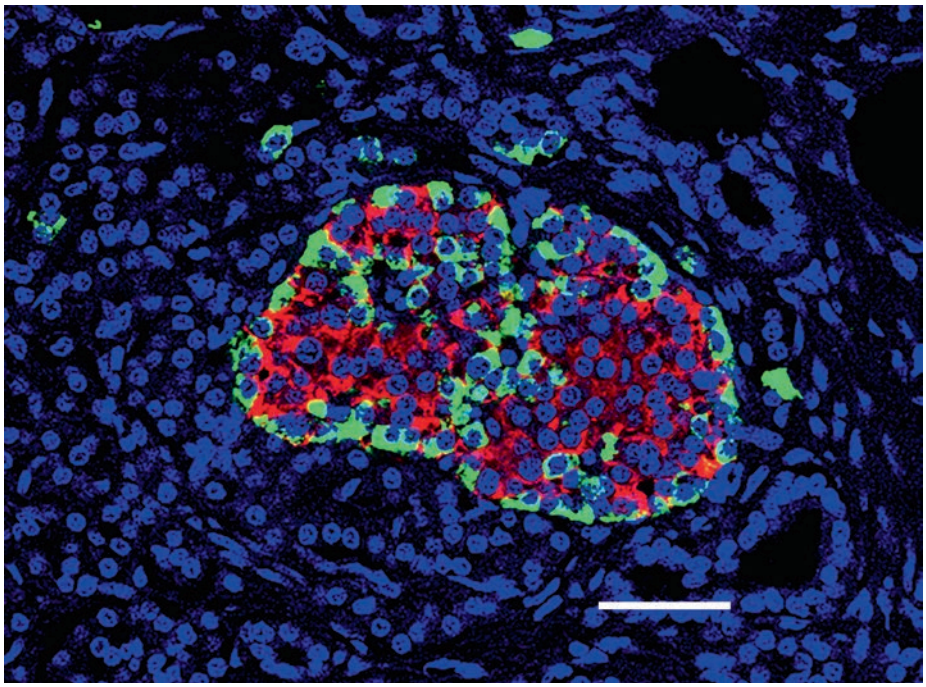
Milestone 2

Islet pathology in diabetes



An adult human islet. Red colour shows insulin staining, green shows glucagon and blue shows nuclei. Scale bar 50 μm.

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The discovery of insulin in 1921 (Milestone 1) revolutionized the treatment of people with diabetes. However, the pathophysiology of diabetes remained uncertain for many decades. In 1965, important histological findings were published that revealed the pathological anatomy of the pancreas in early-onset (prior to age 31 years) diabetes, which we now know as type 1 diabetes (T1D).

The classic view was that T1D was caused by an absolute deficiency of insulin secretion owing to a severe inadequacy of insulin-secreting tissue. The advent of histological techniques that could identify insulin-secreting β-cells, as well as α-cells, within pancreatic islets enabled this early hypothesis to be tested. In a 1965 study, researchers examined pancreatic tissue samples obtained at autopsy from 56 patients with early-onset diabetes, as well as 26 samples from young people without diabetes. Notable differences were seen between patients who died within 6 months of diagnosis (acute disease) and those who had the disease for longer than 1 year (chronic disease).

The findings from this study informed a new hypothesis that β-cells are under the influence of an 'extrapancreatic diabetogenic factor' that causes a progressive deterioration in T1D. For example, patients with acute disease showed decreased numbers of β-cells (<10% of normal values); however, the remaining β-cells showed signs of hyperactivity. Furthermore, 68% of patients with acute disease had peri-islet and intra-islet inflammatory infiltrates. By contrast, these infiltrates were never seen in patients with chronic early-onset diabetes, and the majority of these patients had a complete absence of β-cells. At disease onset, three types of islet were found — atrophic without β-cells, with β-cells and inflammatory infiltrates, and normal looking without infiltrates — thereby suggesting ongoing β-cell destruction.

> **"The findings supported the model of immune-mediated β-cell destruction in T1D"**

The findings of this study contrasted with previous histological findings from patients who had diabetes diagnosed at an older age. These patients, who had what we now call type 2 diabetes (T2D), typically showed a moderate decrease in islet tissue and β-cell mass that was 40–50% of normal values.

Further insights into the pathogenesis of T1D were made in a 1984 autopsy study of pancreatic tissue from 11 children with T1D, 9 of whom had died within 24 h of their initial presentation (recent-onset). In the children with recent-onset T1D, two populations of islets were present: small insulin-deficient islets and large islets containing β-cells. Notably, eight of these children had inflammation of their pancreatic islets, which affected 18% of insulin-containing islets but only 1% of insulin-deficient islets. The findings supported the model of immune-mediated β-cell destruction in T1D.

A case report published in 1985 of a 12-year-old girl who died as a result of recent-onset T1D showed that many of the cells infiltrating the pancreas were cytotoxic or regulatory T cells, some of which were activated. The affected islets also showed upregulated expression of HLA class I molecules, which present peptides to T cells. Taken together, these findings and others helped inform our understanding of the autoimmune mechanisms of β-cell loss in T1D.

The pathogenesis of T2D is different, being characterized by tissue insulin resistance as well as impaired insulin secretion. T2D is associated with obesity and older age, although a large proportion of individuals with obesity do not develop T2D. A comprehensive 2003 autopsy study of pancreatic tissue from 124 people with obesity and/or T2D or prediabetes or of lean individuals with or without T2D helped inform our understanding of islet pathology in T2D. The study confirmed that levels of β-cells were decreased in T2D and the underlying mechanism was proposed to be increased β-cell apoptosis.

These early studies of individuals who died have helped inform us of the pathological processes occurring in pancreatic islets during diabetes and ultimately have led to the design of treatments that will improve patient outcomes.

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Nature Reviews Endocrinology

Milestone study

Gepts, W. Pathologic anatomy of the pancreas in juvenile diabetes mellitus. *Diabetes* **14**, 619–633 (1965)

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