MERCK CAPACITY
ADVANCEMENT PROGRAM
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METFORMIN: History and Clinical Evidence

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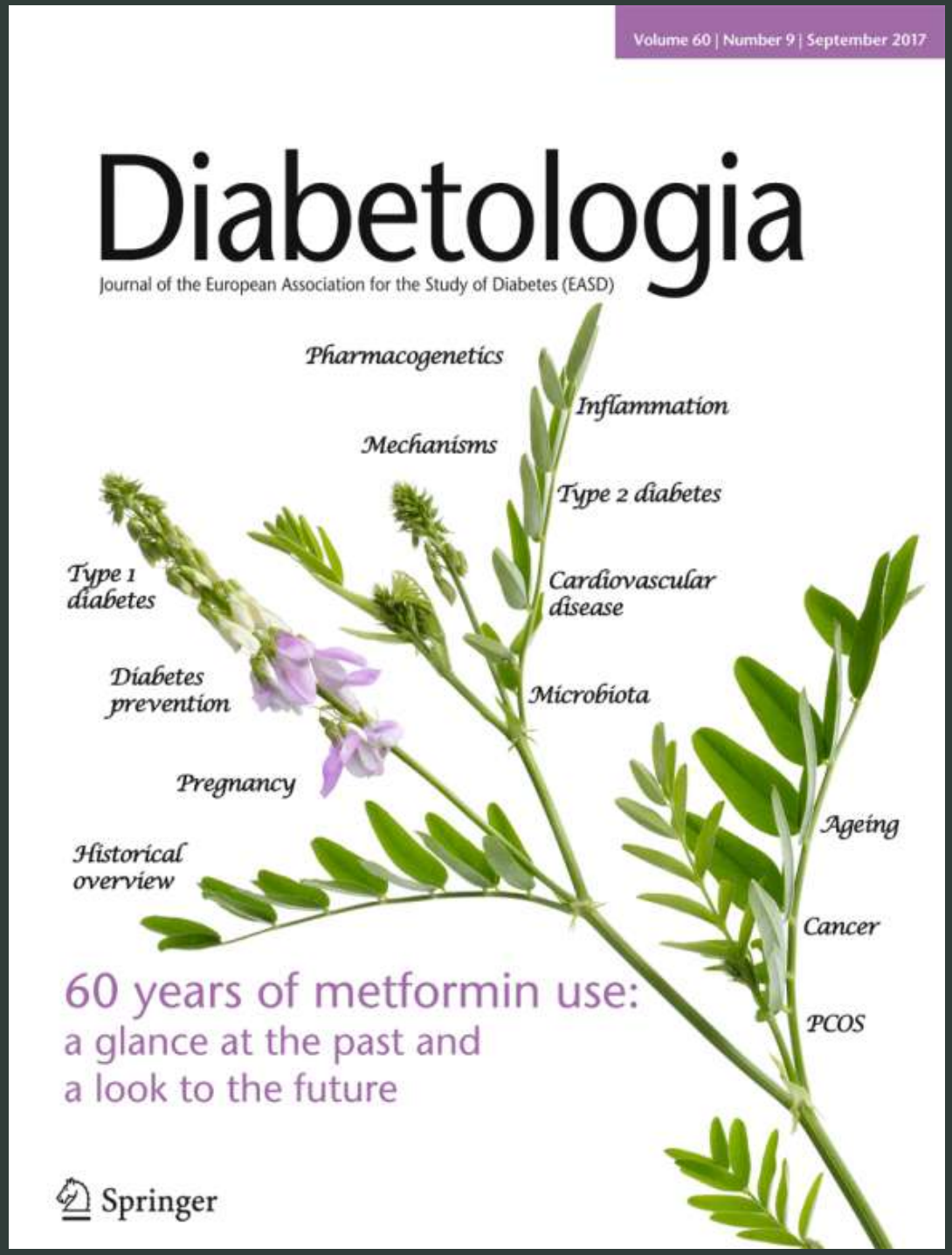
60 years of Metformin use

- 1957-2017
- **24,690** paper in ScienceDirect



Source of literature

Diabetologia (2017) 60:1566–1576
DOI 10.1007/s00125-017-4318-z

CrossMark

COMMENTARY

Metformin: historical overview

Clifford J. Bailey[1]

Received: 14 March 2017 / Accepted: 10 May 2017 / Published online: 3 August 2017

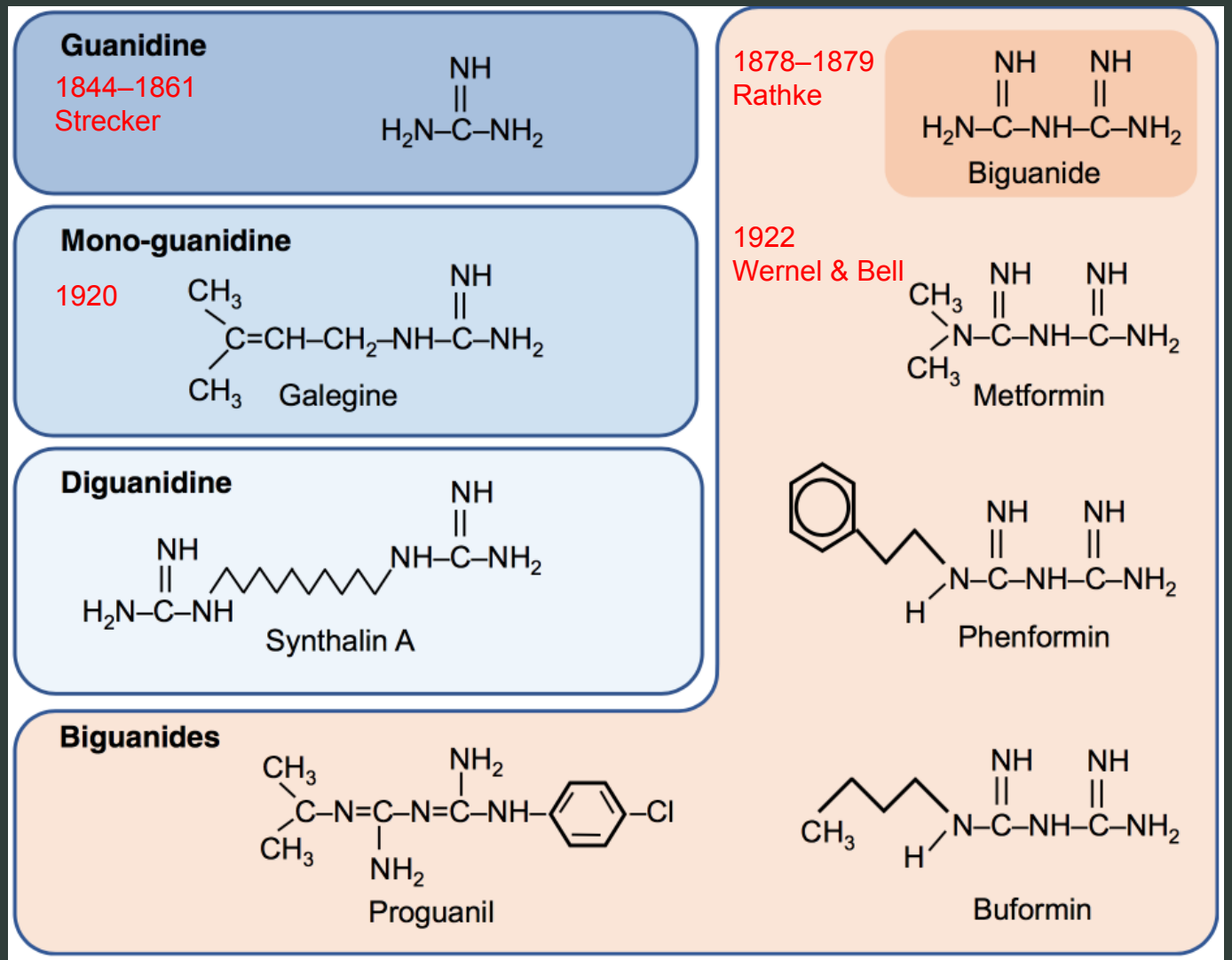
History of Metformin

- The discovery of metformin began with the synthesis of galegine -like compounds derived from *Gallega officinalis*, a plant traditionally employed in Europe as a drug for diabetes treatment for centuries.
- *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

Galega officinalis L

- Goat's rue, French lilac, Italian fitch, Spanish sainfoin or professor weed as a traditional medicine in medieval Europe.
- 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
- Chemical analyses of *G. officinalis* dating from the mid-1800s found the plant to be rich in guanidine and related compounds
- The active ingredient in the French lilac is galegine or isoamylene guanidine

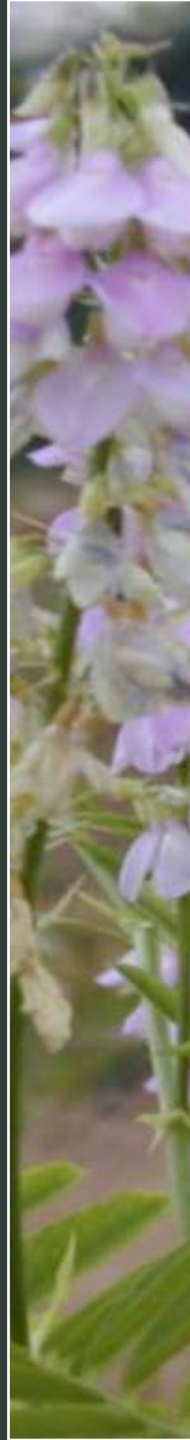
Structure of guanidine and related compounds



1772

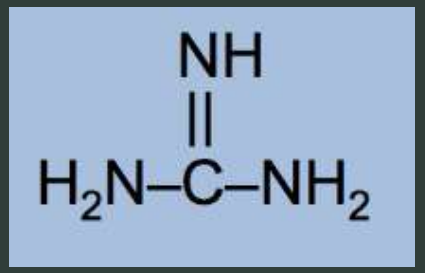
- John Hill recommended *Galega officinalis* to treat conditions of thirst and frequent urination (symptoms of diabetes)

Hill J (1772). The vegetable system. Or the internal structure and the life of plants; their parts, and nourishment, explained; their classes, orders, genera, and species, ascertained, and described; in a methods altogether new: comprehending an artificial index, and a natural system. With figures of all the plants; designed and en- graved by the author. The whole from nature only. Vol. XXI, containing plants and four-petal'd irregular flowers. London, p54



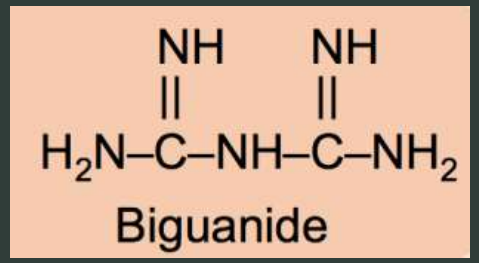
1844–1861

- Identification and synthesis of guanidine (Strecker)



1878–1879

- Synthesis of biguanide (Rathke)



Rathke, B (1879) Ueber die Einwirkung von Phenylsenföl auf Diphenylguanidin, Berichte der deutschen chemischen Gesellschaft, 12(1) 774-776

B. Rathke (1879) **Ueber Biguanid**, Berichte der deutschen chemischen Gesellschaft,12(1) 776-784

1918

- Guanidine lowers blood glucose in animals (Watanabe)

Watanabe CK (1918) Studies in the metabolic changes induced by administration of guanidine bases. Influence of injected guanidine hydrochloride upon blood sugar content. J Biol Chem 33:253–265

STUDIES IN THE METABOLIC CHANGES INDUCED BY ADMINISTRATION OF GUANIDINE BASES.

I. INFLUENCE OF INJECTED GUANIDINE HYDROCHLORIDE UPON BLOOD SUGAR CONTENT.

By C. K. WATANABE.

(From the Laboratory of Pathological Chemistry, School of Medicine, and the Sheffield Laboratory of Physiological Chemistry, Yale University, New Haven.)

(Received for publication, December 13, 1917.)

Methods.

Rabbits were used in this investigation. Blood was usually drawn from the ear vein before and after the subcutaneous injection of a 10 per cent solution of guanidine hydrochloride. McDanell's (21) modification of the Lewis-Benedict method was used for the estimation of sugar in the blood and Fehling's test for sugar in the urine. Duplicate determinations were done on the blood sugar to avoid technical errors. It was necessary to take some blood samples at night. In this case the specimen was immediately evaporated to dryness with the picric acid and determined colorimetrically the following morning. All specimens were evaporated to dryness with picric acid immediately on being drawn in order to avoid disappearance of sugar.

For the determination of total solids, the blood was drawn from the ear vein into a weighed crucible and dried to constant weight in an electric oven. About 2 cc. of blood were used for this determination and the sample for the blood sugar determination was taken at the same time. Comparison was made between normal rabbits and rabbits which had been injected with guanidine.

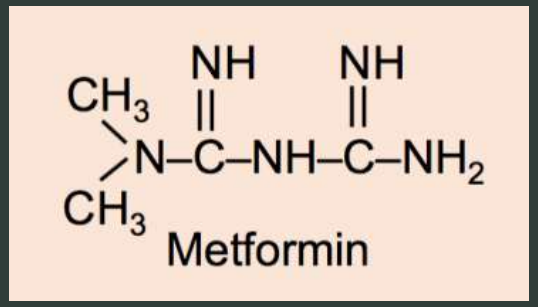
Hypoglycemia after the Injection of Guanidine Hydrochloride.

Rabbit No.	Date.	Weight.	Guanidine per kilo at 9.10 a.m.	Blood sugar.										
				9 a.m.	10 a.m.	11 a.m.	12 n.	1 p.m.	2 p.m.	4 p.m.	5 p.m.	8 p.m.	Next day at 9 a.m.	2 p.m.
	1917	gm.	gm.	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent
7	June 30	2,220	0.15	0.101	0.100	0.122	0.124	0.100	0.098	0.085	0.077	0.073	0.099	0.095
8	July 2	2,240	0.20	0.121	0.112	0.125	0.127	0.108	0.111	0.100	0.101	0.054	0.081	

Watanabe CK (1918) Studies in the metabolic changes induced by administration of guanidine bases. Influence of injected guanidine hydrochloride upon blood sugar content. J Biol Chem 33:253–265

1922

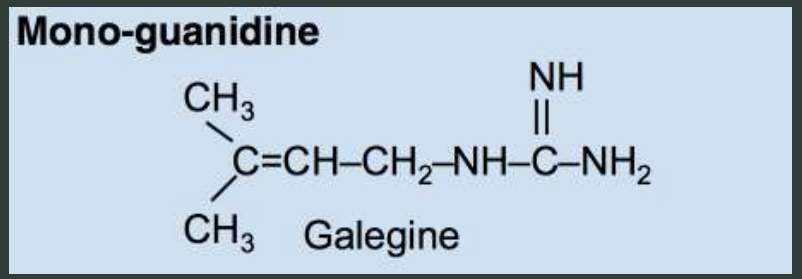
- Synthesis of dimethylbiguanide (Werner and Bell)

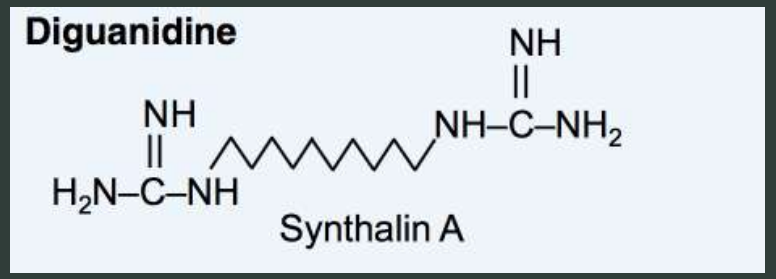


Werner EA, Bell J (1922) The preparation of methylguanidine, and of ββ-dimethylguanidine by the interaction of dicyandiamide, and methylammonium and dimethylammonium chlorides respectively. J Chem Soc Trans 121:1790–1794

1926–1928

- Galegine and synthalin lower blood glucose in animals and humans





1. Frank E, Nothmann M, Wagner A (1926) Uber synthetisch dargestellte Körper mit insulinartiger Wirkung auf den normalen und diabetischen Organismus. Klin Wchnschr 5:2100–2107 [article in German]
2. Simonnet H, Tanret G (1927). Sur les proprietes hypoglycemiantes du sulfate de galegine. Bull Soc Chim Biol Paris, 8 [article in French]
3. Bischoff F, Sahyun M, Long ML (1928) Guanidine structure and hypoglycemia. J Biol Chem 81:325–349
4. Muller H, Reinwein H (1927) Zur Pharmakologie des Galegins. Arch Exp Path Pharmacol 125:212–228 [article in German]
5. Rabinowiz IM (1927) Observations on the use of synthalin in the treatment of diabetes mellitus. Can Med Assoc J 17:901–904
6. Leclerc H. Le galega. Presse Med 1928, 22 décembre [article in French]

1929

- Metformin and other biguanides lower blood glucose in animals (Hesse and Taubmann; Slotta and Tschesche)

1. Hesse G, Taubmann G (1929) Die Wirkung des Biguanids und seiner Derivate auf den Zuckerstoffwechsel. Arch Exp Path Pharmacol 142:290–308 [article in German]
2. Slotta KH, Tschesche R (1929) Uber Biguanide. Die blutzuckersenkende Wirkung der Biguanides. Ber Dtsch Chem Ges 62:1398–1405 [article in German]

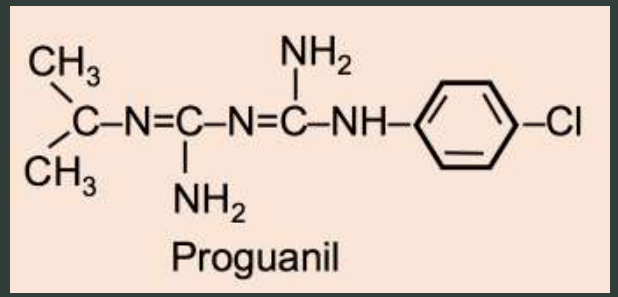
1930s

- Use of guanidine derivatives to treat diabetes initially grows
- Declines due to toxicity
- Importantly, biguanides were deemed to be less toxic than mono- and diguanidines and, of the various methyl biguanides tested, metformin exerted the least toxicity
- The real potential of these agents was underappreciated at the time
- The biguanides were not developed for diabetes therapy and were forgotten during the following decade.
- Additionally, because the availability of insulin.

Pasik C (1997) Diabetes and the biguanides: the mystery of each. In: Pasik C (ed) Glucophage: serving diabetology for 40 years. Groupe Lipha, Lyon, p79

1944-1947

- Guanidine-based antimalarial agent, proguanil (Paludrine),
- Lowers blood glucose in animals



Proguanil

1. Curd FHS, Davey DG, Rose FL (1945) Studies on synthetic antimalarial drugs. Some biguanide derivatives as new types of antimalarial substances with both therapeutic and causal prophylactic activity. Ann Trop Med Parasitol 39:208–216
2. Chen KK, Anderson RC (1947) The toxicity and general pharmacology of N1-p-chlorophenyl-N5-isopropyl biguanide. J Pharmacol Exp Ther 91:157–160

1949-1950

- Dimethylbiguanide (flumamine) tested as potential antimalarial agent and used to treat influenza in Philippines.
- During clinical tests, proved useful to treat influenza when it sometimes lowered blood glucose.
- It found to potentially lower blood glucose (Garcia)

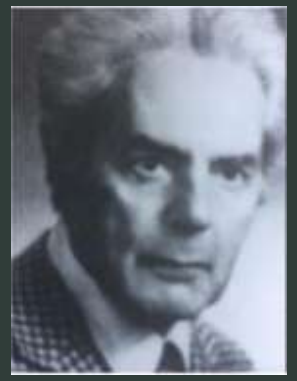
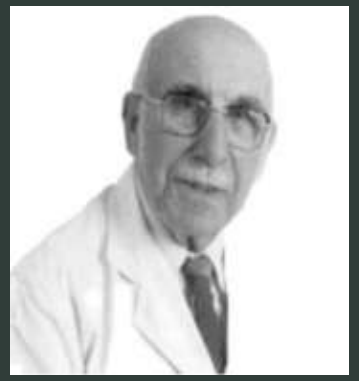
Garcia EY (1950) Flumamine, a new synthetic analgesic and antiflu drug.
J Philippine Med Assoc 26:287–293

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.
- 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.
- 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

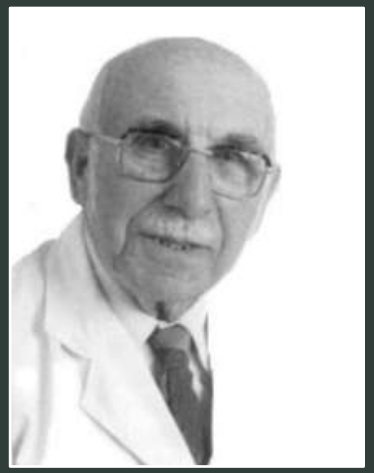
1956

- Jan Aron encourages Jean Sterne and Denise Duval to study guanidine-based glucose-lowering agents


1957

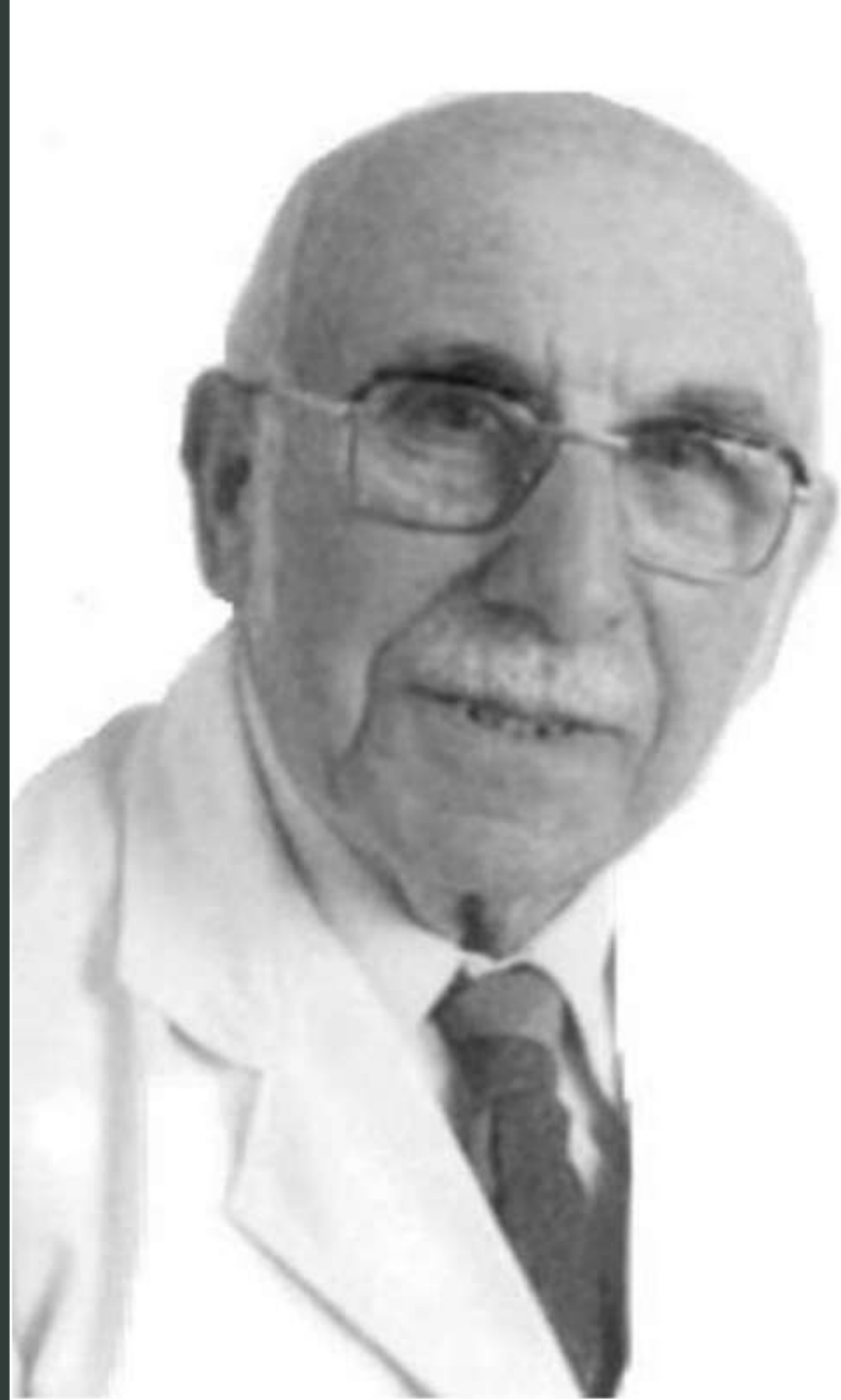
- Jean Sterne publishes use of metformin to treat diabetes



Sterne J (1957) Du nouveau dans les antidiabétiques. La NN dimethylamine guanyl guanidine (N.N.D.G.) Maroc Med 36: 1295–1296 [article in French]

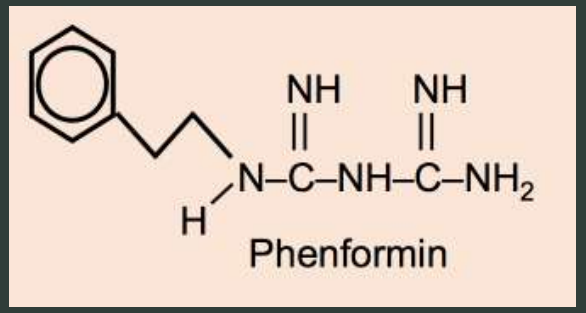
Jean Sterne (1909-1997)

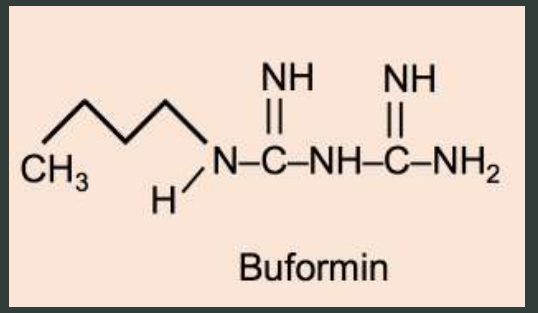
- Sterne suggested the name '**glucophage**' (meaning glucose eater), which was adopted by Aron to market metformin, and Sterne played a prominent role in ongoing research and physician education to assist the introduction of metformin into clinical practice in Europe



1957-1959

- Phenformin and buformin reported as treatments for diabetes



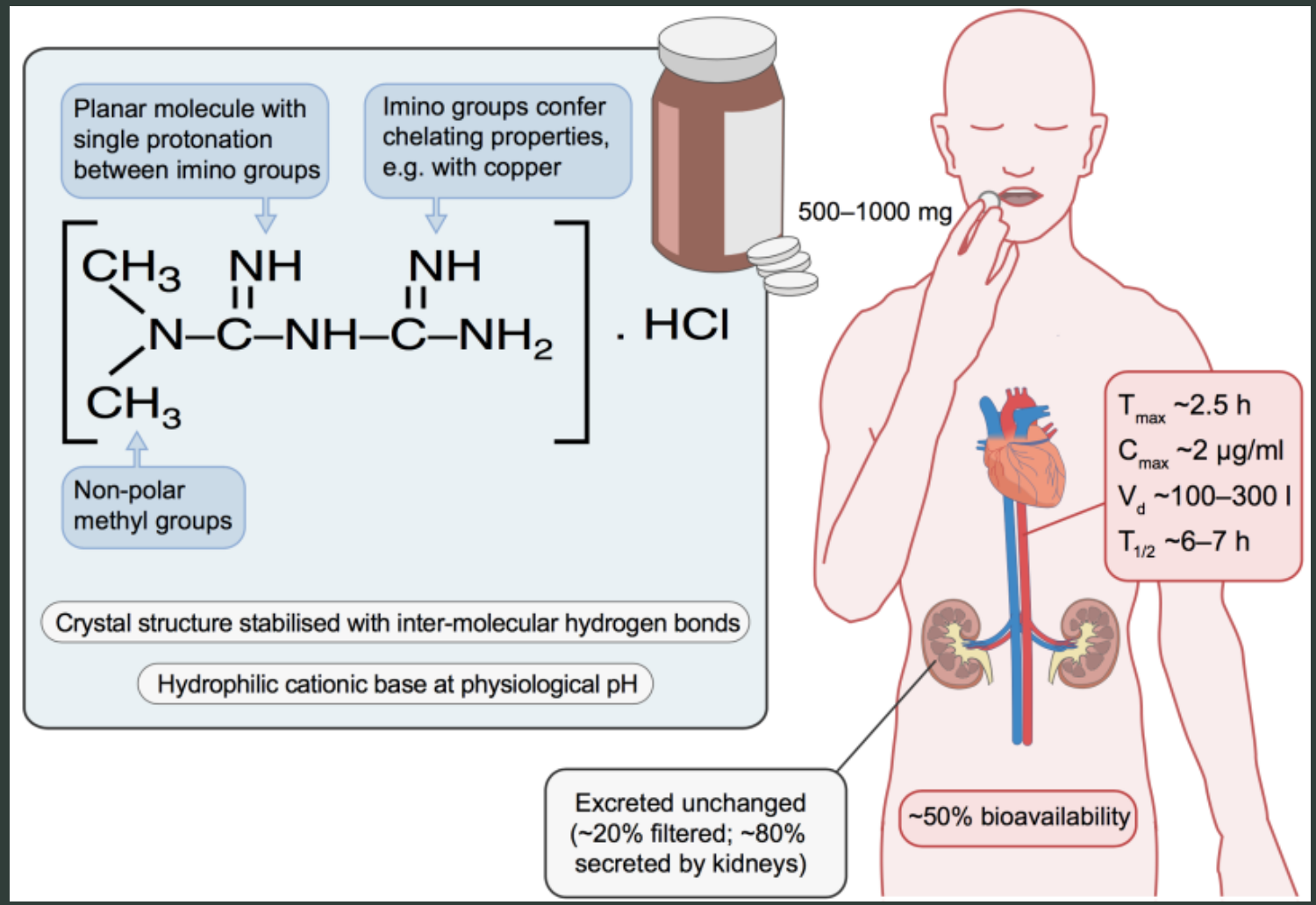


1. Ungar G, Freedman L, Shapiro SL (1957) Pharmacological studies of a new oral hypoglycemic drug. Proc Soc Exp Biol Med 95:190– 192
2. Beringer A (1958) Zur Behandlung der Zuckerkrankheiten mit Biguaniden. Wien Med Wschr 108:880–882 [article in German]
3. McKendry JB, Kuwayti K, Rado PP (1959) Clinical experience with DBI (phenformin) in the management of diabetes. Can Med Assoc J 80:773–778
4. Mehnert H, Seitz W (1958) Weitere Ergebnisse der Diabetesbehandlung mit blutzuckersenkenden Biguaniden. Münch Med Wochenschr 100:1849–1851 [article in German]

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

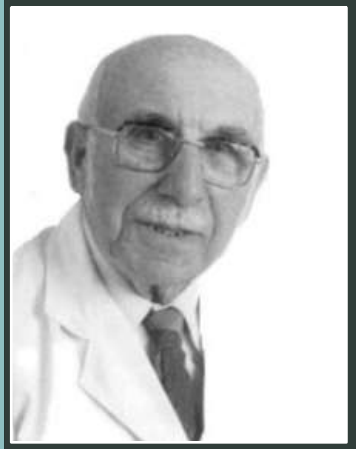
Metformin structure and pharmacokinetics



1958

- Metformin introduced to treat diabetes in the UK and other European countries

1958-1964



- Sterne and colleagues (especially Azerad) further evaluate metformin in individuals with diabetes
- Their initial studies, mostly in insulin- treated individuals, included a mix of juvenile-onset and maturity-onset presentations of diabetes.

1. Sterne J (1958) Blood sugar-lowering effect of 1,1- dimethylbiguanide. Therapie 13:650–659 article in French
2. Sterne J (1959) Treatment of diabetes mellitus with N,N- dimethylguanylguanidine (LA. 6023, glucophage). Therapie 14: 625–630 [article in French]
3. Sterne J (1963) Report on 5-years' experience with dimethylbiguanide (metformin, glucophage) in diabetic therapy. Wien Med Wochenschr 113:599–602 [article in German]
4. Sterne J, Hirsch C (1964) Experimental basis for combined treat- ment of diabetes with the biguanide-sulfonamide association. Diabete 12:171–175 [article in French]
5. Beckmann R (1971) Biguanide (Experimenteller Teil). Handb Exp Pharmacol 29:439–596 [article in German]

1968

- First large prospective comparator trial of metformin (Edinburgh, UK; notably Duncan, Clarke and Campbell)

Clarke BF, Duncan LJP (1968) Comparison of chlorpropamide and metformin treatment on weight and blood-glucose response of un- controlled obese diabetics. Lancet 291:123–126
Clarke B, Campbell IW (1977) Comparison of metformin and chlorpropamide in non-obese maturity-onset diabetic uncontrolled on diet. Br Med J 275:1576–1578

1980-1977

- Phenformin and buformin withdrawn in most countries because of risk of lactic acidosis
- Lactate uptake by the liver is diminished with phenformin and buformin administration because lactate is a substrate for hepatic gluconeogenesis

Lactic Acidosis

- The risk of lactic acidosis, especially with phenformin and buformin, was evident from the outset
- Controversy was fuelled when phenformin was withdrawn from the University Group Diabetes Program (UGDP) trial in the USA in 1971
- Phenformin was removed from the market in the USA in 1978

Lactic Acidosis related to CYP2D6

- 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
- A problem that modern pharmacogenomics could deal with.

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)

1. Hermann LS (1979) Metformin: a review of its pharmacological properties and therapeutic use. Diabete Metab 5:233–245
2. Clarke BF, Duncan LJP (1968) Comparison of chlorpropamide and metformin treatment on weight and blood-glucose response of uncontrolled obese diabetics. Lancet 291:123–126
3. Clarke B, Campbell IW (1977) Comparison of metformin and chlorpropamide in non-obese maturity-onset diabetic uncontrolled on diet. Br Med J 275:1576–1578
4. Campbell IW, Howlett HC (1995) Worldwide experience of metformin as an effective glucose-lowering agent: a meta-analysis. Diabetes Metab Res Rev 11(Suppl 1):S57–S62
5. Howlett HCS, Bailey CJ (2007) Metformin: a chemical perspective. In: Bailey CJ, Campbell IW, Chan JCN et al (eds) Metformin, the gold standard. A scientific handbook. Wiley, Chichester, pp 23–28
6. Bailey CJ, Puah JA (1986) Effect of metformin on glucose metab- olism in mouse soleus muscle. Diabete Metab 12:212–218
7. Wollen N, Bailey CJ (1988) Inhibition of hepatic gluconeogenesis by metformin: synergism with insulin. Biochem Pharmacol 37: 4353–4358
8. Bailey CJ, Wilcock C, Day C (1992) Effect of metformin on glu- cose metabolism in the splanchnic bed. Br J Pharmacol 105:1009– 1013
9. Wilcock C, Bailey CJ (1994) Accumulation of metformin by tissues of the normal and diabetic mouse. Xenobiotica 24:49–57
10. Bailey CJ, Mynett KJ, Page T (1994) Importance of the intestine as a site of metformin-stimulated glucose utilization. Brit J Pharmacol 112:671–675
11. Wiernsperger NF, Bailey CJ (1999) The antihyperglycaemic effect of metformin: therapeutic and cellular mechanisms. Drugs 58(Suppl 1):31–39

1994-1995

- Metformin approved (1994) and introduced (1995) in the USA

1995-1996

- Key publications confirm favourable benefit:risk ratio of metformin in management of T2D

1. DeFronzo RA, Goodman AM, Multicenter Metformin Study Group (1995) Efficacy of metformin in patients with non-insulin- dependent diabetes mellitus. N Engl J Med 333:541–549
2. Bailey CJ, Turner RC (1996) Drug therapy: metformin. N Engl J Med 334:574–579

1998

- UKPDS (UK Prospective Diabetes Study) reports long-term metabolic effects of metformin and reduced cardiovascular risk with use

UK Prospective Diabetes Study (UKPDS) Group (1998) Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 352: 854–865

2000-2002

- Extended-release formulation and fixed-dose combination drugs with metformin as the primary active ingredient are approved in the USA

2011

- Metformin became first-line pharmacological choice
- Metformin has become the most prescribed glucose-lowering therapy world-wide and it is now included in the World Health Organization's (WHO's) essential medicines list.

World Health Organization (2015). WHO model list of essential medicines. Available from www.who.int/medicines/publications/ essentialmedicines/EML_2015_FINAL_amended_NOV2015.pdf? ua=1.

Timeline

Year	Landmark
1918	Guanidine, a traditional herbal medicine (*Galega officinalis*) compound, lowers blood glucose in animal.
1920s	Guanidine derivatives, including metformin, were synthesised.
1930	some (not metformin) were used to treat diabetes.
1942	Metformin was rediscovered in the search for **anti-malarial agents**. During clinical tests, proved useful to treat influenza when it sometimes lowered blood glucose.
1957	Jean Sterne (French physycian), who first reported the use of metformin to treat diabetes.
1995	Metformin was introduced into the USA.
1998	Long-term cardiovascular benefits of metformin were identified by the UK Prospective Diabetes Study (UKPDS)

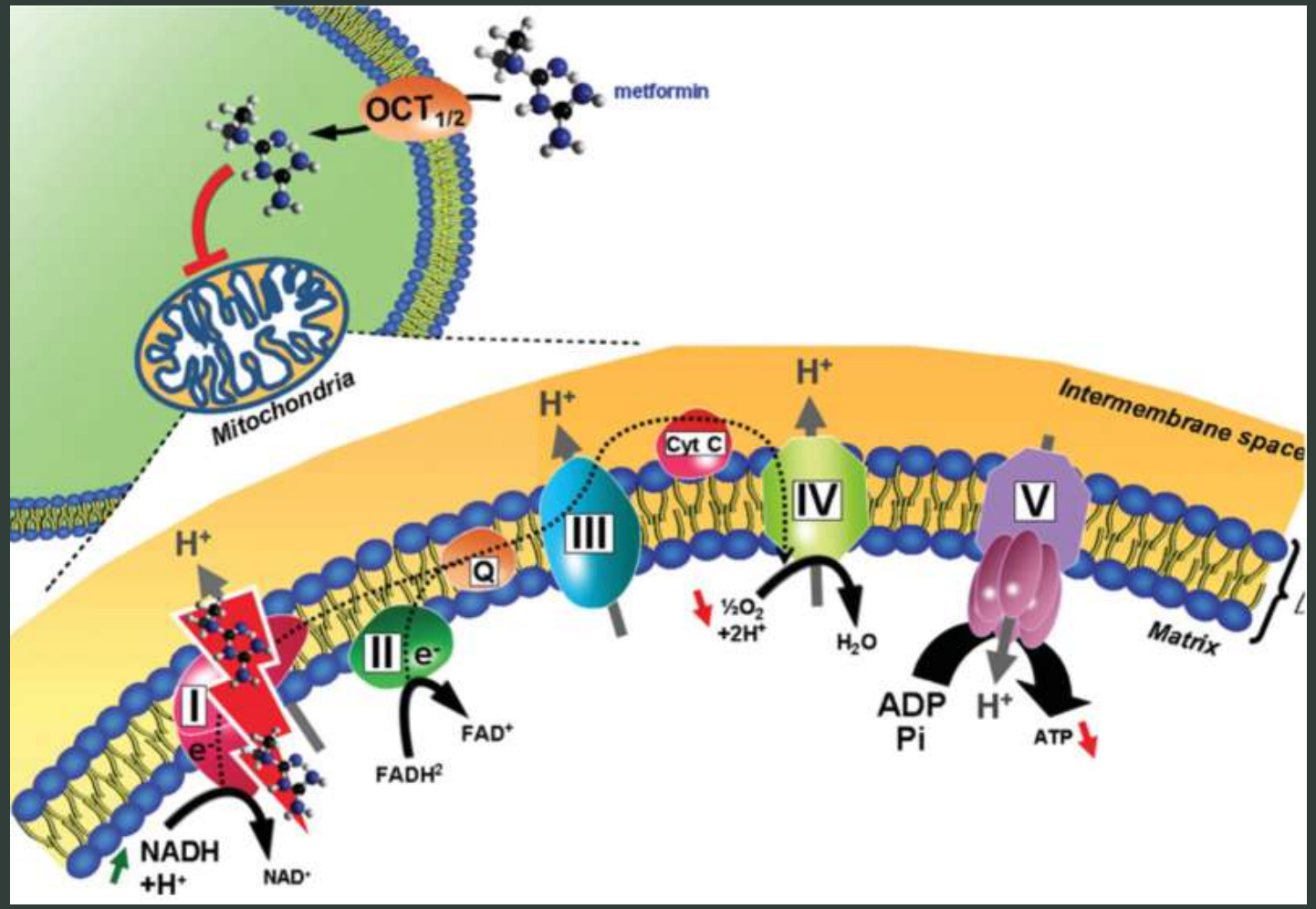
Mechanism of Action

- Metformin is also frequently described as an insulin-sensitizer, leading to reduction in insulin resistance and a significant decrease in plasma fasting insulin levels.
- The improvement in insulin sensitivity by metformin could be ascribed to its positive effects on insulin receptor expression and tyrosine kinase activity

Gunton, J. E., Delhanty, P. J., Takahashi, S. and Baxter, R. C. (2003)
Metformin rapidly increases insulin receptor activation in human liver and signals preferentially through insulin-receptor substrate-2.
J. Clin. Endocrinol. Metab. **88**, 1323–1332

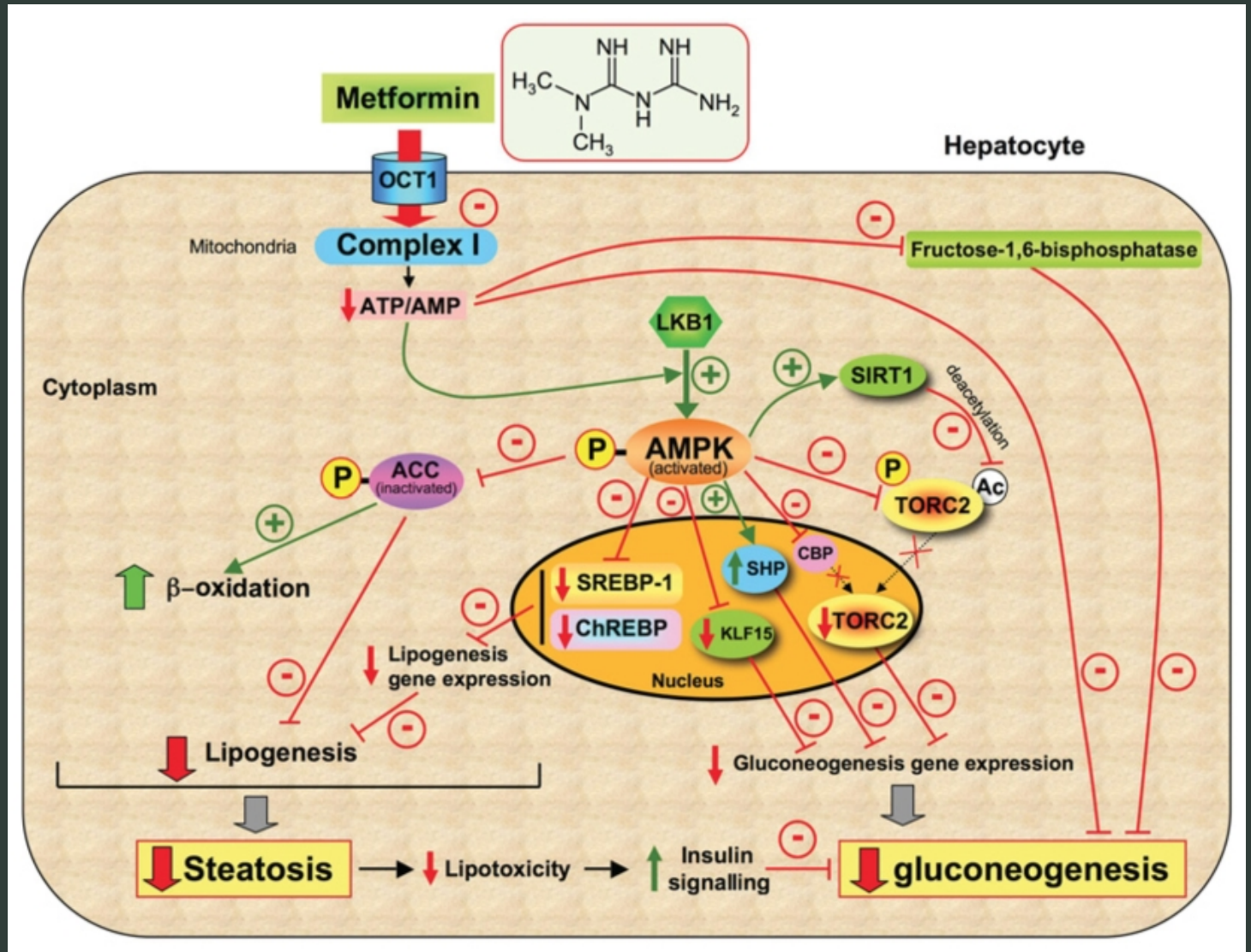
Celullar and molecular Mechanism of Metformin

The mitochondrial respiratory chain complex 1 is the primary target of metformin

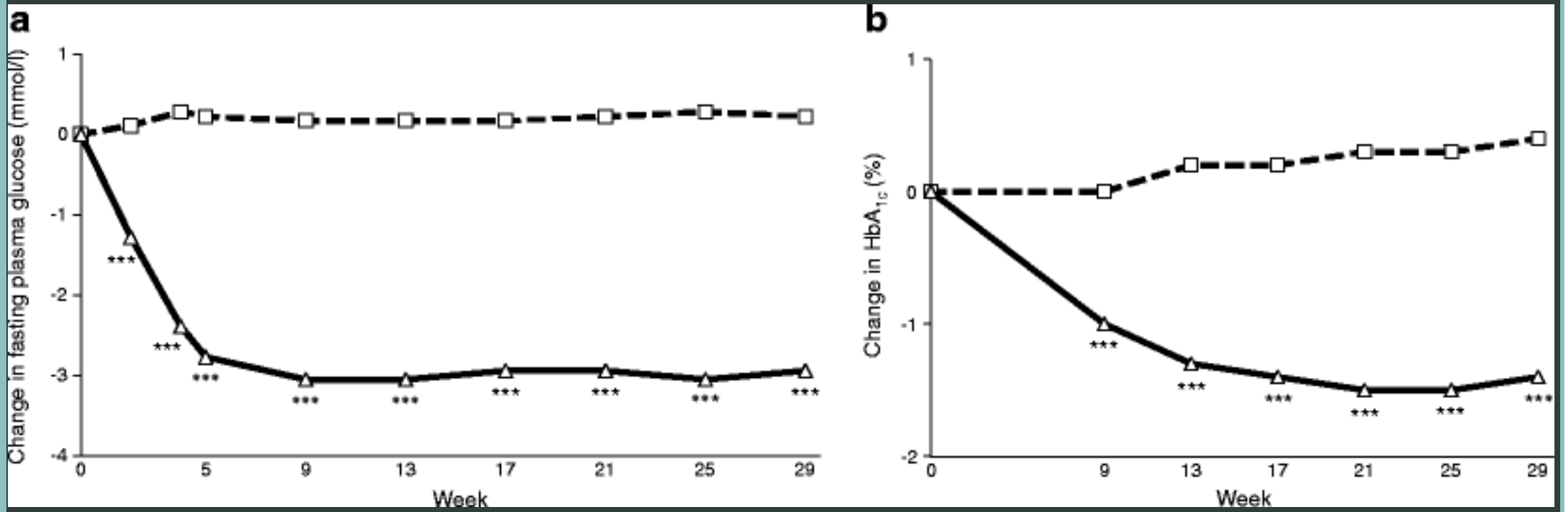


Viollet, B., et al, Clinical Science (2012) 122, 253–270 doi:10.1042/CS20110386

Potential molecular mechanisms of the action of metformin on hepatic gluconeogenesis



Efficacy of Metformin



DeFronzo RA1, Goodman AM., Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. N Engl J Med. 1995 Aug 31;333(9):541-9.
DOI: 10.1056/NEJM199508313330902

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

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

Other indications/Future direction

- Opportunities for its use in type 1 diabetes to improve glycaemic control and reduce required insulin dose.
- To slow or prevent progression of impaired glucose tolerance (IGT)/impaired fasting glucose (IFG) (‘prediabetes’) to type 2 diabetes.
- Gestational diabetes.
- 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.
- Metformin might protect against certain cancers in individuals with type 2 diabetes.
- 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.

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.

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.

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THANK YOU