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Rebirth of the Incretin Concept: Its conception and early development

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ABSTRACT

This paper describes the resurrection of the Incretin Concept in the early 1960s. It began with the more or less simultaneous discovery by three groups working independently in London. Dupre demonstrated that secretin given intravenously with glucose increased its rate of disappearance from the blood, McIntyre and co-workers established that hyperglycaemia evoked by oral glucose stimulated more insulin secretion than comparable hyperglycaemia produced by intravenous glucose and Marks and Samols established the insulinotropic properties of glucagon. The concept evolved with the discovery by Samols and co-workers that oral glucose stimulated the release of immunoreactive glucagon-like substances from the gut mucosa and the subsequent isolation of glucagon immunoreactive compounds, most notably oxyntomodulin and glicentin, and of gastic inhibitory polypeptide (GIP). It concluded with the isolation and characterisation of glucagon-like peptide 1 (7-36) amide.

1. Introduction

I was invited, as one of those involved in the re-discovery of the incretin effect in the early nineteen-sixties, to produce a personal account of the developments in scientific knowledge that led to the current academic, clinical and commercial interests in the hormones that are the subject of this special issue on anti-diabetic peptides.

2. Pre-1960 background

Although many experiments and observations made between 1902 and 1940 appeared to suggest that partially purified extracts of intestinal mucosa had the ability to lower blood glucose levels in animals they ceased to have any credibility after Andrew Ivy – whose eponymous units have been used to define secretin and pancreozymin activity – and his colleagues concluded [27] that "the entire evidence which had been advanced in support of the theory that the duodenum exerts a hormonal control over carbohydrate metabolism by producing a hypoglycaemic substance" was false.

Ivy, who was president of the American Physiological Society at the time was held by many to be "the most famous doctor in the country" [47]. His authority on all matters gastroenterological was unquestioned. Is it any wonder that interest in an incretin – which had been named [25] but neither purified nor characterised – came to an abrupt end in 1940 [11] and remained so until rekindled some 25 years later [40].

What re-awakened interest in *incretine* [25] – subsequently Anglicized to incretin – was the invention by Yalow and Berson of radio-immunoassay [75] the basis of all future one and two site immuno-assays – competitive and sandwich. Radio-immunoassay made accurate measurement of insulin and other peptide hormones in blood a practicable proposition for the first time and changed the face of laboratory medicine for ever.

3. Ellis Samols

Ellis Samols (Fig. 1) [16] was a brilliant young South African medical graduate who came to learn and work in Russell Fraser's laboratory at the Hammersmith Hospital London in 1959. He was assigned the task of measuring insulin in blood by the then fashionable rat diaphragm method. Unhappy about this, Samols took the opportunity, whilst on honeymoon in New York, to visit Berson and Yalow's laboratory and become familiar with their technique [75] which was just about to be published in full [74]. Like many scenario-changing discoveries it was not met with the approval by the bio-analytical establishment in the USA and consequently they had difficulty in getting their definitive paper published in their journal of first-choice.

On his return to the UK Samols found that Fraser, like most of the American Medical Hierarchy, was also hostile to the idea of radio-immunoassay and he was more or less told to leave. Samols found himself a new home in Sheila Sherlock's recently established department of medicine at the Royal Free Hospital. It was there that I first met him at a meeting of the Medical Research Society.

Samols and I immediately established a rapport; me because of my

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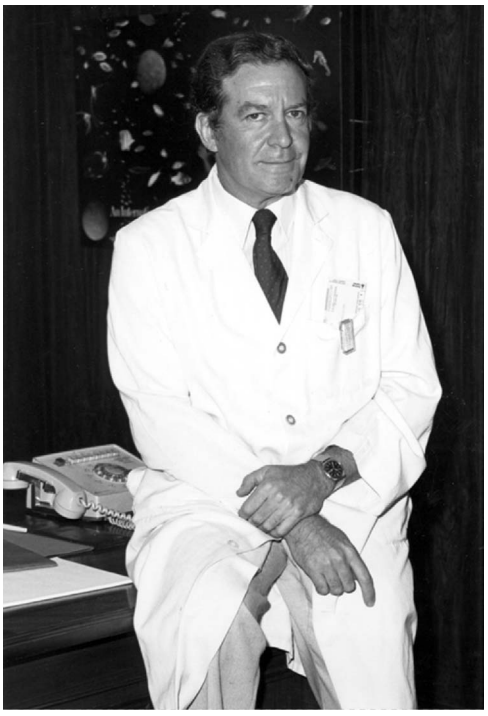

Fig. 1. Dr Ellis Samols in Louisville circa 1990.

interest in the investigation of spontaneous hypoglycaemia and the need for an insulin assay; he because he needed a clinician with an interest in carbohydrate metabolism with whom to work [53].

4. Glucagon

Glucagon was named for its ability to raise the blood glucose concentration by activating glycogenolysis in the liver. Unlike insulin, whose existence had been predicted, glucagon's was not. Its existence first came to light as a contaminant of the purest preparation of insulin then available and held to be responsible for the rise in blood glucose that preceded the fall in blood glucose whenever "insulin" was injected into an animal or person [9].

Despite being purified, studied and named [23] within a few years of its discovery, glucagon was not considered a true hormone and had no immediate commercial value. Academic and clinical interest in it remained low until the 1940s. By then a role for using it to terminate hypoglycaemia [62] in patients undergoing Sakel's [52] insulin coma for schizophrenia had been identified – just a few years before it went out of fashion.

5. Insulinoma

Like Samols, I was undergoing training in laboratory medicine during the course of which I published the first easy-to-use glucose oxidase method for measuring blood glucose [38]. It enabled me to identify the many patients with insulinoma referred to the Institute of Neurology for obscure neurological conditions and whose diagnosis had been missed elsewhere. In the course of my research I found that patients with insulinomas responded to glucagon – not yet available commercially but given to me as a gift by Mary Root of Eli Lilly – by developing an early and profound hypoglycaemia when given it by subcutaneous or intravenous injection [37].

David Marrack and I, with Ellis Samols' help, subsequently found that the rise in plasma insulin in 4 of our patients with insulinoma was far greater than would be anticipated from the rise in blood glucose it produced. We mentioned [34] *en passant*, that there was evidence that "glucagon *enhances the glucose assimilation in normal subjects* …" without going into details intending to publish them separately some time in the future. This observation, along with the ability of glucagon to produce profound hypoglycaemia in insulinoma patients who otherwise required many hours of fasting to produce it, led me to believe that glucagon might stimulate insulin secretion by direct action on islet B-cells just like the recently discovered tolbutamide [39].

At a Conference held at the Royal College of Physicians [36] in London March 1962 I said that there was now evidence suggesting "*direct stimulation of the B-cells of the pancreas by glucagon and* (that*) this possibility is now being investigated*". This was contrary to everything that was then believed about the physiological role of glucagon in glucose homeostasis [19] if indeed there was one.

Samols and I were not the first to observe a rise in plasma insulin levels in response to glucagon but were the first to suggest that it did so by directly acting on the insulin secreting B-cells. Yalow and Berson [76] had observed a larger than normal rise in plasma insulin levels 30 min after injecting an insulinoma patient with glucagon but, in keeping with conventional opinion, had attributed it to the rise in blood glucose provoked by the glycogenolytic action of glucagon on the liver. Had they measured the insulin and glucose responses immediately after intravenous injection, as we did, they would have seen that this could not possibly be the explanation. The same applies to the case reported by Alivisatos and McCullough [1] who, though not measuring plasma insulin, did observe a hypoglycaemic response to glucagon in an insulinoma patient (Fig. 2).

Testing the hypothesis that glucagon stimulates insulin secretion independently of its ability to raise blood glucose levels was on Samols' and my list of things to do with the insulin immunoassay it was not however at the very top – which was to establish its clinical usefulness [53,54,32]. It had therefore to await Samols' return from the USA where he had spent a year's sabbatical in Robert Williams' laboratory Seattle in 1964 in order to learn more about the clinical and laboratory aspects of diabetes. Nevertheless we were the first in 1965 to establish, by actually measuring the plasma insulin response, the extremely potent insulinotropic effects of glucagon – the first pure peptide shown to do so.

6. Royal Free Hospital group

Whilst he was away in the USA, Samols' entrusted his immunoassay laboratory to Neil McIntyre – a gastroenterologist in training with Sheila Sherlock and her ultimate successor as Professor of Medicine at the Royal Free Hospital Medical School.

Fig. 2. The author (left) with Dr Solomon Berson Laussane circa 1968.