

THE EFFECTS OF PARTIAL PANCREATECTOMY AND ACUTE STAPHYLOCOCCAL  
ALPHA-TOXIN PANCREATITIS ON THE PLASMA GLUCOSE, INSULIN AND  
GLUCAGON DURING A H-IVGTT IN THE DOG

by

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To My Parents and Wife

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LITERATURE REVIEW

## INSULIN

Von Mering and Minkowski, in 1889, showed that removal of the pancreas of dogs caused serious disturbances of glucose metabolism, with elevation of the blood glucose concentration and the clinical picture of diabetes mellitus. The assumption that this effect was due to removal of a necessary hormone was confirmed in 1921 when Banting, Best and MacLeod prepared a pancreatic extract capable of decreasing blood glucose concentration. This substance, insulin, has since been purified and its composition determined.<sup>7</sup>

### Biosynthesis

Insulin is synthesized by the beta cells of the islets of Langerhans as a single chain precursor, proinsulin, which is later cleaved to insulin.<sup>94</sup> Biosynthesis of proinsulin occurs on the rough endoplasmic reticulum, is passed into the Golgi apparatus and transferred to storage granules formed by vesiculation from the Golgi periphery. Insulin is released from beta cells by extrusion (emiocytosis) of intact granules.<sup>65</sup> Transformation of proinsulin to insulin by proteolytic cleavage occurs either in the Golgi apparatus or during granule maturation.<sup>45,68,76</sup> In either case, insulin rather than proinsulin is the storage and secretory form of the hormone; however, small amounts of proinsulin do escape into the circulation. Proinsulin does cross-react to some degree with antibodies to insulin.<sup>34</sup>

### Circulating Insulin

The earliest attempts to determine insulin in body fluids depended on bioassay in animals made sensitive by hypophysectomy and adrenalectomy. In vitro assays using tissue slices to measure the glucose uptake replaced earlier techniques. It became apparent that measurement of glucose uptake

is, by itself, nonspecific for the action of insulin. A more precise method of measuring insulin was introduced by Berson and Yalow, who used antibody against insulin to measure the concentration of immunologically reactive insulin-like material in plasma.<sup>45,68,76</sup> Immunoreactive insulin (IRI) rises appropriately after a glucose load, is absent after pancreatectomy and is absent from the plasma and pancreas of juvenile diabetics. It is now generally accepted that immunoreactive insulin is the most specific and reliable measurement of biologically active insulin available.

Insulin is secreted directly into the portal vein, with 40 per cent or more removed by the liver; consequently the concentration of insulin in the portal vein is three to ten times greater than in peripheral plasma.<sup>6,26</sup> This portal-peripheral gradient is of physiological significance inasmuch as small increments in insulin secretion may result in alterations of hepatic glucose metabolism in the absence of changes in peripheral glucose utilization.<sup>5,28</sup>

#### CONTROL OF INSULIN SECRETION

It is not yet possible to determine directly the rate of insulin secretion, and calculations of insulin delivery rates involve a large number of assumptions and fail to take into account the portal-peripheral insulin gradient.<sup>26,79</sup> Studies with radioiodinated insulin reveal a direct linear correlation between insulin degradation and plasma insulin concentration over a wide range of steady state insulin levels, suggesting lack of saturability of the insulin removal mechanism.<sup>77</sup> It appears that changes in plasma insulin concentration reflect changes in hormone secretion rather than alterations in the rate of insulin removal.<sup>68</sup>