

# Sanger, Hodgkin, Yalow and the impact of insulin analogues

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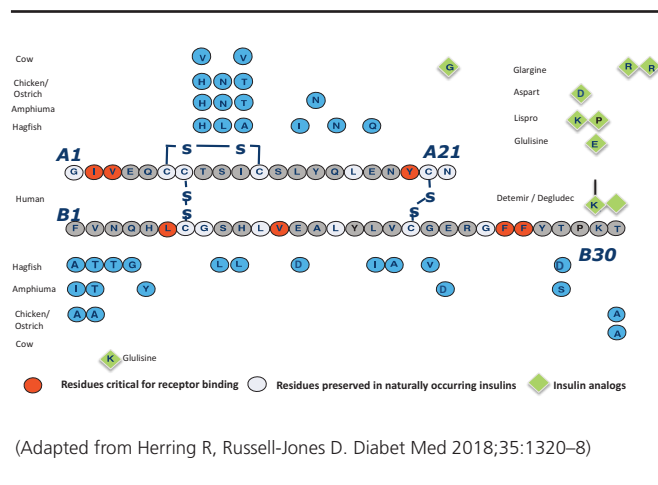
## History

The discovery of insulin by Banting, Best, Collip and Macleod is considered to be one of the great medical and scientific triumphs.<sup>1</sup> The year was 1921: it also happens to be the year that another Nobel Prize-winning scientist, Rosalyn Yalow, was born and a year in which Dorothy Crowfoot was at school in Norfolk. She wanted to study chemistry but girls had few such opportunities so she had to travel to the boys' grammar school to be allowed to study this subject. Both of these girls would grow up to be Nobel Prize-winning scientists who made outstanding contributions to the understanding of insulin. Frederick Sanger, while working at Cambridge, won his first Nobel prize for elucidating the amino acid sequence of insulin.<sup>2</sup> Following this discovery and using insulin crystals, x-ray crystallography studies were performed and the discovery of the 3-dimensional structure of insulin was achieved by Dorothy Crowfoot (who became Dorothy Hodgkin on her marriage).<sup>3</sup> Thus, insulin had led the way as being the first hormone to be isolated (Banting, Best, Collip and Macleod), the first protein to have its amino acid structure determined (Sanger) and finally, the first to have its 3-dimensional structure elucidated (Dorothy Hodgkin).<sup>1,2,3</sup> All of these advances were groundbreaking and led to the award of Nobel prizes. The last major problem was that peptide hormones were at such low concentrations in the bloodstream (picomol) that measurement was only possible using bioassays and the glucose-lowering effect in live animals. Rosalyn Yalow and her colleague Solomon Berson were able to construct and invent the radio-immunoassay, which allowed insulin to be measured even though it is in picomolar concentrations.<sup>4</sup> This great advance was also rewarded with a Nobel Prize.

## Physiology and evolution of insulin

Following these landmark studies many people became captivated by the physiology of insulin; many elegant studies have led to our physiological understanding that insulin lowers glucose by suppress-

**Figure 1.** The evolution of insulin and insulin analogue structures



ing endogenous (predominantly hepatic) glucose production through a receptor-mediated action on glycogenolysis and gluconeogenesis.<sup>5</sup> In addition, at higher concentration insulin stimulates peripheral glucose uptake, also reducing blood levels. Insulin has major regulatory effects on free fatty acid liberation from adipose and protein metabolism.<sup>5</sup> Its homeostatic function is a central controlling mechanism in metabolism of all animals. Following the discovery of the insulin receptor, maps of insulin and insulin receptor interaction were produced. These have allowed a great physiological understanding of insulin structure and functional relationships to be developed.

Although insulin is highly conserved in evolution, there are some differences in amino acid structure between species (see Figure 1).<sup>6</sup> Insulin can be identified in very simple organisms and a recognisable insulin molecule is present in invertebrates and all vertebrates.<sup>6</sup> Strong evolutionary pressure has led to the conservation of amino acids particularly in areas that are known to be involved in close association and binding to the insulin receptor and also those important for 3-dimensional conformation.

## Insulin analogues

From a position of understanding of specific amino acid interactions, it has been possible to modify the insulin structure for therapeutic benefit to create insulin analogues with altered pharmacokinetic and pharmacodynamic properties. Both short- and long-duration analogues have enabled more physiological insulin replacement via the subcutaneous route, which has led

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