

Sanger, Hodgkin, Yalow and the impact of insulin analogues

DAVID RUSSELL-JONES

Br J Diabetes 2022;**22**(Suppl1):S40-S41

Key words: insulin analogues, insulin structure, insulin treatment

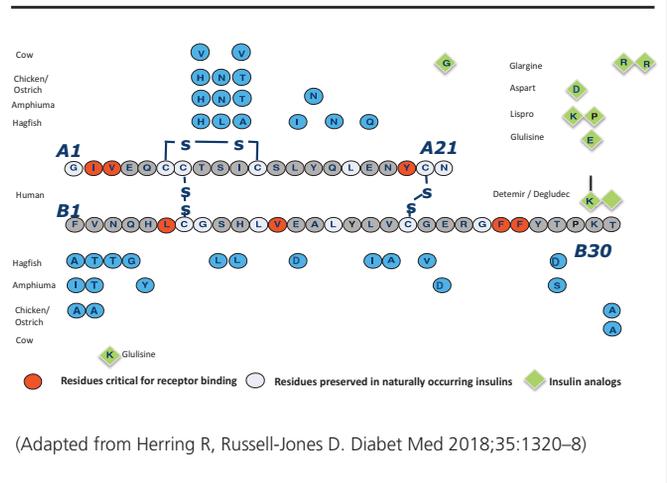
History

The discovery of insulin by Banting, Best, Collip and Macleod is considered to be one of the great medical and scientific triumphs.¹ 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.² 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).³ 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).^{1,2,3} 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.⁴ 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



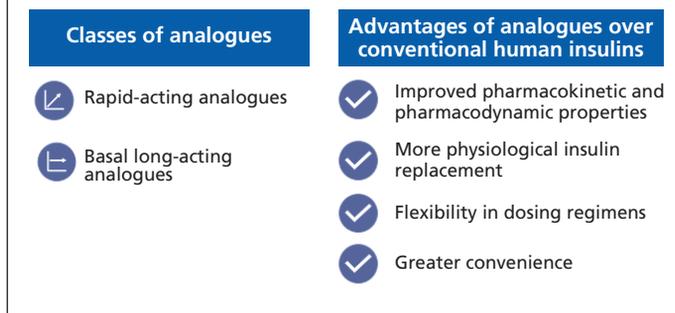
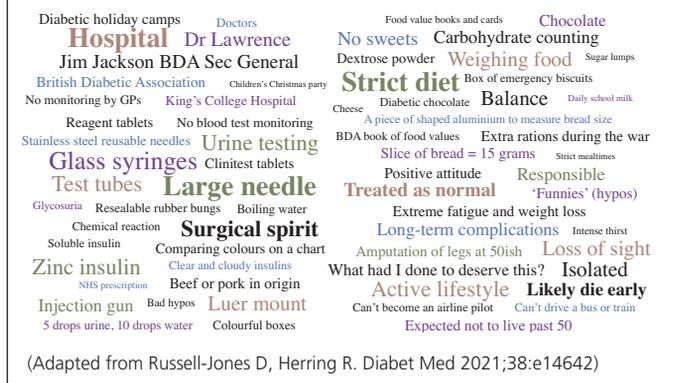
ing endogenous (predominantly hepatic) glucose production through a receptor-mediated action on glycogenolysis and gluconeogenesis.⁵ In addition, at higher concentration insulin stimulates peripheral glucose uptake, also reducing blood levels. Insulin has major regulatory effects on free fatty acid liberation from adipose and protein metabolism.⁵ 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).⁶ Insulin can be identified in very simple organisms and a recognisable insulin molecule is present in invertebrates and all vertebrates.⁶ 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

Address for correspondence: Professor David Russell-Jones
Professor of Diabetes & Endocrinology, University of Surrey and Royal Surrey Foundation Trust, Cedar Centre, Egerton Road, Guildford, GU2 7XX, UK
E-mail: Davidrussell-jones@nhs.net
<https://doi.org/10.15277/bjd.2022.361>

Figure 2. Impact of insulin analogues**Figure 3.** Life with diabetes 50 years ago

to improved diabetes control and convenience for millions of people with diabetes treated with insulin. In 1978, the first successful production of human insulin was produced by recombinant DNA technology in *Escherichia coli*. This was achieved by a team of specialists led by Robert Crea and David Goeddel.⁵ Insulin became the first genetically manufactured drug to be approved by the FDA. The development of these technologies has allowed the production of pure insulin analogues in unlimited supply for the benefit of people with diabetes worldwide. These insulin analogues have transformed diabetes care and have allowed better insulin replacement, producing superior diabetes glucose control and ultimately fewer complications and lesser morbidity. The advantages of analogues are displayed in Figure 2.

Impact of treatment in different eras

To illustrate the impact of improved diabetes care on people with T1DM we performed an interesting study in which we contacted people who had received 50-year, 60-year and 70-year medals for living with diabetes. Their recollections and views on what it was like when they were first diagnosed were gauged by words and phrases that they submitted to us. From this we created a word cloud of their experiences, which is seen in Figure 3. In addition, we asked young adults and teenagers who have been diagnosed recently to provide similar short words and

Figure 4. Life with diabetes in 2021

(Adapted from Russell-Jones D, Herring R. *Diabet Med* 2021;38:e14642)



Key messages

- Insulin was the first peptide hormone to have its amino acid sequence and 3 D structure to be determined
- Insulin Analogues have been designed from a position of knowledge of receptor binding and function
- Insulin treatment has changed dramatically over the last 100 years leading to benefit

phrases. A word cloud of their experiences has also been created, as shown in Figure 4. As can be seen from looking at the two figures, there is a marked difference in the patient experience between the ages, highlighting the advances made in treatment and life in general. These word clouds succinctly sum up the advances made in diabetes care and the impact of modern treatments over the last 100 years.

Conflict of interest I Have received research grants and honoraria for advisory boards from Dexcom, AstraZeneca, Novo Lilly, Nordisk and Sanofi, **Funding** None.

References

1. Fralick M, Zinman B. The discovery of insulin in Toronto: beginning a 100 year journey of research and clinical achievement. *Diabetologia* 2021; **64**:947–53. <https://doi.org/10.1007/s00125-020-05371-6>
2. Ryle AP, Sanger F, Smith LF, Kitai R. The disulphide bonds of insulin. *Biochem J* 1955; **60**:541–56. <https://doi.org/10.1042/bj0060541>
3. Hodgkin DC. The Banting Memorial Lecture. The structure of insulin. *Diabetes* 1972; **21**:1131–50. <https://doi.org/10.2337/diab.21.12.1131>
4. Yalow RS, Berson SA. Immunoassay of endogenous plasma insulin in man. *J Clin Invest* 1960; **39**:1157–73. <https://doi.org/10.1172/JCI104130>
5. Herring R, Russell-Jones DL. Lessons for modern insulin development. *Diabet Med* 2018; **35**(10):1320–8. <https://doi.org/10.1111/dme.13692>
6. Herring R, Jones RH, Russell-Jones DL. Hepatoselectivity and the evolution of insulin. *Diabetes Obesity Metabolism* 2014; **16**(1):1–8. <https://doi.org/10.1111/dom.12117>
7. Russell-Jones D, Herring R. 100 years of physiology, discrimination and wonder. *Diabet Med* 2021; **38**:e14642. <https://doi.org/10.1111/dme.14642>