Hidden Gems

Tim Holt
Contributing Editor

Shining a light into the past for the articles that continue to shape our diabetes clinical practice today

This issue: Janbon M, Chaptal J, Vedel A, Schaap J (1942) "Accidents hypoglycémiques graves par un sulfamidothiodiazol (le VK 57 ou 2254 RP)". *Montpellier Med* 441: 21–2

The serendipitous discovery of the early sulphonylureas.

Sulphonamide antibiotics came into use from 1932 and were mass produced from the mid-1930s. Ten years after their discovery, Marcel Janbon and colleagues recognised that a number of deaths among people treated in Montpellier, France, with these drugs for typhoid fever were in fact due to hypoglycaemia. Turning this insight into an opportunity for a novel class of oral hypoglycaemic drug took a further 13 years, a process led by the French scientist Auguste Loubatières. The first generation sulphonylureas were used from 1955 and were followed by the more familiar modern formulations. The last in a series of eight articles tracing the literary roots of our modern diabetes management, this article describes one of the best examples of serendipitous drug discovery in medicine.

The early 20th century witnessed the discovery of a number of antimicrobial compounds. While perhaps the most famous, Alexander Fleming's isolation of penicillin in 1929 did not lead to significant clinical use until the 1940s due to problems with purification and stabilisation (American Chemical Society, 1999). In the meantime, a completely different class of compound, the sulphonamides, was established and produced the first available antibacterial drug Prontosil, discovered in 1932 and increasingly used during the mid-1930s (Torok et al, 2009). This opened up the modern era of antibiotic therapy and, arguably, the advent of modern medicine itself.

As is still the case with newer drugs, studying the beneficial effects dominated the research effort prior to licensing, whilst important adverse effects became evident later. During the decade following their introduction, evidence emerged of a blood glucose-lowering effect of sulphonamides, but prior to 1942 the full significance of this finding was not recognised. By this time, the new drugs had found numerous clinical uses for treating infections. One of these was typhoid fever, a serious infection at the time promoted by lack of clean water supplies and fresh food. This was particularly the case in Montpellier during World War II. Located on the south coast, Montpellier belonged to an area of France that had avoided German occupation, and as a result was isolated from other regions. Shortage of essential provisions had led to the consumption of rotting food, including shellfish, and the drinking of contaminated water. Typhoid fever, caused by the bacterium *Salmonella typhi*, is spread by the faeco-oral route and carried a high mortality in under-nourished people if untreated.

The Hidden Gem

Two Frenchmen, Marcel Janbon and Auguste Loubatières, are central to the story. Janbon was a clinician working at the Montpellier Medical School Infectious Diseases Clinic, where typhoid fever was treated with the newly available drug therapy, and many of his patients received this treatment. Janbon et al's 1942 paper records the finding that several patients with typhoid treated with the sulphonamide 2254 RP had died of prolonged coma and convulsions, in some cases associated with documented reductions in blood glucose. At the time mortality was significant in people with typhoid whether treated or not, and under-nourishment made the patients prone to hypoglycaemia anyway, but Janbon and colleagues recognised that the fatalities were actually triggered by the drug therapy rather than the disease, through reductions in blood glucose.

Janbon was aware that Loubatières, a local colleague, had been working during the prior decade on diabetes using animal models. Loubatières had started work in the Physiological Laboratory of Montpellier Medical School in 1933, a laboratory already famous for the scientific study of experimental diabetes (Loubatières-Mariani, 2007). His main interest during the 1930s was the effects of the newly developed insulin protamine zinc, which he had observed and reported in

Affiliation
Senior Clinical Research Fellow, Nuffield Department of Primary Care Health Sciences, Oxford University

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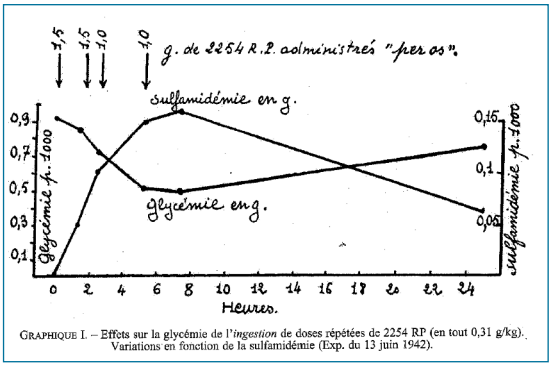

GRAPHIQUE I. – Effets sur la glycémie de l'*ingestion* de doses répétées de 2254 RP (en tout 0,31 g/kg). Variations en fonction de la sulfamidémie (Exp. du 13 juin 1942).

Figure 1. Graph from June 1942 demonstrating the inverse relationship between levels of sulphonamide and glucose in the blood over 24 hours following repeated oral dosing in a normal fasting dog.

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1938 could cause hypoglycaemic convulsions and coma in pancreatectomised dogs (Loubatières, 1957). Janbon, recognising similar phenomena in sulphonamide-treated patients with typhoid fever, asked him to investigate further.

Responding to the approach from Janbon, Loubatières went on to confirm the hypoglycaemic effects of sulphonamides, initially in animal models and later in humans. He was also able to demonstrate that the sulphonamide effect did not occur in pancreatectomised dogs stabilised on insulin. This confirmed that the mechanism was not the release of insulin from circulating proteins, but the promotion of insulin secretion itself from the beta-cells. The later conclusion was that some residual insulin secretion was necessary in order for a person with type 2 diabetes to respond to this drug class.

The 1942 paper by Janbon et al certainly is a hidden, if not a lost, gem. Published in the local journal *Montpellier Med* in March of that year, but no longer available in the journal's archives, the full manuscript has so far escaped me. However, an interesting overview is given by Professor Louis Monnier (2014), who kindly contacted Loubatières' wife, Marie-Madeleine Loubatières-Mariani (herself a professor of pharmacology), on my behalf. She was also unable to retrieve the 1942 manuscript from her personal collection, but had written a subsequent article describing the history of these discoveries (Loubatières-Mariani, 2007). It includes a diagram from an experiment on 13th June 1942, just 3 months after the Janbon paper, demonstrating the inverse relationship between levels of sulphonamide and of glucose in the blood over the 24 hours following repeated oral dosing (*Figure 1*).

Why it still shines today

Loubatières' work on the mechanism through which sulphonamides reduce glycaemia was a critical step in turning a serendipitous discovery in the hospital clinics of Montpellier into an effective therapy for a totally different condition. Sulphonylureas became the major class of drug after biguanides for treating the hyperglycaemia of type 2 diabetes, and are still the typical second-line choice although novel agents are beginning to displace them. It is difficult to estimate the scale of their usage since the 1950s and the numbers of people who have been treated with them, but it certainly runs into millions. The first generation (e.g. carbutamide, acetohexamide, chlorpropamide and tolbutamide) were followed by the second (e.g. gliclazide, glibenclamide and glipizide). Later, the third generation included the modified release formulation of gliclazide, which was studied in one of the large modern randomised trials, ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; ADVANCE Collaborative Group [2008]).

Understanding the mechanism of action has become important both in selecting appropriate patients (those with some remaining beta-cell function) and in recognising the potential for hypoglycaemia, which is still an issue with this drug class. This, and many other issues related to the discovery of sulphonylureas, was discussed in a special edition of the *Annals of the New York Academy of Sciences* (1957), first made available online in 2007.

Janbon et al (1942) reports fatalities directly attributable to the drug therapy that patients received in his clinic. These people were not enrolled in a research trial but were nevertheless exposed to a new drug that had only recently become available. In celebrating the benefit to future generations of people with type 2 diabetes through the discovery of the sulphonylureas, we should not forget these iatrogenic deaths. In a population at high risk anyway through acute infection and under-nourishment, Janbon should be acknowledged for recognising that the drug was in fact responsible, and for exposing the dangers of the new treatment that was well-meaningly delivered to these patients, in many cases no doubt to substantial benefit.

In researching this final hidden gem in the series, I came across innumerable papers citing the Janbon et al article, which I have not myself managed to catch sight of despite considerable effort. Some of these papers were written by contempories of Janbon and Loubatières, who will have of course read the paper closer to the time that it was published. But others will have simply cited it because it is, as much as any article in this series, an undisputed landmark in the diabetes literature. So in writing this piece, I am adding my name to a long list of people whom I suspect have cited this gem without actually reading it.

For those interested in previous hidden gems, a list of the articles covered in this series, inevitably

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a reflection of my own preferences, is given below (*Box 1*). I hope that they will be rediscovered and aired on an ongoing basis, and invite anyone interested in further discussion to contact me. ■

ADVANCE Collaborative Group (2008) Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* **358**: 2560–72

American Chemical Society (1999) *The discovery and development of penicillin*. American Chemical Society, Washington, DC, USA. Available at: http://bit.ly/1jhPu4tl (accessed 24.11.15)

Annals of the New York Academy of Sciences (1957) Volume 71: The Effects of the Sulfonylureas and Related Compounds in Experimental and Clinical Diabetes. *Ann N Y Acad Sci* **71**: 3–291

Loubatières A (1957) The hypoglycaemic sulfonamides: History and development of the problem from 1942 to 1955. *Ann N Y Acad Sci* **71**: 4–11

Loubatières-Mariani MM (2007) [The discovery of hypoglycemic sulfonamides]. *J Soc Biol* **201**: 121–5

Monnier L (2014) Auguste Loubatières: The hypoglycemic sulfamides' story. *Médecine des Maladies Métaboliques* **8**: 107–11

Torok L, Moran E, Cooke F (2009) *Oxford Handbook of Infectious Diseases and Microbiology (Oxford Medical Handbooks)*. Oxford University Press, Oxford: 56

Box 1. Articles highlighted in the Hidden Gems series.

- Beetham WP, Aiello LM, Balodimos MC, Koncz L (1969) Ruby-laser photocoagulation of early diabetic neovascular retinopathy: preliminary report of a longterm controlled study. *Trans Am Ophthalmol Soc* **67**: 39–67
  Holt T (2014) Hidden Gem. *Diabetes Digest* **13**: 9–10
- Banting FG, Best CH, Collip JB, Campbell WR, Fletcher AA (1922) Pancreatic extracts in the treatment of diabetes mellitus: preliminary report. *CMAJ* **12**: 141–6
  Holt T (2014) Hidden Gem. *Diabetes Digest* **13**: 60–2
- McIntyre N, Holdsworth CD, Turner DS (1965) Intestinal factors in the control of insulin secretion. *J Clin Endocrinol Metab* **25**: 1317–24
  Holt T (2014) Hidden Gem. *Diabetes Digest* **13**: 110–12
- Koenig RJ, Peterson CM, Jones RL et al (1976) Correlation of glucose regulation and hemoglobin A1c in diabetes mellitus. *N Engl J Med* **295**: 417–20
  Holt T (2014) Hidden Gem. *Diabetes Digest* **13**: 168–71
- Pickup JC, Keen H, Parsons JA, Alberti KG (1978) Continuous subcutaneous insulin infusion: An approach to achieving normoglycaemia. *Br Med J* **1**: 204–7
  Holt T (2015) Hidden Gem. *Diabetes Digest* **14**: 8–12
- Mühlhauser I, Jörgens V, Berger M et al (1983) Bicentric evaluation of a teaching and treatment programme for type 1 (insulin-dependent) diabetic patients: improvement of metabolic control and other measures of diabetes care for up to 22 months. *Diabetologia* **25**: 470–6
  Holt T (2015) Hidden Gem. *Diabetes Digest* **14**: 60–4
- Goeddel DV, Kleid DG, Bolivar F et al (1979) Expression in Escherichia coli of chemically synthesized genes for human insulin. *Proc Natl Acad Sci U S A* **76**: 106–10
  Holt T (2015) Hidden Gem. *Diabetes Digest* **14**: 108–10
- Janbon M, Chaptal J, Vedel A, Schaap J (1942) "Accidents hypoglycémiques graves par un sulfamidothiodiazol (le VK 57 ou 2254 RP)". *Montpellier Med* **441**: 21–2
  Holt T (2015) Hidden Gem. *Diabetes Digest* **14**: 162–6

Dr Tim Holt has been a Contributing Editor for Diabetes Digest *for the past 2 years. Dr David Kerr and the Publisher would like to thank Tim for his valuable contribution to the journal and his interesting and thought-provoking comments on the articles from the past that have shaped clinical practice today; we wish him well.*