Institution:
ASTON UNIVERSITY

Unit of Assessment:
3: ALLIED HEALTH PROFESSIONS, DENTISTRY, NURSING AND PHARMACY

Title of case study:
1) METFORMIN: CHANGING THE TREATMENT ALGORITHM FOR TYPE 2 DIABETES

1. Summary of the impact (indicative maximum 100 words)

Metformin is now the most prescribed medication for type 2 diabetes worldwide. Pre - 1990 it received trivial use and was on the verge of withdrawal. Research at Aston (1993 - 1996) generated a new appreciation of its mechanisms of action and therapeutic potential. Aston research was reinforced with a concerted education programme for healthcare professionals, including high-profile reviews and treatment guidelines. We claim impact on health & welfare and health practitioners as Aston research has provided a foundation for improved care of type 2 diabetes patients on a global scale.

2. Underpinning research (indicative maximum 500 words)

Background: Research at Aston (1993 - 1996) revealed new mechanisms of action of metformin relating to efficacy and safety, providing the impetus for clinical research and renewed therapeutic application (S3.1). Although metformin had been introduced as a diabetes therapy in the 1950s, it was little used and all but discontinued in the 1980s, condemned by class association with other biguanides that caused lactic acidosis.

Research insights/findings: The Aston research established that the major concern about metformin, namely lactate production, was mostly of intestinal (not hepatic) origin and was mostly attributed to misuse that could be avoided by judicious respect for contraindications and exclusion criteria. The work identified multiple actions of metformin, opening avenues of investigation into insulin-dependent and insulin-independent mechanisms that form the basis of our present appreciation of this drug (S3.1; S3.2).

Underpinning research: Building on earlier work, research at Aston involved development and application of a novel simultaneous multi-site blood and tissue sampling technique in small rodents together with isotope distribution studies which were used to identify the origin and disposal of nutrients and metabolites during exposure to metformin. This work was conducted from 1993 - 1996 by Professor Cliff Bailey (then Senior Lecturer and later Professor, 1973 - date) with Carol Wilcock (Research Fellow 1990 - 1993), Paul Nicklin (Research Fellow, 1992 - 1995), Tony Page (visiting Research Fellow, 1990 - 1994) and Kurt Mynett (Research Assistant, 1993 - 1995). The work established that metformin was accumulated in the walls of the intestine where it promoted the conversion of glucose to lactate (S3.3 - 3.6). The lactate was then cycled back to glucose in

liver and other tissues for storage as glycogen and use in energy metabolism, contributing to lower blood glucose concentrations while increasing energy expenditure. This in turn provided an explanation for the origin of risk for hyper-lactataemia and the lack of weight gain with this agent. Additional studies distinguished insulin-dependent and insulin-independent effects of metformin to reduce hepatic glucose output and increase peripheral glucose disposal. Overall these studies gave rise to a new appreciation of the anti-diabetic capability and application of metformin.

Research grant support for this research was difficult to obtain in the 1990s because research into pharmaceuticals was considered to reside within commercial organisations: also metformin was considered to be defunct. This research represents an early, and against the trend, collaboration between academic and commercial bodies and provides an example of what has now become a model of collaborative enterprise. To initiate and persevere with this research at Aston therefore required special commitment, and initial investment by the University to generate commercial support.

3. References to the research (indicative maximum of six references)

1. Bailey CJ et al., (eds) Metformin: the gold standard. Scientific handbook. Wiley, Chichester, 2007, 288pp. ISBN 978-0-470-72644-0. Copy available on request.

2. Bailey CJ, Turner RC. Metformin. New Engl J Med 334, 574-579,1996 doi: 10.1056/ NEJM199602293340906, citations 1065.

3. Wilcock C, Bailey CJ. Accumulation of metformin by tissues of the normal and diabetic mouse. Xenobiotica 24, 49-57, 1994. doi: 10.3109/00498259409043220, citations 100.

4. Bailey CJ, Mynett KJ. Insulin requirement for the anti-hyperglycaemic effect of metformin. Brit J Pharmacol 111, 793-796, 1994. PMC1910090, citations 4.

5. Bailey CJ, Mynett KJ, Page T. Importance of the intestine as a site of metformin-stimulated glucose utilization. Brit J. Pharmacol 112, 671-675, 1994. PMC1910373, citations 32.

6. Nicklin P, Keates AC, Page T, Bailey CJ. Transfer of metformin across monolayers of human intestinal Caco-2 cells and across rat intestine. Int J Pharmaceutics,128, 155-162, 1996. doi:10.1016/0378-5173(95)04259-8, citations 15.

Refs 1 and 2 verify the historical context and global clinical impact of research described in section 2. Refs 3-6 provide peer-reviewed examples of the quality of laboratory research that generated a new appreciation of the anti-diabetic mechanisms and therapeutic potential of metformin as described in section 2.

4. Details of the impact (indicative maximum 750 words)

Research described in section 2 made a major impact on the revival and application of metformin as the primary pharmacological treatment for type 2 diabetes worldwide. The research findings prompted clinical studies that gave confidence and understanding for use of this drug, The work

has received particular recognition through the UK Prospective Diabetes Study (S3.1; S5.1) and in recent treatment guidelines (S3.1; S5.2).

The impact of the research at Aston may be traced from its use to inform the regulatory assessment process for the introduction of metformin into the USA (1995), when Professor Bailey was accorded the unusual privilege of being the expert witness to the US Food and Drug Administration (FDA) for the evaluation of metformin and advisor for the design and evaluation of the phase 3 clinical trials. The trial design became the standard for new diabetes therapies trials throughout the last decade (S5.3). Having authored the expert report on metformin to the European Medicines Agency (EMA), which placed into context the implications of Aston research as part of the periodic reassessment of approved drugs, Professor Bailey was elected to serve on the EMA Committee for Human Medicinal Products Healthcare Professional Working Group and Scientific Advisory Group from 2006-2011 (S5.4).

Through the regulatory process, the research on metformin at Aston has informed clinical practice. This has been translated into patient care via the development of treatment algorithms. For example, metformin has been adopted as first line treatment in the 2012 consensus guideline from the American Diabetes Association and the European Diabetes Association for the Study of Diabetes (S5.2). The guideline, which is now accepted internationally, repositioned metformin as the preferred first-line treatment for type 2 diabetes, citing work authored by Professor Bailey as part of the justification for this decision (S5.2; S5.5). Metformin has recently become the most prescribed medicinal product for the treatment of diabetes in North America and Europe (S3.1), and the 9th most prescribed drug in the USA in 2010, accounting for 48.3 million prescriptions in that year (S5.6). The predominance of metformin is also acknowledged in the current NICE guideline for England and Wales (published in 2008) and in the Scottish guideline (published in 2010), with reference to work described above from Aston (S5.7; S5.8). Metformin is also listed as preferred initial drug therapy for type 2 diabetes by most other national and international guidelines, for example the Diabetes Australia guideline published in 2009 (S5.9) and the diabetes guidelines for Latin America (S5.10).

Related research at Aston has also been instrumental in the development of other medicines for diabetes and obesity. Use of the techniques devised and applied to the study of metformin has provided metabolic information that was pivotal for the development of the anti-obesity agent sibutramine, and Professor Bailey is one of the named inventors on one of the patents (Bailey CJ, Jones RB, and Jackson HC. Use of sibutramine analogues to prevent the development of diabetes. WO 98/11884).

In summary, metformin has risen from a drug destined for withdrawal in the 1980s to the most prescribed medication for type-2 diabetes worldwide. We can claim a substantial contribution to this through early research studies at Aston University (e.g. S3.3 - S3.6), along with follow-through education (e.g. S3.1; S3.2). The impact on health and prevention of diabetes complications is recognised with the prime positioning of metformin in treatment algorithms and guidelines (S5.3;

S5.5; S5.7; S5.8), and the use of the drug by about half of all patients with type 2 diabetes in the West (about 30 million patients with a commercial value of $1.6 billion in 2003) (S3.1; S5.2; S5.5; S5.6; S5.6; S5.7; S5.8; S5.9; S5.10).

As a post-script, metformin is now being investigated for potential use in the treatment of vascular disease, polycystic ovary syndrome and cancer. It may yet have more benefits to give, since being saved from oblivion.

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. Holman RR et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359:1577-89.

2. Inzucchi SE et al, Management of hyperglycaemia in type 2 diabetes: a patient-centred approach. Position statement of the American Diabetes association (ADA) and European Association for the Study of Diabetes (EASD). Diabetologia 2012; 55: 1577-96 and simultaneously Diabetes Care 2012; 35:1364-79.

3. Guidance for Industry Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), February 2008. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071624.pdf

4. European Medicines Agency. EMEA/CHMP Working Group with Healthcare Professionals Organisations (HCP WG), February 2009. http://www.emea.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500018430.pdf

5. American Standards of Medical Care in Diabetes. Diabetes Care 2012, 35, Suppl 1, S1-63. http://care.diabetesjournals.org/content/35/Supplement_1/S11.full

6. IMS Health USA, National Prescription Audit, Dec 2010 http://www.imshealth.com/deployedfiles/imshealth/Global/Content/IMS%20Institute/Static%20File/IHII_UseOfMed_report.pdf

7. NICE clinical guideline 66. The management of type 2 diabetes. 2008. http://www.nice.org.uk/nicemedia/pdf/CG66NICEGuideline.pdf

8. SIGN guideline 116. The management of diabetes, 2010. http://www.sign.ac.uk/pdf/sign116.pdf

9. National Evidence based guideline for blood glucose control in type 2 diabetes. Diabetes Australia Guideline Development Consortium, 2009. http://www.diabetesaustralia.com.au/For-Health-Professionals/Diabetes-National-Guidelines/

10. Gurzman JR et al. Treatment of type 2 diabetes in Latin America: a consensus statement by the medical associations of 17 Latin American countries. Rev Panam Salud Publica 2010, 28, 463-71**.** http://www.alad-latinoamerica.org/DOCConsenso/08--SPEC--Guzman---463-471.pdf