Metformin: its botanical background

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ABSTRACT

This article traces the roots of the antihyperglycaemic biguanide metformin from the use of *Galega officinalis* (goat's rue or French lilac) as a herbal treatment for the symptoms of diabetes. *G. officinalis* was found to be rich in guanidine, a substance with blood glucose-lowering activity that formed the chemical basis of metformin. This insulin sensitising drug was introduced in 1957. Copyright © 2004 John Wiley & Sons, Ltd.

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KEY WORDS

Galega officinalis; metformin; antidiabetic

Introduction

Metformin (dimethylbiguanide) is now reputed to be the most widely prescribed agent in the treatment of diabetes. Its history can be traced back to the use of *Galega officinalis* Linn as a herbal medicine in medieval Europe.[1] *G. officinalis* (Leguminosae) is a perennial herb with white, blue or purple flowers that grows over three feet high and is found in most temperate regions, including Britain. Its common names include goat's rue, French lilac, Spanish sanfoin and false indigo (Figure 1). Aerial parts of the plant were used medicinally in medieval Europe to treat plague, worms, snake bites, miasma, dysuria and St Vitus dance, and the plant was fed to livestock to increase milk yield.[2]

It is believed that *G. officinalis* was also used in folklore medicine to treat symptoms now ascribed to type 2 diabetes and some versions of Culpeper's herbal suggest it has antidiabetic properties.[3] Nicholas Culpeper's treatise was first published in the 17th century,[4] around the time that English physicians were becoming aware of diabetes, and discrepancies in later editions may be due to differences in translation and interpretation. There are more detailed accounts of extracts of *G. officinalis* being used to treat diabetes in France up to the 1930s.[5,6] Indeed, *G. officinalis* continues to be cited for the treatment of diabetes in modern herbal pharmacopoeias.[7,8]

Guanidines, galegine and diguanides

Studies in the late 1800s indicated that *G. officinalis* was rich in guanidine (Figure 2), and in 1918 guanidine was shown to possess hypoglycaemic activity in animals.[9–11] However, guanidine was too toxic for clinical use and attention turned to galegine (isoamylene guanidine), a less toxic extract of *G. officinalis* that was used briefly as an antidiabetic agent in the 1920s.[12,13]

Two synthetic diguanides, namely decamethylene diguanide (Synthalin A) and dodecamethylene diguanide (Synthalin B), were better tolerated and more effective, and these were used clinically in the 1920s. However, insulin was becoming more widely available and increased appreciation of the toxicity and limited efficacy of hypoglycaemic guanidine derivatives led to discontinuation of the Synthalins by the early 1930s, although Synthalin B survived in Germany until the mid-1940s.[14]

Early biguanides

In 1929, several glucose-lowering biguanides were synthesised, including dimethylbiguanide.[15,16] These were non-toxic in animals but were not tested in humans. During the 1940s the antimalarial agent chloroguanidine hydrochloride was found to have a weak glucose-lowering effect,[17] and in 1949 a preparation of dimethylbiguanide (known as flumamine) was used against influenza in the Philippines.[18] The latter prompted Jean Sterne to investigate the glucose-lowering activity of dimethylbiguanide.

Jean Sterne

Jean Sterne (1909–1997) (Figure 3) was a physician and clinical pharmacologist who trained in diabetology under Francis Rathery at the Hôpital de la Pitie in Paris. It was here that Sterne first conducted studies with galegine. In 1956, he held positions at Aron Laboratories and the Hôpital Laennec in Paris. In collaboration with Denise Duval and others he explored the antidiabetic properties of several biguanides, unaware of the German studies in 1929.[15,16] Sterne selected dimethylbiguanide (metformin) for clinical development and proposed the name 'Glucophage' (glucose eater). His results were published in 1957[19] and the rest, as they say, is history. Also in 1957, Ungar published trials with phenformin[20] and in 1958 Mehnert reported on buformin.[21]

Rise of metformin

Phenformin and buformin were more potent than metformin and they initially enjoyed greater acclaim and use,[22] but their association with lactic acidosis led to discontinuation in most countries by the end of the 1970s.[23]

The reputation of metformin may have been tarnished by association with phenformin and buformin, but increasing evidence confirmed the antihyperglycaemic efficacy of

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metformin without causing overt hypoglycaemia or weight gain.[24,25] There was also growing awareness that metformin offered a unique range of effects that countered insulin resistance.[26,27] This was substantiated by the United Kingdom Prospective Diabetes Study which found that early use of metformin reduced cardiovascular mortality and increased survival in overweight and obese type 2 diabetic patients beyond that expected for the prevailing level of glycaemic control.[28]

The commercial side

Aron Laboratories was acquired by Lipha Pharmaceuticals (now Merck), and in 1995 the US Chief Executive Officer, Dr Gerry Daniel, brought metformin to the USA where it enjoyed blockbuster status under franchise to Bristol Myers Squibb. The popularity of metformin has continued with fixed combination tablets in which metformin is mixed with other antidiabetic agents.

Many biguanides and related guanidine derivatives have been examined as potential antidiabetic agents,[11,29] although much of this work pre-dates the availability of present models of insulin resistance. However, the multiple mechanisms of action and unique pharmacokinetic and pharmacodynamic properties of metformin confer a favourable risk–benefit ratio that has established metformin as a leading treatment for patients with type 2 diabetes.[30,31]

Postscript of ironies

There are several ironies about metformin. In our high-tech era of drug discovery and development this first-line treatment for type 2 diabetes is little removed from a herbal remedy of the middle ages. Despite its chemical simplicity and detailed investigation, metformin continues to evade a complete exposé of its cellular activity. While endless pharmacovigilance has monitored the safety profile of metformin, its natural ancestor, *G. officinalis* (known as Professor Weed in the USA) is a Class A Federal Noxious Weed in 35 states of America, and appears on the database of poisonous plants.[32,33] It

Figure 1. *Galega officinalis* (goat's rue).
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Figure 2. Chemical structure of guanidine, galegine (isoamylene guanidine), Synthalin A (decamethylene diguanide), Synthalin B (dodecamethylene diguanide), biguanide (guanylguanidine), metformin (dimethyl biguanide), phenformin (phenethyl biguanide) and buformin (butyl biguanide)

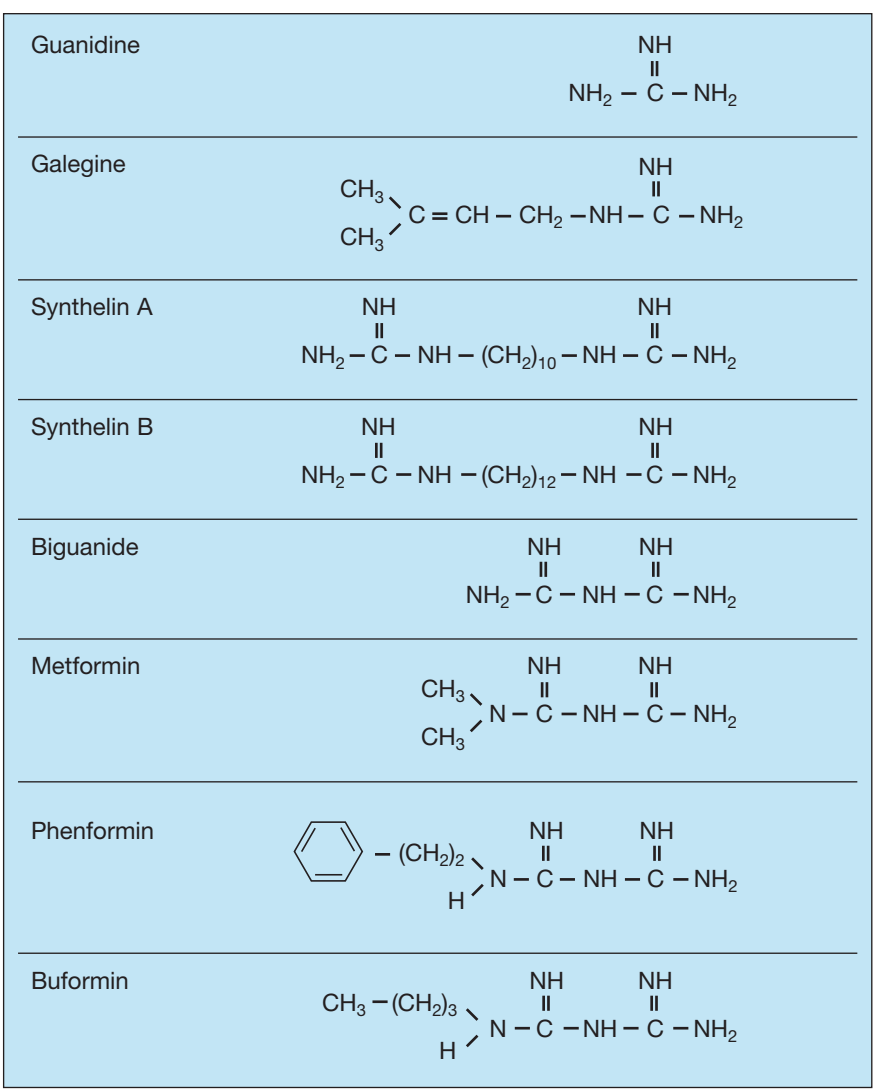
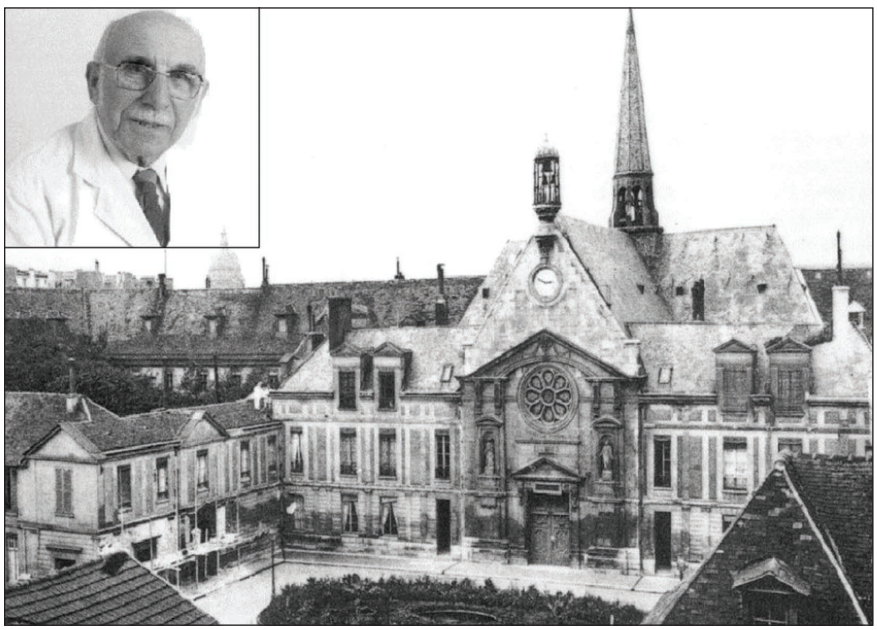


Figure 3. Jean Sterne (1909–1997) inset above the Hôpital Laennec in Paris, where he tested the antidiabetic effect of metformin



is perhaps apt to conclude with a quote from the Swiss born physician Theopharastus Bombastus von Hohenhein (1493–1541), better known as Paracelsus: 'The right dose differentiates a poison from a useful medicine'.

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