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COMMENTARY

Metformin: historical overview

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Abstract Metformin (dimethylbiguanide) has become the preferred first-line oral blood glucose-lowering agent to manage type 2 diabetes. Its history is linked to *Galega officinalis* (also known as goat's rue), a traditional herbal medicine in Europe, found to be rich in guanidine, which, in 1918, was shown to lower blood glucose. Guanidine derivatives, including metformin, were synthesised and some (not metformin) were used to treat diabetes in the 1920s and 1930s but were discontinued due to toxicity and the increased availability of insulin. Metformin was rediscovered in the search for antimalarial agents in the 1940s and, during clinical tests, proved useful to treat influenza when it sometimes lowered blood glucose. This property was pursued by the French physician Jean Sterne, who first reported the use of metformin to treat diabetes in 1957. However, metformin received limited attention as it was less potent than other glucose-lowering biguanides (phenformin and buformin), which were generally discontinued in the late 1970s due to high risk of lactic acidosis. Metformin's future was precarious, its reputation tarnished by association with other biguanides despite evident differences. The ability of metformin to counter insulin resistance and address adult-onset hyperglycaemia without weight gain or increased risk of hypoglycaemia gradually gathered credence in Europe, and after intensive scrutiny metformin was introduced into the USA in 1995. Long-term cardiovascular benefits of metformin were identified by the UK Prospective Diabetes Study (UKPDS) in 1998, providing a new rationale to adopt metformin as initial therapy to manage hyperglycaemia in type 2 diabetes. Sixty years after its introduction in diabetes treatment, metformin has become the most prescribed glucose-lowering medicine worldwide with the potential for further therapeutic applications.

Keywords Biguanide · Dimethylbiguanide · *Galega officinalis* · Guanidine · History · Jean Sterne · Metformin · Review · Type 2 diabetes

Abbreviations

FDA	Food and Drug Administration
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
UKPDS	UK Prospective Diabetes Study

Introduction

This short biography of metformin (1,1-dimethylbiguanide hydrochloride) plots a chequered history from herbal ancestry in Europe to synthesis, and the discovery of its glucose-lowering activity in the 1920s: information that was disregarded and forgotten. In the 1940s, metformin was rediscovered in the search for antimalarial agents and repurposed to treat influenza, before its introduction, in 1957, for the treatment of adult-onset diabetes (Table 1). However, metformin was considered weaker than other glucose-lowering biguanides and received limited use. When the other biguanides (phenformin and buformin) were withdrawn in the late 1970s because of links to lactic acidosis, metformin was spared, but mostly rejected. However, ongoing research and minimal clinical use in the 1980s and early 1990s

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Table 1 Landmark events in the history of metformin for the management of type 2 diabetes

Year	Landmark	Reference
1772	*Galega officinalis* used to treat symptoms of diabetes (Hill)	[3]
1844–1861	Identification and synthesis of guanidine (Strecker)	[6]
1878–1879	Synthesis of biguanide (Rathke)	[6]
1918	Guanidine lowers blood glucose in animals (Watanabe)	[7]
1922	Synthesis of dimethylbiguanide (Werner and Bell)	[17]
1926–1928	Galegine and synthalin lower blood glucose in animals and humans	[8–13]
1929	Metformin and other biguanides lower blood glucose in animals (Hesse and Taubmann; Slotta and Tschesche)	[18, 19]
1930s	Use of guanidine derivatives to treat diabetes initially grows then declines due to toxicity and also availability of insulin	[6]
1944–1947	Guanidine-based antimalarial agent, proguanil (Paludrine), lowers blood glucose in animals	[20, 21]
1949–1950	Dimethylbiguanide (flumamine) tested as potential antimalarial agent and used to treat influenza in Philippines. Also found to potentially lower blood glucose (Garcia)	[22]
1956	Jan Aron encourages Jean Sterne and Denise Duval to study guanidine-based glucose-lowering agents	[6]
1957	Jean Sterne publishes use of metformin to treat diabetes	[24]
1957–1959	Phenformin and buformin reported as treatments for diabetes	[32, 33, 37, 38]
1958	Metformin introduced to treat diabetes in the UK and other European countries	[6]
1958–1964	Sterne and colleagues (especially Azerad) further evaluate metformin in individuals with diabetes	[25–28, 36]
1968	First large prospective comparator trial of metformin (Edinburgh, UK; notably Duncan, Clarke and Campbell)	[42]
1977–1980	Phenformin and buformin withdrawn in most countries because of risk of lactic acidosis	[49]
1980–1994	Substantial new scientific and clinical evidence (e.g. Hermann, Noel, Wiernsperger and Bailey), strategic input by Lipha pharmaceuticals (e.g. Howlett, Meynaud, Daniel, Goodman) and discussions with the FDA (Reaven, DeFronzo, Bailey, Turner, Garber)	[6, 41, 44, 56–62]
1994–1995	Metformin approved (1994) and introduced (1995) in the USA	[6]
1995–1996	Key publications confirm favourable benefit:risk ratio of metformin in management of T2D	[63, 64]
1995–2000	Extensive diabetes education programme by Bristol-Myers Squibb (e.g. Cryer)	[6]
1998	UKPDS reports long-term metabolic effects of metformin and reduced cardiovascular risk with use	[69]
2000–2002	Extended-release formulation and fixed-dose combination drugs with metformin as the primary active ingredient are approved in the USA	[65, 67]
2002	Metformin reduced progression of 'prediabetes' (IGT and/or IFG) to T2D in the DPP	[82]
2005	The IDF recommends metformin as an initial glucose-lowering pharmacotherapy for T2D. Other guidelines adopt metformin as an initial glucose-lowering agent	[75]
2008	UKPDS follow-up: continued reduction of cardiovascular risk with use of metformin (Holman)	[74]
2011	Metformin included in WHO's essential medicines list	[79]

DPP, Diabetes Prevention Program; IDF, International Diabetes Federation; T2D, type 2 diabetes; WHO, World Health Organization

demonstrated a uniqueness and utility of metformin that fostered its rescue. The introduction of metformin into the USA in 1995 boosted research and clinical use and long-term evidence from the UK Prospective Diabetes Study (UKPDS) in 1998 set metformin on course for its current position as the preferred initial agent to manage hyperglycaemia in type 2 diabetes. Now exonerated, metformin is being assessed for further clinical indications. How could such a medicinal servant have received such a tempestuous journey?

Herbal history

The herbal lineage of metformin can be traced from the use of *Galega officinalis* (a.k.a. goat's rue, French lilac, Italian fitch, Spanish sainfoin or professor weed; Fig. 1) as a traditional medicine in medieval Europe [1]. Also known as *Herba rutae caprariae* in some herbals, *G. officinalis* was ascribed benefits against worms, epilepsy ('falling-sickness'), fever and pestilence in *Culpeper's Complete Herbal* of 1653, whilst in 1772, John Hill recommended *Galega* to treat conditions of thirst and frequent urination [2–4]. In Europe, wild *G. officinalis* was widely recognised as an animal galactagogue from which it gained its name ('*Galega*' being derived from the Greek for 'milk stimulant'). The plant was introduced into North America in 1891 and is now classed as a noxious weed in many states of the USA [5]. Chemical analyses of *G. officinalis* dating from the mid-1800s found the plant to be rich in guanidine and related compounds (shown in Fig. 2), especially the immature seed pods [6]. In 1918, guanidine was

Fig. 1 *Galega officinalis*. *G. officinalis*, the herbal lineage of metformin, is also known as goat's rue, French lilac, Italian fitch, Spanish sainfoin or professor weed. This plant was used as a traditional medicine in medieval Europe; it is now classed as a noxious weed in many states of the USA. Copyright Malcolm Storey, www.bioimages.org.uk (photograph taken in Berkshire, UK, 1 July 2000)

reported to reduce blood glucose in animals, and during the 1920s several mono-guanidine derivatives, notably galegine (isoamylene guanidine) and diguanidines, such as synthalin (two guanidines separated by a methylene chain; see Fig. 2), were also shown to lower blood glucose in animals [6–10]. This led to the introduction of galegine and the more potent synthalin in diabetes treatment. However, initial optimism was tempered with disappointment as toxicity was observed, curtailing their use during the 1930s as insulin became more widely available [6, 11–15].

From *Galega* to biguanides

The chemical origins of metformin run in parallel with its herbal origins and date from the preparation of guanidine by Adolph Strecker (1840s–1860s) and the subsequent work of Bernhard Rathke in 1879, resulting in the fusion of two guanidines to form biguanide (Fig. 2) [6, 16]. These developments provide the background for the synthesis of metformin (dimethylbiguanide) by Werner and Bell in 1922 [17]. Despite structural proximity to the glucose-lowering mono- and diguanidines, it was not until 1929 that metformin and other biguanides were reported to lower blood glucose levels in animals (rabbits and dogs) by Hesse and Taubmann and Slotta and Tschesche [18, 19]. Importantly, biguanides were deemed to be less toxic than mono- and diguanidines and, of the various methyl biguanides tested, metformin exerted the least toxicity [19]. However, the real potential of these agents was underappreciated at the time because of the high doses required to achieve modest glucose-lowering effects in non-diabetic animals (compared with subsequent evidence in models of diabetes). Hence, the biguanides were not developed for diabetes therapy and were forgotten during the following decade, along with the other guanidine-based agents.

Rediscovery via malaria and influenza

A third strand in the history of metformin is the independent development of a guanidine-based antimalarial agent proguanil (Paludrine) in the mid 1940s. This drug was reported to cause a lowering of blood glucose in animal studies [20, 21]. In a search for other guanidine-based antimalarials, proguanil was modified to metformin, and tests for antimalarial activity by Eusebio Garcia in the Philippines, in 1949, found metformin to be helpful in treating a local influenza outbreak [22]. This gave rise to the use of metformin hydrochloride as an anti-influenza agent called flumamine, and a tendency for metformin to lower blood glucose in some of the influenza patients was duly noted [6, 22].

Step forward Jean Sterne

The visionary who translated the blood-glucose lowering potential of metformin into a therapeutic reality was Jean Sterne, a physician at the Aron Laboratories in Suresnes, in the west of Paris, France (Fig. 3). In 1956, encouraged by laboratory owner, Jan Aron, Sterne critically assessed the evidence around flumamine, and recalled his involvement in a disappointing study of galegine as an intern with Professor Francis Rathery at Hôpital de la Pitié in Paris many years earlier [23]. Maybe metformin would be better? Working at Aron Laboratories with his pharmacist colleague, Denise Duval, the duo embarked on an ambitious programme of research into the pharmacodynamics of several guanidine-based compounds, including metformin and phenformin, in normal and diabetic animal models. Unknowingly they duplicated and extended studies on guanidine-based compounds from the 1920s and noted afresh the issues of high dose, limited glucose-lowering properties and high toxicity. They singled out metformin for study in the diabetes clinic based on its glucose-lowering efficacy and minimal adverse effects in normal and diabetic animal models, coupled with the documented experience of flumamine use in humans [6].

Sterne had a position at Hôpital Laennec in Paris where he started metformin studies with his patients; he also persuaded Dr. Elie Azerad at Hôpital Beaujon in Clichy (northwestern Paris) to collaborate. Their initial studies, mostly in insulin-treated individuals, included a mix of juvenile-onset and maturity-onset presentations of diabetes. The studies indicated that metformin could replace the need for insulin in some individuals with maturity-onset diabetes and reduce the insulin dose required by others, but it did not eliminate the need for

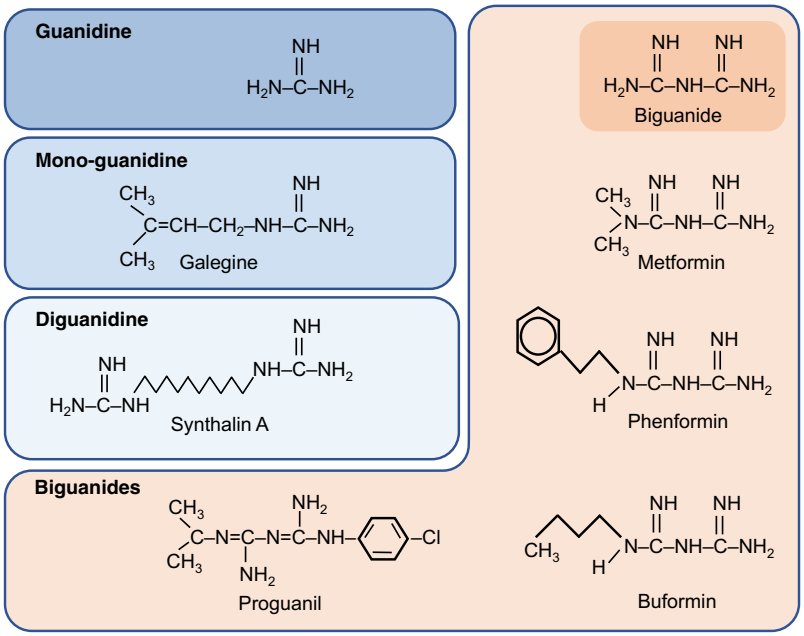

Fig. 2 Structure of guanidine and related compounds. *G. officinalis* is rich in guanidine, which is known to reduce blood glucose levels in animals. Some mono-guanidine (e.g. galegine) and diguanidine (e.g. synthalin) derivatives have blood glucose-lowering properties, as do biguanides (formed via fusion of two guanidine molecules) and their derivatives (metformin, phenformin, buformin and proguanil). However, the mono- and diguanidine derivatives proved to be too toxic for continued clinical use, while phenformin and buformin were discontinued in most countries because of increased risk of lactic acidosis; only metformin is widely approved for use as a glucose-lowering agent in the management of type 2 diabetes

insulin in individuals with juvenile-onset diabetes [6]. They also noted no occurrence of frank hypoglycaemia (as had recently been reported with sulfonylureas) and little or no effect of metformin use in individuals without diabetes. This was enough for Sterne to publish a brief account of his findings in a Moroccan medical journal in 1957 [24], a paper that is now recognised as a landmark paper for the emergence of metformin as a diabetes therapy. In his report, Sterne made the following prophetic remarks (translated from French): 'LA6023 [metformin] is…well tolerated, which, even after very prolonged administration, does not damage the organism. At low doses, it is hypoglycaemic by mouth in the rabbit, chicken, rat, guinea pig, dog, alloxan-diabetic rabbit, and the diabetic human…and its ultimate place in the management of diabetes requires further study'. Later publications would elaborate details of these animal studies, revealing Sterne's insight, skill and persistence [25–31].

Fig. 3 Jean Sterne (1909–1997). Jean Sterne trained in medicine in Paris and gained experience in diabetology with Francis Rathery at Hôpital de la Pitié, as well as taking specialisms in infectious diseases, cardiology, psychiatry and neurology. During the second world war, he was a battalion medic; he was taken prisoner, escaped to Morocco where he worked as a musician, and later returned to France to assist in the liberation of Toulouse. In 1956, after several years of being back in Morocco, directing the medicines unit at a hospital in Casablanca, Sterne took a position with Aron Laboratories in Suresnes, Paris. Here he investigated guanidine derivatives with Denise Duval. The rest, as they say, is history. At the end of an interview in 1996, Sterne commented, 'When I look back on my life, I definitely can say that I've served a purpose on Earth'. Metformin is his testament [23]. Photograph courtesy of Christophe Pasik, Merck-Lipha Pharmaceuticals (Lyon, France)

Sterne suggested the name 'glucophage' (meaning glucose eater), which was adopted by Aron to market metformin, and Sterne played a prominent role in ongoing research and physician education to assist the introduction of metformin into clinical practice in Europe [6]. History might be tempted to consider the diabetes indication of metformin as serendipitous, but we must gratefully acknowledge Sterne's sharp enquiring mind, his prodigious experimentation and his perceptive clinical sixth sense.

The biguanide opportunity

During the 1950s, other groups investigated guanidine derivatives, and the glucose-lowering properties of phenformin were rediscovered and published in 1957 by Ungar and colleagues (based in the USA) [32]. This was followed by reports

of buformin's ability to reduce blood sugar levels in 1958, by A. Beringer (Germany) [32, 33]. A vast selection of guanidine derivatives was then synthesised and evaluated, but enthusiasm was dampened by their lesser glucose-lowering efficacy in non-diabetic animals compared with agents that stimulate insulin secretion [34, 35]. However, studies in human maturity-onset diabetes indicated greater glucose-lowering efficacy of phenformin compared with other biguanides and this agent gained global popularity as an alternative to sulfonylureas, especially in the USA [36–38]. At this time, metformin and buformin were not introduced for use in the USA and received relatively minor use in Europe, although metformin became available in the UK in 1958 and in Canada in 1972 and was championed in several respected diabetes clinics. In the early 1960s, buformin became available across Europe (but not the UK), with its use particularly being adopted in Germany; nonetheless, it remained in the shadow of phenformin [39, 40].

Clinical experience with metformin use in small studies and anecdotal accounts from individuals with maturity-onset diabetes typically portrayed modest efficacy but generally good tolerability, accepting the gastrointestinal incommode experienced by some patients [6, 41]. Large comparative trials (notably in Edinburgh, UK) showed that metformin could achieve similar long-term glycaemic control as sulfonylureas, without significant hypoglycaemia or weight gain [42–44]. Later studies reported that basal insulin concentrations were often reduced with metformin use, consistent with the amelioration of insulin resistance, while lipid-lowering effects and improved haemodynamics were evident in some individuals [41, 45]. The requirement for renal monitoring was consolidated, contraindications were appreciated and a possible decrease of vitamin B_{12} absorption was recognised [41, 45].

Lactic acidosis

The risk of lactic acidosis, especially with phenformin and buformin, was evident from the outset, and the controversy was fuelled when phenformin was withdrawn from the University Group Diabetes Program (UGDP) trial in the USA in 1971 [46–48]. Phenformin was removed from the market in the USA in 1978, and phenformin and buformin were discontinued in much of Europe around this time, although both agents can still be obtained in some countries [49]. The incidence of lactic acidosis amongst users of metformin was much lower and most cases could be attributed to inappropriate use in contraindicated patients with chronically impaired renal function or in those with acute kidney disease [47, 50, 51]. Moreover, in some studies it was debatable whether incidence rates of lactic acidosis with metformin were higher than background rates amongst individuals with maturity-onset diabetes. Nevertheless, the reputation of metformin was tarnished by association with the other biguanides, causing metformin to teeter on the very brink of discontinuation [49].

Ironically, soon after withdrawal of phenformin it was noted that about 9% of Europids have a mutation in the *CYP2D6* gene, encoding the cytochrome P450 2D6 (CYP2D6) hydroxylation enzyme, causing a build-up of unmetabolised phenformin, leading to lactic acidosis [52, 53]: a problem that modern pharmacogenomics could deal with.

How did metformin survive the biguanide cull?

Clinical experience with metformin, albeit limited compared with phenformin, generally suggested a more favourable safety profile, and there were pharmacokinetic data to indicate distinct differences between metformin and the other biguanides (Fig. 4; Table 2) [40, 41]. During the 1980s, 'non-insulin-dependent diabetes' (replacing the term 'maturity-onset diabetes'), as a condition, became viewed as much from the perspective of insulin resistance as beta cell failure, and the ability of metformin to counter insulin resistance generated interest [54, 55]. New information in the 1980s and early 1990s indicated that the ability of metformin to reduce hepatic gluconeogenesis and increase peripheral glucose utilisation was not merely an anaerobic consequence of respiratory-chain disruption [45]. Rather, metformin affected a raft of insulin-dependent and insulin-independent effects in ways that varied in different tissues because of the difference in the amount of drug exposure to these tissues and the activity of insulin, glucagon and pathways of nutrient metabolism within these tissues. In particular, it became evident that high levels of metformin in the intestinal wall exert insulin-independent effects that account for most of the excess lactate production associated with its use, whereas liver and muscle tissues are exposed to lower concentrations of metformin that alter post-receptor insulin signalling pathways and redirect energy-generating and storage pathways [56–62].

Metformin enters the USA

With reverberations from phenformin, the US Food and Drug Administration (FDA) was hesitant about metformin, but in 1986 an approach by Lipha Pharmaceuticals (having acquired Aron Laboratories) sparked an inordinately thorough reassessment of metformin by the FDA and the sponsor. The Lipha team was led by Dr. Gerard Daniel, an inspired, meticulous and pragmatic physician reminiscent of Jean Sterne. Daniel worked tirelessly alongside another very accomplished physician, Dr. Anita Goodman, to deliver answers to an avalanche of questions from the FDA [6]. This involved a proliferation of studies by Lipha Europe plus input from a group of

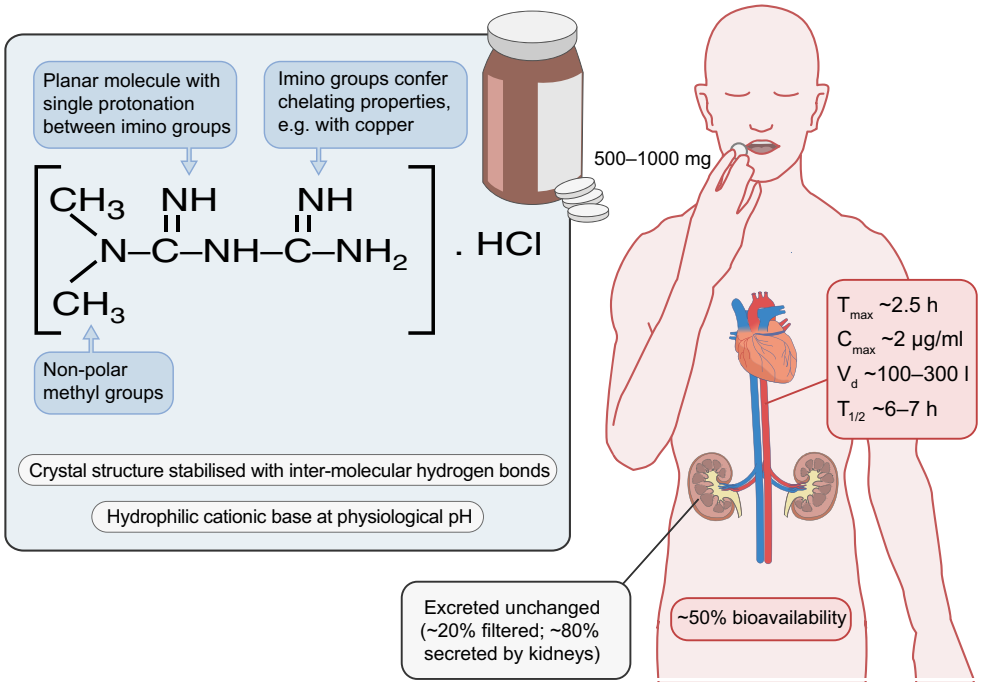

Fig. 4 Metformin structure and pharmacokinetics. Metformin (1,1-dimethylbiguanide hydrochloride) is a relatively planar hydrophilic molecule, monoprotonated at neutral pH with several tautomeric configurations. Oral doses of 500 to1000 mg of the standard immediate-release tablet formulation are rapidly absorbed in the small intestine (time for drug to reach maximum plasma concentration after administration (T_{max}), ~2.5 h; approximately 50% bioavailability), typically giving a peak plasma concentration (C_{max}) of about 2 μg/ml, and rarely >4 μg/ml, with a steady-state concentration range of 0.3–1.5 μg/ml. Plasma protein binding is negligible and distribution is extensive (usual volume of distribution [V_d], 100–300 l). Metformin has an elimination half-life ($T_{1/2}$) of ~6–7 h, or longer if renal function is impaired. It is not metabolised and is excreted in the urine unchanged, with approximately 20% of the drug being filtered, with the remaining ~80% being secreted by the kidney [92]

independent clinical scientists (initially Gerald Reaven, Ralph DeFronzo and Clifford Bailey, later joined by Robert Turner and Alan Garber) who engaged with the FDA to design the clinical trials, discuss the data and consider the implications for routine clinical use in the USA [6, 56]. The FDA approved metformin on 29 December 1994 and soon after its launch in the USA, in 1995, new key trial data were published in the *New England Journal of Medicine* [63]. These and later clinical studies confirmed and extended the findings from the aforementioned comparative trials conducted in Edinburgh

Table 2 Comparisons between metformin vs phenformin and buformin

Feature	Metformin	Phenformin	Buformin
Solubility	More hydrophilic than phenformin or buformin	More lipophilic than metformin or buformin	Intermediate between metformin and phenformin
Log *P* (octanol-water)	−1.43	−0.83	−1.20
Binding to mitochondrial membranes and inhibition of respiratory chain	Weaker	Stronger	Stronger
Location of anaerobic glycolysis	Mostly intestinal tissue exposed to high drug concentration	More generalised, including muscle	More generalised, including muscle
Metabolism	Not metabolised, eliminated unchanged	About one-third hydroxylated by CYP2D6 (~9% Europids have *CYP2D6* polymorphisms)	Almost all eliminated unchanged
Risk of lactic acidosis (events per 1000 patient-years)	0.03–0.09	0.40–0.90	> 0.10

Data extracted from [40, 45, 92].

CYP2D6, cytochrome P450 2D6; *P*, partition coefficient

two decades earlier, and the design of the FDA registration trials for metformin has provided a template for phase 3 evaluation of subsequent glucose-lowering agents [63, 64]. Bristol Myers Squibb acquired US marketing rights to metformin and instigated an education programme of unprecedented proportion to facilitate safe introduction of the drug, emphasising its different mode of action to sulfonylureas and the necessary cautions associated with renal impairment and hypoxaemic conditions. The value of this safety-first approach accorded with the FDA's 'black box warning' reminder that is inserted in the product label and played an important role in maintaining the acknowledged safety profile of the drug [64]. As prescriber confidence grew, an extended-release formulation of metformin was approved in 2000 with reduced gastrointestinal side effects [65, 66]. Also, new fixed-dose combinations of metformin with sulfonylureas, and later with other classes of oral glucose-lowering agents, became available, taking advantage of additive efficacy when combining agents with different modes of action [67]. The key difference from earlier European fixed-dose combinations was that the dosages were based around metformin as the primary component, with doses of the second agent tailored to complement the administration schedule for metformin and to minimise risk of hypoglycaemia [68].

The UKPDS and long-term retrospective studies

In 1998, the UKPDS revealed data from newly diagnosed type 2 diabetes individuals receiving glucose-lowering treatment for more than a decade. This epic study, which redefined the therapeutic strategy for the management of type 2 diabetes, noted that in addition to glucose-lowering effects, weight neutrality and low hypoglycaemia risk, long-term metformin therapy might reduce cardiovascular events and improve survival [69]. Reduced cardiovascular risk appeared to be largely independent of glucose-lowering efficacy and attention is drawn to a substantial literature noting potentially advantageous effects of the drug on the macro- and microvasculature (Table 3) [70, 71]. Interrogation of large databases that captured long-term treatment of type 2 diabetes consistently confirmed the reduced cardiovascular risk with metformin, and a 10-year follow-up of the UKPDS in 2008 showed a continued cardiovascular benefit of early use of the drug [72–74].

First-line pharmacological choice

Many studies on the pharmacokinetics, pharmacodynamics, clinical efficacy and cellular mechanisms of metformin have informed a favourable benefit:risk ratio that, alongside cost-effectiveness, has elevated this agent to the preferred first-line glucose-lowering pharmacological therapy for type 2 diabetes in major national and international treatment guidelines and algorithms (for examples, see [75–78]). Metformin has become the most prescribed glucose-lowering therapy worldwide and it is now included in the World Health Organization's (WHO's) essential medicines list [79]. A citizens' petition in the USA prompted an update to the product label in 2016 to extend prescribing for individuals with mild renal impairment. Overall, the prominent position of metformin reflects judicious prescribing, emphasising that contraindications should not be over-relaxed if the safety profile is to be retained (Table 4).

Table 3 Pharmacodynamic effects of metformin in the treatment of type 2 diabetes

Clinical feature	Effect of metformin
Hyperglycaemia	Improves glycaemic control in T2D; reduces progression of IGT and IFG to T2D
Insulin resistance	Counters insulin resistance by several insulin-dependent and -independent actions that reduce hepatic glucose output, improve peripheral glucose disposal, increase intestinal anaerobic glucose metabolism and assist endothelial function
Hyperinsulinaemia	Reduces fasting hyperinsulinaemia
Abdominal obesity	Usually stabilises body weight; can facilitate reduction of excess adiposity
Dyslipidaemia	May modestly improve blood lipid profile in some hypertriacylglycerolaemic and hypercholesterolaemic individuals
Blood pressure	No significant effect on blood pressure in most studies but blood pressure control may be improved in overweight individuals achieving weight loss
Proinflammatory state	May reduce CRP and some adipocytokines
Procoagulant state	Some antithrombotic activity, e.g. decrease in PAI-1, fibrinogen and platelet aggregation; improved capillary perfusion
Atherosclerosis	Reduced myocardial infarction and increased survival in T2D: reduced carotid intima-media thickness and reduced levels of adhesion molecules; other evidence for antiatherogenic activity, mostly from animal studies

CRP, C-reactive protein; PAI-1, plasminogen activator inhibitor-1; T2D, type 2 diabetes

Table 4 Clinical use of metformin in the treatment of type 2 diabetes

Feature	Comment
Indications[a]	Monotherapy or in combination with other glucose-lowering agents including insulin in type 2 diabetes patients inadequately controlled by diet, exercise, and health education
Dosage forms[b]	500, 850 and 1000 mg standard (IR) tablets (taken with meals); 500, 750 and 1000 mg XR tablets (mostly taken with evening meal); 500 mg/5 ml liquid formulation; 500 mg powder sachets
Titration	Increase dose slowly; monitor glycaemic control; maximal dose is 2550 or 3000 mg/day, depending on country (2000 mg/day in children)
Contraindications[a]	Renal and hepatic disease; cardiac or respiratory insufficiency; any hypoxic condition; severe infection; alcohol abuse; history of lactic acidosis; temporarily discontinue during use of i.v. radiographic contrast agents; pregnancy (although safe use is demonstrated in several studies) N.B. Some guidelines have relaxed the renal contraindication and suggest: reduce metformin dose in renal impairment if eGFR <60 ml/min/1.73m^2 (MDRD); avoid initiating metformin if eGFR <45 ml/min/1.73m^2; stop metformin if eGFR <30 ml/min/1.73m^2
Side effects	Gastrointestinal symptoms (may include diarrhoea) and metallic taste, likely to improve with dose reduction and re-titration; may impair absorption of vitamin B_{12} and folic acid
Adverse reactions	Risk of lactic acidosis in patients with a contraindication; hypoglycaemia can occur when taken in combination with another glucose-lowering drug or during alcohol abuse
Monitoring	Check for contraindications; check plasma creatinine level or eGFR and haemoglobin periodically; possible interaction with cimetidine therapy

The information in this table is based on the approved labelling of metformin by the FDA and European Medicines Agency (EMA), and recommendations of the National Institute for Health and Care Excellence (NICE) in the UK.

[a] The exact wording of indications and contraindications varies according to the labelling approved in different countries and regional and national guidelines

[b] Dose and formulation varies depending on country

eGFR, estimated glomerular filtration rate; IR, immediate-release; MDRD, modification of diet in renal disease; XR, extended-release/slow-release

Other indications

Possible additional indications for metformin are under investigation; opportunities for its use in type 1 diabetes to improve glycaemic control and reduce required insulin dose have been appreciated since the very first clinical studies [6, 80]. Several studies have affirmed the value of metformin to slow or prevent progression of impaired glucose tolerance (IGT)/impaired fasting glucose (IFG) ('prediabetes') to type 2 diabetes and other studies have suggested a place for metformin in the

Fig. 5 Gallery of people who 'made metformin happen'. Upper row: Jean Sterne, Denise Duval, Jan Aron, Elie Azerad, Leslie Duncan, Basil Clarke, Ian Campbell, Leif Sparre Hermann, Harry Howlett, Michel Noel. Lower row: Andre Meynaud, Nicolas Wiernsperger, Gerard Daniel, Anita Goodman, Gerald Reaven, Ralph DeFronzo, Clifford Bailey, Robert Turner, Alan Garber, Dennis Cryer, Rury Holman. Missing: C. K. Watanabe, Emil Werner and James Bell, Erich Hesse and Gert Taubmann, Karl Slotta and Rudolf Tschesche, Eusebio Garcia. Apologies to the thousands of scientists, healthcare professionals and pharmaceutical personnel listed in reference [56] who have made important contributions to the journey of metformin but who have not been listed here. Copyright for each photograph lies with the respective holders

treatment of gestational diabetes [81–83]. Various insulin-resistant states in which metformin has improved prognosis include polycystic ovary syndrome (PCOS), human immunodeficiency virus (HIV)-associated lipodystrophy, acanthosis nigricans and, possibly, dementia-type neurodegenerative disorders [84–87]. Reduced cancer risk was tentatively indicated in the UKPDS and has subsequently been identified in large database analyses, suggesting that metformin might protect against certain cancers in individuals with type 2 diabetes, notably in the bowel where drug exposure is high, and this has opened a whole new research arena [69, 88, 89]. Advances in pharmacogenomics may better inform responsiveness to metformin and effects on the gut microbiome, and animal studies have intriguingly noted anti-ageing effects of metformin [90, 91].

Some lessons

There are endless generic lessons for medical research thinly disguised within the history of metformin. With hindsight, we are reminded that time spent searching early original literature can save valuable laboratory time, effort and money: vital clues can be concealed amidst throw-away observations in other areas of research. We are also reminded that the selection and interpretation of experimental models is fundamental, scrutiny within a drug class can reveal important differences, and we don't have to know exactly how a drug works to reap benefit, but we do need to appreciate how to use it safely.

Conclusion

The awesome voyage of metformin from herbal beginnings to respected therapeutic agent has been turbulent. It was discovered, forgotten, rediscovered, repurposed, rejected, rescued, exonerated and may have further secrets to reveal. Each chapter has a cast of champions who helped it on its way (Fig. 5), but the pivotal work of Jean Sterne stands aloft [6, 56]. Metformin is unusual amongst pharmacotherapies as it does not appear to have a single mechanistic target: rather it counters insulin resistance and impacts metabolic, vascular and other physiological functions through multiple effects that are individually modest but collectively substantial. The value of such a favourably versatile medication requires that the contraindications (especially renal and hypoxaemic restrictions) are respected and that further potential therapeutic opportunities are explored.

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