A History of Diabetes at the Rockefeller Archive Center: The Development of Oral Hypoglycaemic Drugs and the UGDP Debate

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Abstract

With very generous research funding provided by the Rockefeller Archive Center (RAC), I was able to travel from Scotland in early August 2018. This was my first trip to the RAC, as well as my first time in the United States. Having just finished up at a three-month internship at the Scottish government, I was thrilled to be granted time and financial support for archival research. This report presents a summary of my time at the RAC and how the material I accessed there has supported my thesis. For those interested in the history of pharmacy in the second half of the twentieth century, or specifically the history of diabetes, this report provides an overview of the history of the development of the first oral anti-diabetic agents. It highlights the debate that followed one of the most contentious medical trials in the history of medicine, the University Group Diabetes Program.

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My doctoral thesis, titled "A Spoonful of Sugar: Diet and Diabetes in the United States, 1945-2015," examines the history of type 2 diabetes, utilising oral histories and archival material from both Britain and the United States. My thesis provides the first history of type 2 diabetes of its kind. It brings together the voices of patients, physicians, and policy makers in order to uncover the contributory factors leading to the rise of type 2 diabetes and the social and political factors which have shaped treatment options in the second half of the twentieth century. What ties my thesis together is an overarching aim which seeks to understand the fate of post-war interest in prevention, specifically as it applied to diabetes. My research examines the wider developments, such as the discovery of oral hypoglycaemic drugs, developments in epidemiology such as the use of mass screening of asymptomatic populations, and the larger debates occurring in the field of nutrition. It demonstrates three core developments which shifted attention from the primary prevention of illness towards the long-term management of diabetes and its complications. Examining these developments and their impact on understandings of diabetes and treatments offered to patients aid a clearer understanding of the contemporary management of diabetes. In particular, my study sheds light on the marginalisation of diet and the dominance of oral hypoglycaemic drugs that is evident in diabetes care today.

One of the key areas of my research considers the shift from diet therapy to the increasing use of oral hypoglycaemic drugs. To understand this shift, my research examines the development of the new oral agents of the 1950s and 1960s and the key individuals who both facilitated and resisted this shift. Curiously, despite becoming the principal form of therapy in the modern treatment of diabetes and consistently ranking among the top ten prescribed drugs globally, little has been published on the history of oral hypoglycaemic drugs over the last decade. Where

scholars have studied their development, they have focused on either the way drugs are regulated (Marks, 1997), the role of anti-diabetic drugs in transforming disease, and the relationship between the science and the business of health (Greene, 2007), or have provided cursory accounts of anti-diabetic drugs as a progressive development in modern treatment (Tattersall, 2009).

To fill this gap in the literature and ascertain the role of the new oral drugs which became available in the 1950s and 1960s, my research explores the origins of the demand for anti-diabetic agents, their subsequent development, and crucially, the responses of the medical community and the debate which ensued regarding their use. By scrutinising the contentions within the medical profession over the use of the new drugs, my thesis challenges the notion that the development and mass availability of oral agents represent a neat tale of medicalisation. While the pharmaceutical industry was unrelenting in its attempts to frame diabetes as a disease most amenable to pharmaceutical treatment, this monolithic narrative tends to offer a simplistic historical interpretation and suggests a consensus to medicalise diabetes by the entire profession. As my research conducted at the Rockefeller Archive Center attests, this was certainly not the case. The use of oral agents for diabetes, particularly following the controversy of the UGDP trial and subsequent removal of diabetic medications from the market, aroused considerable suspicion and uncertainty, prompting influential sections of the profession to question the reasoning behind their use, as well as their safety.

The purpose of my research undertaken at the Rockefeller Archive Center was to explore records pertaining to this era in order to piece together the response of the medical profession and industry to the University Group Diabetes Program (UGDP) debate. The UGDP was a randomised, controlled, multicentre clinical trial which was designed to evaluate the effectiveness of long-term oral hypoglycaemic drug therapy in preventing or delaying the vascular complications caused by diabetes. The need for the trial arose out of uncertainty over the use of the first drugs to emerge out of post-war experimentation with oral hypoglycaemic therapy. The focus of the trial was on one drug in particular, tolbutamide, or Orinase, as it was marketed by Michigan firm Upjohn Company. While both Upjohn and the media confidently promoted Orinase as a new wonder

drug, archival evidence suggests that sections of the medical profession were hesitant and continued to uphold the importance of diet as the principal treatment for mild diabetes. Primarily, troubled physicians questioned the safety of oral hypoglycaemic agents and were concerned that patients would see a prescription of pills as an easy alternative to a controlled diet. With so many questions and uncertainty over the use of the new anti-diabetic drugs, it was thus decided that the only way to determine their value would be to test them against traditional treatment types in a long-term clinical trial.

As one of the main drugs on the market, the UGDP sought to understand if tolbutamide (Orinase) could prevent diabetic complications, particularly cardiovascular disease while also determining how the oral agents fared against insulin and diet. The study aimed to address three questions which plagued the diabetes medical community about mild and asymptomatic diabetes; 1) Did tolbutamide have a favourable impact on vascular disease; 2) Did lowering blood sugar levels help decrease the risks of vascular disease?; 3) What methods were useful in clinical trials for diabetes?[1] The study began in 1961 with patient's allocated one of four regimens; *insulin variable*, *insulin standard*, *tolbutamide,* and a *placebo* group (lactose capsules and diet). Subsequently, in 1962 a fixed-dose Phenformin group was also added.[2] It was predicted that the results of the trial would show mortality to be lower in the insulin and oral groups than diet alone. However, in 1969 the tolbutamide arm of the study was stopped prematurely, when a significantly higher death rate in the tolbutamide group was discovered; 12.7% compared with 4.9% in the placebo group.[3] The results of the UGDP study suggested that rather than being beneficial to diabetics, the new drugs appeared to be harmful, and for milder patients at least, appeared to be of no greater benefit to them than diet alone. The results sparked an enormous debate among diabetes specialists in both the United States and Britain. However, existing accounts of the UGDP and its impact on diabetic management have primarily focused on those who refuted its results and have yet to examine responses to the trial elsewhere. While those at the Joslin Clinic in Boston and Mount Sinai in New York, both of which had been at the forefront of trialling the new oral agents, mounted a concerted defence of the continued use of oral agents, going as far as to launch a publicity stunt to publicise their dissent, elsewhere,

sections of the medical profession defended the UGDP's results and cautioned against the use of drugs as a first-line therapy.

Resistance to the continued use of oral agents, particularly tolbutamide, came most strongly from physicians at the *Medical Letter on Drugs and Therapeutics*. The *Medical Letter* is a respected, peer-reviewed publication issued to physicians throughout the US which provided evaluations on new pharmaceuticals. Fortuitously, the Rockefeller Archive Center holds the records of the *Medical Letter*, included among which are the drafts of the *Medical Letter*'s publication on tolbutamide, alongside a wealth of industry correspondence and physician responses. Examining the review process of the *Medical Letter*'s issue on tolbutamide, following the provisional conclusions of the UGDP, allows for a new perspective on the controversy, illuminating the heart of the debate through hundreds of comments and responses to each draft and re-draft of the article by Chairman of the *Medical Letter* Harold Aaron. The aim of Aaron's article was to simply present the conclusions of the UGDP; that tolbutamide provided no advantage over diet alone in the absence of symptoms, that tolbutamide and other oral hypoglycaemic drugs should not be used simply because of mild elevation of blood sugar and glycosuria, and that tolbutamide was associated with higher cardiovascular mortality than diet alone or diet with insulin.[4] While noting how the results of the UGDP had "evoked an adverse response from many clinicians, on the grounds that it ran counter to their personal experience" with the drugs, consultants at the *Medical Letter*, including statisticians, carefully evaluated the complete report of the UGDP and could find no flaws in the study design, samples or analyses of the data. The *Medical Letter*'s conclusion put forth in the article was thus:

> The increased mortality associated with Tolbutamide clearly demands a change in the present management of maturity-onset diabetes. The *Medical Letter* recommends that 1) when a patient remains symptom-free on diet alone this is the preferred treatment, even if it is associated with mild hyperglycaemia and glycosuria. There is no need to use tolbutamide to maintain the blood sugar in the normal range in such patients in view of the increased cardiovascular mortality associated with its use. 2) It is not known that the other oral hypoglycaemic agents are safer; and 3) If a patient's diabetic symptoms cannot be controlled by diet alone, insulin should be used. As oral agent can be

> prescribed however, for patients who cannot or will not follow a strict diet and who cannot accept injections of insulin. Until the UGDP follow-up report on phenformin appears, that agent may be preferred to tolbutamide or other sulphonylureas.[5]

The responses to the *Medical Letter*'s position on the study highlights just how divided American physicians were on the matter. That the *Medical Letter*, considered the mouthpiece on the use of pharmaceuticals for physicians across America, had sided so resolutely with the UGDP's findings and disparaged the use of oral agents, was met with some vehement responses. Replying to the draft article, Charles Nechemias, then chief of Mount Sinai Diabetes Clinic, contested the *Medical Letter*'s position entirely, calling the claim that tolbutamide was no more effective than diet alone "palpable nonsense".[6] Like those at the Joslin Clinic, Nechemias and his colleagues at Mount Sinai had been at the forefront of experimenting with oral agents since the mid-1950s. Consequently, he shared in their criticisms of the UGDP, in particular the *Medical Letter*'s implication that all oral agents be rejected on the basis of tolbutamide's apparent failure. Sharing these sentiments, physician Alvan Feinstein from Yale, commissioned by Upjohn to carry out an intensive analysis of the UGDP, went as far as to say that Upjohn had been the victims of a "pharmaceutical witch-hunt conducted to mask scientific failure."[7] The RAC records further highlight industry responses to the *Medical Letter*'s position. In a letter from Eli Lilly dated 20 October 1970, Lilly's director of communications urged Aaron to delay publication of the article until they could form their own opinion and rebrand their own oral agents in line with the publication's comments.[8] Likewise, Pfizer responded with concerns regarding how the *Medical Letter*'s position would harm its own product, Diabinese. In their response to the draft article, Pfizer questioned "the scientific validity of extrapolating the study findings to Diabinese in view of the notable pharmacological differences between Diabinese and Orinase."[9]

Despite receiving such a barrage of dissent, physicians at the *Medical Letter* stood by their original statement and when the article finally reached publication, their position on the importance of diet as the principal method of treatment and warning against the use of oral hypoglycaemic drugs remained. Going through the responses to the draft article on tolbutamide by the *Medical Letter* reveals that

its physicians were not the only ones concerned about the drugs. An increasing number of reports and clinical alerts began to appear that raised concerns about tolbutamide's side effects and urged physicians to keep in mind that oral agents should be secondary to diet and insulin.[10] In a letter to Paul Lavietes at the *Medical Letter*, a concerned physician from Cleveland wrote how:

> I am greatly concerned about the action, or rather inaction, of the FDA regarding the labelling for Orinase. The pressure of the drug companies and clinicians like the Joslinites has apparently been effective in delaying and weakening the change in labeling.[11]

By the mid-1970s, reports were also beginning to appear in the media which reflected the unease at the rate at which tolbutamide and other diabetic medications were being prescribed. As an article which appeared in the *Boston Herald* protested:

> We are all witness these days to one of the most infuriating situations in modern medical practice. And many of us may well become its victims. The case in point concerns the stubborn refusal of many physicians to stop or cut back on their prescriptions of certain oral, antidiabetic medicines, until they see incontrovertible proof that these drugs might hurt someone. This attitude persists despite considerable circumstantial evidence that users of these drugs have a significantly higher death rate than diabetics who don't use them.[12]

The article warned that for diabetes specialists and family doctors alike, the drugs had become an easy-to-prescribe staple in their therapeutic cupboards, particularly for elderly and mild patients for whom "a proper diet that they can understand and adhere to is the only necessary treatment."[13] Ultimately, the article decried the over-prescription of anti-diabetic drugs and argued that the physician's time would be better invested in constructing and explaining an appropriate diet prescription to their patient rather than a quick prescription of potent and potentially dangerous drugs.[14] Notwithstanding such unwavering support for oral agents, by 1970 even Joslin himself remained devoted to traditional treatments of diet and insulin. In an article published in 1971, Joslin warned that despite other advances, insulin and diet were still the safest methods of treatment. "For some people, the pills work quite well. Other patients,

possessing great willpower and self-control, are able to handle their condition by diet alone. But if you want to be absolutely sure – insulin is the safest."[15]

The *Medical Letter* article on tolbutamide and the responses it received contributes significantly to this period of diabetes history, in particular adding to our knowledge of the aftermath of the UGDP and the result of these discourses on the future of diabetes management. Ultimately, what transpired by the time the debate reached some conclusions, though it never truly reached a resolution, was that physicians had become reliant on the new drugs and the majority were reluctant to give them up. As the RAC's records of the *Medical Letter* reveal, as the tolbutamide controversy unfolded over the course of the 1970s it came to involve a set of congressional hearings, an FBI investigation, and a court ruling which went all the way to the Supreme Court.[16] One of the most heated and drawn-out conflicts in the history of medicine, the debate over the use of tolbutamide lasted until 1984 but never truly reached a resolution. The nearest the debate got to a conclusion came in 1974 when the American Diabetic Association concluded that the UGDP *had* demonstrated that blood sugar ought to be controlled in order to avoid future complications, but failed to provide a conclusive statement on whether antidiabetic drugs generally should continue to be prescribed.[17] In Britain, the BDA was significantly less compromised by the UGDP's findings, having a much wider range of drugs available which were safer and more effective than tolbutamide and thus decided the drugs could still be taken. By the time the ADA and FDA confirmed that tolbutamide was harmful, its patent had expired, and a new generation of antidiabetic drugs had been developed which quickly took its place.

Examining the *Medical Letter* and its accompanying correspondence further led me to a subsequent *Medical Letter* publication which concerned the use of another oral anti-diabetic agent from the 1970s, Phenformin. I hope to utilise these records in the remainder of my thesis as a further example of the history of the development of oral hypoglycaemic drugs and their legacy on current prescribing practices. Once again, I would like to thank the Rockefeller Archive Center for such generous support and hope this report provides a glimpse into

both my research and the wealth of fantastic materials available at the RAC in the history of medicine and beyond.

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[1] Greene, *Prescribing by Numbers*, (Baltimore: John Hopkins University Press, 2007) pp. 119-120.
[2] M. G. Goldner, G. L. Knatterud, and T.E. Prout, "Effects of Hypoglycaemic Agents on Vascular Complications in Patients with Adult-Onset Diabetes: III. Clinical Implications of UGDP Results," *JAMA*, 218:9 (1971), pp. 1400-1410.
[3] M. G. Goldner, G. L. Knatterud, and T.E. Prout, 'Effects of Hypoglycaemic Agents on Vascular Complications in Patients with Adult-Onset Diabetes: III. Clinical Implications of UGDP Results," *JAMA*, 218:9 (1971), pp. 1400-1410.
[4] H. Aaron, 'Diabetes Therapy: Tolbutamide (Orinase) and Diabetes', Consultants: MD Drafts, issue 310, 12:24 (1970), Box 20, Folder 3, The *Medical Letter* records (MLR), Rockefeller Archive Center (RAC).
[5] Ibid, p.5
[6] Charles Nechemias letter to Harold Aaron at the *Medical Letter*, 23 October 1970, Box 20, Folder 3, MLR, RAC.
[7] Letter from A.R. Feinstein to Harold Aaron at the *Medical Letter*, 3 November 1970, Box 20 Folder 3, MLR, RAC.
[8] Letter from Eli Lilly to Harold Aaron at the *Medical Letter*, 20 October 1970, Box 20 Folder 3, MLR, RAC.
[9] Letter from Pfizer to Harold Aaron at the *Medical Letter*, 6 November 1970, Box 20 Folder 3, MLR, RAC.
[10] 'Clini-alert', *Science Editors*, 2 October 1970; "Council Urges Tolbutamide Curb," *American Medical News,* 2 November 1970, Box 20, Folder 3, MLR, RAC.
[11] Letter to Paul Lavietes from Ohio physician, Box 20, Folder 3, MLR, RAC.
[12] J. Rodgers, 'Doctors, Patients 'in Middle' in Row over Anti-Diabetic Medicines," *The Boston Herald*, 26 October 1975, Joslin Diabetes Center Archive.
[13] Ibid.
[14] Ibid.
[15] "Dr Joslin Warns: Despite Other Advances, Insulin Still Safest," *The Boston Daily Advertiser*, 8th August 1971, Joslin Diabetes Center Archive.
[16] Greene, *Prescribing by Numbers*, p. 117.
[17] R. F. Bradley, H. Dolger, and P. H. Forsham, 'Settling the UGDP Controversy?' *JAMA*, 232:8 (1975), pp. 813-817.