical support for a difference between the incidence of diabetes mellitus in males and females.[7]

The earliest clinical signs of diabetes mellitus in cats include polyuria, polydipsia, depression, weakness, decreased appetite or polyphagia, dehydration, and weight loss.[7] Progression of the disease may, in some cases, lead to ketoacidosis and ketonuria. Persistent hyperglycemia, glucosuria, hypercholesterolemia, hyponatremia, and hypokalemia are common laboratory findings. Sustained fasting blood glucose levels ranging from 150 to 800 mg/dl with concomitant glucosuria are characteristic features of the disease. Most diabetic cats have low or low-normal fasting insulin levels with little or no insulin secretion in response to intravenous glucose.[8] However, fasting hyperinsulinemia with rising insulin values following glucose stimulation has also been observed. Mean fasting and glucose-stimulated serum glucagon levels in diabetic cats are significantly higher than corresponding levels in normoglycemic cats.[8]

At necropsy, diabetic cats have considerable variation in condition. Body fat deposits may be extensive or nearly exhausted. Hepatic lipidosis with liver enlargement is common, cataracts are infrequently observed, and cystitis is apparent in some cases. Significant gross changes usually are not apparent in the pancreas.[9] Histologically, islet amyloid is present in the pancreatic islets of over 65% of diabetic cats (Figure 2).[6] Glyco-

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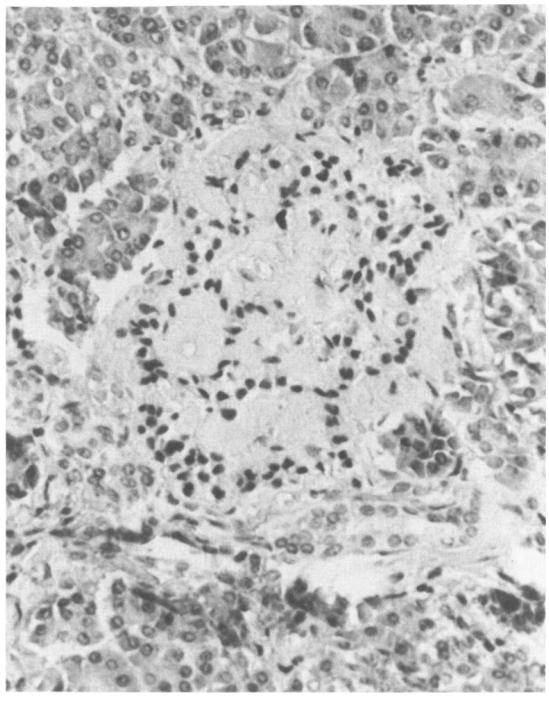

**Figure 1**—An islet of Langerhans from a human patient with islet amyloidosis. The amyloid is strictly limited to the islet. (Congo red, ×300)

gen infiltration, represented by vacuolar change, is evident in the residual cells of affected islets. Vacuolar change is the predominant islet lesion in those diabetic cats not having islet amyloid.

The localized nature of amyloid in islets of diabetic cats is confirmed by the absence of amyloid in other tissues. The islet amyloid has the same staining properties as systemic forms of amyloid with commonly used dyes (eg, Congo red, thioflavine S, thioflavine T, crystal violet, methyl violet), and is composed ultrastructurally of the 75–100 Å nonbranching fibrils common to all forms of amyloid.[10–12] However, the islet amyloid is distinguishable from systemic forms of amyloid, in that this localized form lacks tryptophane and is not extractable with distilled water.[5,12] Additionally, the congophilia of feline islet amyloid is retained after pretreatment with $KMnO_4$, whereas the most common form of systemic amyloid in animals (ie, so-called secondary or reactive amyloid), loses its affinity for Congo red dye when it has been oxidized with $KMnO_4$.[10]

Approximately 45% of nondiabetic cats 5 years of age or older also have islet amyloid deposits,[13] but diabetic cats have a significantly higher mean percentage of islets with amyloid, and these deposits are much more extensive than those in nondiabetic cats.[6]

The recent finding[5] that islet amyloid from diabetic cats has substantial immunoreactivity with antiserum to a B-chain-rich insulin derivative supports the hypothesis that islet amyloid is formed from an insulin-related protein. Amyloid deposits with staining reactions identical to those of islet amyloid have also been demonstrated in pancreatic ganglia and nerves of diabetic cats.[14] The presence of cells with insulin immunoreactivity adjacent to the ganglioneuronal amyloid deposits is also consistent with an insulin-related precursor for these deposits. The presence of insulin-related amyloid in sympathetic and parasympathetic nerves and ganglia that supply neural signals to pancreatic islets also raises the possibility that impaired neural transmission affects islet cell responsiveness to changes in blood glucose concentration, and thus contributes to the progression of the diabetic state.

## Comparison With Human Disease

Comparisons between this disease complex in cats and humans are summarized in Table 1. With the exception of islet fibrosis, which is commonly evident in the islets of human Type 2 diabetics but is not evident in the islets of adult diabetic cats, the islet alterations are very similar.

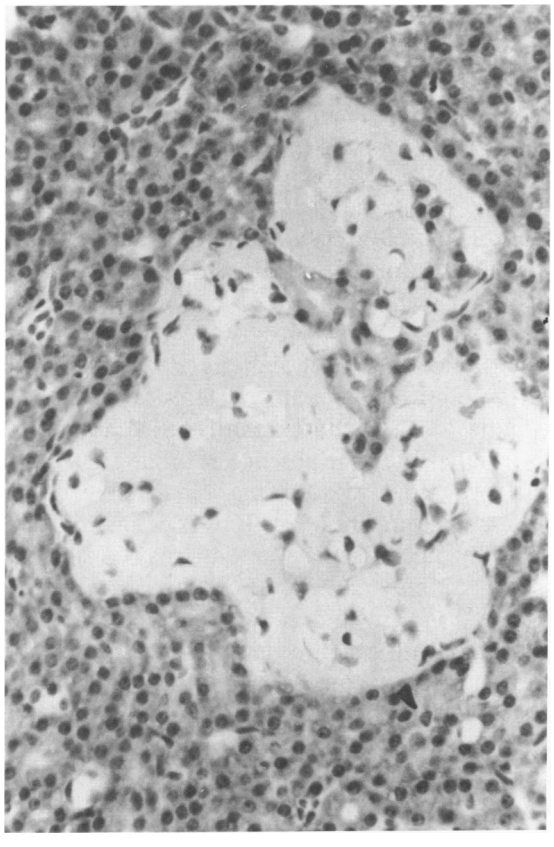

**Figure 2**—Typical appearance of amyloid in a pancreatic islet from a diabetic cat. Amyloid deposits also may be found in pancreatic ganglia and nerves. (Congo red, ×300)

Table 1—Comparison of Diabetes Mellitus in Adult Cats with Type 2 (Non-Insulin-Dependent) Diabetes Mellitus in Humans

| | Human | Cat |
|---|---|---|
| Pancreatic islets/islet amyloid | | |
| Insulitis | – | – |
| Incidence of IA in diabetics | 50–>90% + | >65% |
| Incidence of IA in nondiabetics | <5–60% + | 45% + + |
| IA localized to endocrine pancreas | + | + |
| Tryptophane content | – | – |
| Extractable in water | – | – |
| Immunoreactivity with antiserum to a B-chain-rich insulin derivative | + | + |
| Morphometry of islet cell populations in diabetics with IA: | | |
| B cells | → to ↓ 44% | ↓ 47% |
| A cells | ↑, ↓, or → | ↓ |
| D cells | → | → |
| The diabetic conditions clinically | | |
| Age | Middle age and older | 90% >6 years |
| Ketoacidosis | Resistant | Not usual |
| Genetic predisposition | Yes | Unknown; no known breed predisposition |
| Serum insulin | Variable | Low-normal and no glucose-stimulated response |
| Serum glucagon | Usually elevated | Usually elevated |
| Extrapancreatic complications | Nephropathy | Nephropathy reported |
| | Cataracts | Cataracts uncommon |
| | Neuropathy | Neuropathy reported |
| | Retinopathy | Not reported |
| | Angiopathy | Not reported |

IA, islet amyloid; +, persons over 60 years of age; ++, in cats over 5 years of age; →, no change; ↑, increased; ↓, reduced.

Although islet amyloid occurs in both nondiabetic and diabetic cats and humans, studies support an etiopathogenic relationship between islet amyloid and maturity-onset diabetes mellitus,[1,3,6,13] and aging by itself apparently is not the major factor in the development of islet amyloid deposits.

In both human Type 2 diabetes mellitus and feline diabetes mellitus, morphometric analysis of pancreatic islets indicates that reduction in B-cell volume occurs but is insufficient in the absence of other diabetogenic factors to cause diabetes mellitus.[1,15] Therefore, destruction and replacement of B cells by islet amyloid is not the primary diabetogenic event, but may contribute to the progression by reducing B-cell reserve. The observation that islet amyloid in adult normoglycemic cats is associated with a significantly altered insulin secretion response after glucose stimulation[8] may indicate that islet amyloid formation is linked to primary B-cell derangements in insulin secretion or degradation.

Similarities also exist between the clinical aspects of Type 2 diabetes mellitus in humans and diabetes mellitus in adult cats (Table 1). Study of serum insulin levels in diabetic cats has primarily involved animals in advanced stages of the disease; and, as might be expected, the majority of these cats were hypoinsulinemic and did not respond to glucose challenge.[8] Further studies are necessary to determine the frequency of occurrence of normo- or hyperinsulinemias which are reported in human Type 2 diabetics.

Extrapancreatic complications (eg, nephropathy, neuropathy, and cataracts) have been reported to occur in diabetic cats, but more extensive studies are needed to determine their actual incidence and significance.

In contrast to the human disease, insulin is the most common therapy used in treatment of diabetic cats; however, this is not necessarily an indication of insulin dependency in the diabetic cat. The effectiveness of oral antidiabetic drugs has not been adequately evaluated in diabetic cats.

## Usefulness of the Model

The adult cat provides a model for the study of the diabetes mellitus-islet amyloid complex or "maturity-onset diabetes" as naturally occurring conditions. Histopathologic, histochemical, immunohistochemical, and immunochemical studies of changes occurring in the pancreatic islets of spontaneously diabetic adult cats

have documented many similarities with Type 2 diabetes mellitus in humans. Therefore, this animal model appears especially suited to further investigation of the sequential morphologic and biochemical alterations that occur in islets of individuals with this form of diabetes mellitus associated with aging.

### Availability

The incidence of overt diabetes mellitus in the domestic cat was reported to be 1 in 484 in cats admitted to the Animal Medical Center in New York. Based on the number of cats admitted to the Veterinary Teaching Hospital, University of Minnesota, over a 15-year period (1969–1984), the incidence of diabetes mellitus is estimated to be 1 in 250 for the general cat population. However, the incidence of diabetes mellitus rises dramatically to 1 in 100 for cats 7–10 years of age.

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