PROFILES IN PROGRESS

George Alberti: A Myriad of Contributions to Diabetes and Beyond

Philip Home

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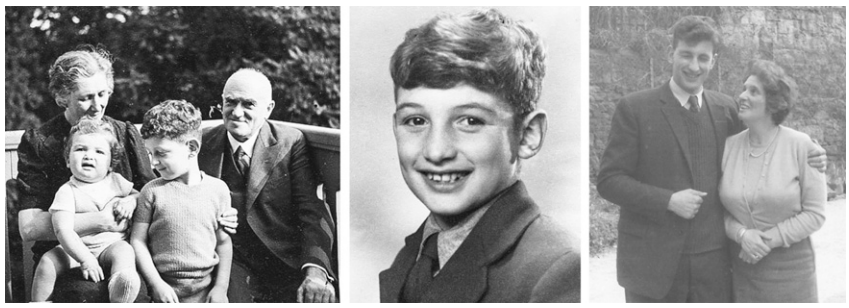
K. George M.M. Alberti

Medawar and Pyke, in *Hitler's Gift* (1), record the movement out of Germany in the 1930s of world-class academic talent from within the Jewish diaspora. But among the Jewish migrants was one too young yet to show such talent, indeed a mere toddler, escaping with mother and brother as the door closed in 1939. Kurt George Matthew Mayer Alberti was born in September of 1937. His father William Peter (after the family's names were duly anglicized) was a printer, and his mother Edith Elizabeth was a research physicist before marriage. Mayer-Alberti-Strasse can still in found in Koblenz, but the young George Alberti settled with his family in Gateshead, U.K.; U.K. citizenship was granted to all in November 1946.

The northeast of England was clearly a hit with the young Alberti—he returned later in life from the south of England to be professor of Clinical Biochemistry and subsequently professor of Medicine in Newcastle (see below). But as a lad he crossed the River Tyne to Newcastle's Royal Grammar School, an institution with a strong record for forwarding its pupils to England's top universities; George went on to Balliol College Oxford. Balliol is perhaps better known as a cradle of high-flying politicians and civil servants, and this may have confirmed George Alberti's (partly correct) view of his own personality as "laid back, iconoclastic, irreverent" in an interview for *The BMJ* in 2016 (2). More Cambridge than Oxford in fact.

Medical students at Oxford usually studied Animal Physiology as an intercalated Bachelor of Arts degree, and it was not unusual for those with academic pretensions to go on to do a DPhil (Oxford's PhD). George chose to do his in the Biochemistry Department, at an exciting and expanding time for the discipline in the early 1960s. The department and the laboratory in which he worked were those of Hans Krebs (one of the greatest of Hitler's gifts) (1), but George was glad not to be supervised by such a taskmaster. His thesis topic was "Amino Acid Metabolism in Mitochondria" (3), so already we see the biochemical interest deviating from the then increasingly fashionable topic of gene expression and protein



Young George. Left: George and older brother (Peter) with grandparents (Willi and Hedwig Lachmann) in Koblenz, Germany, prior to the family's move to England. Middle: George as a schoolboy, circa 1947. Right: George and his mother, Edith, circa 1962

Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, U.K.

Corresponding author: Philip Home, philip.home@newcastle.ac.uk.

synthesis into intermediary metabolism, though at that time at a cellular organelle level.

Serendipity broke the leg of George's supervisor at that time, and George had to take over tutorials of undergraduates. Oxford tutorials were intensive for both parties, and in this case the tutor (George) had to learn rapidly about insulin—and was duly hooked for life to insulin and diabetes. When later asked why he chose the field of diabetes, George responded, "I chose diabetes because of my training in biochemistry and the fact that I suddenly found myself teaching endocrinology as a graduate student . . . and was fascinated by the then dispute about whether insulin acted on the cell surface or within the cell." After this laboratory experience he returned to being a clinical medical student, with one chosen attachment being to the diabetes medical unit in Oxford. Here we get a first public glimpse of an interest in diabetes and clinical biochemistry, with an article in *The Lancet* on the accuracy and precision of the new-fangled near-patient technology of glucose measurement, the Ames Dextrostix (4).

Clearly George's clinical talents were appreciated, for his obligatory supervised postqualification year was on the house (intern) in Oxford at the Radcliffe Infirmary teaching hospital, a post for the selected few. But the restless scientist then moved for further clinical-academic training to Boston, at Harvard in the Endocrine-Metabolic Unit at Peter Bent Brigham Hospital and then the Biochemical Pharmacology Unit at Massachusetts General Hospital. His work there focused on mineralocorticoid activity, but he really wanted to be with diabetes at the Joslin and indeed spent much "spare" time there, notably picking up Stu Soeldner's insulin assay (5). George (with the assay) subsequently returned to the Radcliffe as a clinical fellow in the Nuffield Department of Clinical Medicine, with associated lecturer status at Oriel College. His sole clinical commitment was to the diabetes services.

From that appointment we see the interest in diabetes flowering, notably in work with Derek Hockaday, a talented if idiosyncratic diabetologist. At the time clinical biochemistry had advanced to allow glucose-specific assay in blood/plasma by glucose oxidase, intermediary metabolites by enzymatic dehydrogenase methods, pH by direct measurement, and potassium by flame photometry, to which George added insulin by radioimmunoassay. Together these set the scene for a series of investigations into the biochemical disturbance and management of ketoacidosis. But perhaps it was Turner's recent observation that insulin had a half-life in plasma of 4–5 min that led to the realization that the then current approach to treatment of ketoacidosis (often 100 units as an intravenous bolus and 100 units subcutaneously) made no pharmacological sense. A published letter from George Alberti makes it clear that maintaining intravenous lines as an alternative approach was not found reliable in routine clinical practice at the time, leading to the famous and career-establishing article in *The Lancet* on low-dose hourly intramuscular insulin injection (6). Even now that is worth rereading—the emphasis is as much on fluid replacement and careful monitoring of plasma potassium as on the insulin delivery. And in his bibliography it was already number 31 of what is now over 1,100 original contributions.

A notable temporary influence in Oxford was a visiting professor, Knud Lundbaek, with whom George talked endlessly about diabetes and philosophy. Later George did spend a little time with him in Århus, where he established valuable and lasting collaborations on metabolites and hormones in particular with Hans Ørskov.

But a career needs academic space, and a base, and Oxford could not then offer those in either clinical biochemistry or medicine. Nick Hales, who had recently taken up the clinical biochemistry chair in Cambridge, drew George's attention to the vacancy in Southampton (1973). While George rapidly established his unit in Southampton, using the automated intermediary metabolite assays and adopting the Biostator artificial pancreas, he began to nurture some notable future contributors to academic diabetes. A few years later a new opportunity arose with the vacancy in a similar post in Newcastle (1978), which was doubly attractive, being home territory and having a strong endocrinology unit under Reg Hall. But George's networking had already begun to foster other collaborations, notably with Harry Keen and thus pumped insulin therapy, glucose control and complications, and the trio of the World Health Organization (WHO), European Association for the Study of Diabetes (EASD) (and thus editorship of *Diabetologia*), and the International Diabetes Federation (IDF) (see below). Further German connections were made, notably with the nascent artificial pancreas community, as German science reestablished itself. Industrial contacts were also developed, two of the most fruitful being with Boehringer Mannheim and with Novo Industri, both having strong clinical biochemistry interests, the latter through Lisa Heding's research and development laboratory in Bagsvaerd.

George at the IDF Western Pacific Region meeting in Asia, circa 1980s

This then set the scene for a diversity of activity in diabetes research and care and later beyond. An interesting commentary from 2002 looks back on the impact of George's work and output in the 1970s and 1980s and includes a list of those publications he thought most important (7). Also at that time, George Alberti became a target for those seeking training in diabetes clinical research from around the world, and the Newcastle unit attracted an extraordinary diversity of young fellows from Italy, the Netherlands, Tanzania, Cameroon, Australia, Singapore, Paraguay, and elsewhere. These people returned home and established internationally recognized careers, as of course did a bunch of more homegrown fellows.

Insulin Therapy

The role of insulin science and insulin measurement in stimulating George Alberti's career and the translation of biochemical and pharmacological understandings into a revolution in the management of diabetic ketoacidosis is discussed above. But George in later life highlighted other areas of diabetes management with insulin as being of his greatest contributions (7), and it is difficult to disagree.

Quite how the concept of continuous subcutaneous insulin infusion (CSII) was generated between John Parsons, Harry Keen, and George Alberti, apparently in the back of a London taxi, may never be known. But its potential appeal as a tool in studying insulin pharmacokinetics and in improving blood glucose control to address the issue of control and complications was immediately compelling to George and Harry. The initial work began at Guy's Hospital, London, in March 1976, as Harry Keen had medical beds there. The early articles followed later after a research fellow was recruited (8); the articles rapidly received global attention, uptake and diversification, and challenge. Indeed multiple daily insulin injections (MDI, mealtime and basal insulin) grew as a general paradigm from that challenge, and the need for measures of control ensured the success of Boehringer's 20-800 test strip and the glycated hemoglobin assay, both the subject of studies in Newcastle. The Newcastle laboratory under Jackie Burrin also tried very hard to develop and automate chemical methods for measurement of the latter, trumped eventually by high-performance liquid chromatography.

Not all ventures were a success then, and the Newcastle/Guy's collaboration plunged into the deployment of insulin pumps and, by diverse routes, into brittle diabetes. George's prize lecture to the EASD in 1980 addressed the topic and echoed around the world, but it would now be seen as missing the essence of the problem.

As noted above, one interest in CSII was its possible use to test the diabetes control and complications hypothesis. Another key article from his own bibliography that George highlights is that of the Kroc study, for which Newcastle was the central laboratory, the feasibility study for the Diabetes Control and Complications Trial (DCCT) (9). An intercontinental study, it taught us many lessons and enabled funding for the DCCT; however, the international courier system for biochemical samples was proved unreliable in the 1980s, and the DCCT was therefore performed in North America alone.

Three other areas are worth noting. Human insulin for clinical trials became available from Eli Lilly (again via Harry Keen) in 1980 and from Novo through George's Copenhagen and U.K. connections. With his insulin pharmacology background George immediately saw the potential for "reversing" the glucose clamp in order to compare animal and human insulins in terms of potency and clearance kinetics when given intravenously (10,11), using the Biostator. Newcastle then led the first multicenter randomized clinical trial of the new Novo human insulins in the early 1980s, although by today's standards it looks like a limited and weak effort.

Further work, which George later said he felt was a particularly important contribution, concerned management of diabetes in surgery (12), work begun in Southampton. At that time surgical care had a poor record for acute hyper- and hypoglycemic complications. The essence was glucose-insulin-potassium infusion together with bedside monitoring and specialist service training and supervision. This further expanded the role of the diabetes specialist nurse, and, with the need for their skills in patient education, insulin dose adjustment through self-monitoring, and use of pen-injectors, made for a major expansion in the make-up of George's clinical team at Freeman Hospital. But the surgical collaboration also extended to open heart surgery (13) and intensive care management, along with a series of impactful articles in that area, notably with Martin Elliott and Geoff Gill.

The article that has perhaps touched the largest number of people with diabetes, but is now largely forgotten, also dates from the 1980s and also derived from an understanding of insulin absorption profiles, this time of extended-acting insulins. A long-running controversy had been as to whether prebreakfast hyperglycemia was reactive to night hypoglycemia or to insulin deficiency due to the limited duration of action of NPH and zinc-complexed insulins. The article, in *The BMJ* in 1983, established the advantage of giving the extended-acting insulin late in the evening (14); it is now difficult to understand how radical not giving an insulin before a meal seemed at the time, but of course the new timing rapidly became standard, even for the new long-acting insulin analogs 20 years later.

The Newcastle unit retained an interest in continuous glucose sensing in the 1980s, but other activities under the leadership of Alberti appointees from that decade blossomed and continue to this day, including international names like Roy Taylor (insulin insensitivity), Loranne Agius (hepatocyte biochemistry), Sally Marshall (nephropathy), and Mark Walker (genetics). Others made their mark outside Newcastle, notably Murray Stewart, the current chief medical officer for pharmaceuticals at GlaxoSmithKline.

International Initiatives

It is quite difficult to give an overview of George Alberti's international activities in diabetes and indeed in noncommunicable diseases more widely. As a flavor his curriculum vitae lists 16 WHO-related positions over 30 years (1979–2009). And then there are the EASD activities, numerous roles in the IDF, and work on major projects in Tanzania and in Cameroon. A number of the WHO and IDF activities were in close collaboration with his close friend Paul Zimmet (Melbourne; >100 joint articles), and this includes the extensive health surveys and population preventive activity in Mauritius over several decades (15), after the regional WHO office became concerned at the high diabetes prevalence on that sugarcane-growing island.

George is listed not as a member but rather the rapporteur of the 1980 report from the WHO Expert Committee on classification and diagnosis of diabetes, and his hand (or brain) can be strongly detected in the writings (16). This was carried through to the 1997, 2005, and 2009 Expert Committees, two of which he co-chaired. These take us through changes in diagnostic levels, changes in terminology (to "type 1" and "type 2" diabetes), alignment with U.S. national recommendations, and the like. Beyond diagnosis and classification are documents on diabetes complications, prevention of diabetes, and later the metabolic syndrome. Aligned with this activity were important contributions to the IDF, beginning with the WHO/IDF (joint) Executive Committee in the 1980s, which he chaired for 3 years. In IDF he rose to president in 2000–2003, but he has continued to contribute since to expert groups notably in collaboration with Paul Zimmet on such topics as the metabolic syndrome (17), sleep apnea, and, as late as 2016, bariatric surgery.

Initiation into the realities of international life began early. The 1982 IDF World Diabetes Congress was in Nairobi. George was the chair of the scientific program and arrived early to find a congress

center designed for political performances, not a scientific meeting. Slide projectors were acquired, white bedsheets hung as display screens, and various materials taped over windows for blackout. The congress was a success. Meanwhile George led a party to a local diabetes education program at Kisumu on Lake Victoria—an 8-h, 225-mile (360-km) drive. He opened the meeting in a subterranean lecture theater that promptly lost all lighting, but he continued in pitch blackness for a further 8 min (no mobile phones then). His voice then suggested we move upstairs, and the meeting continued successfully without electric teaching aids for the rest of the day.

His two biggest international projects were (and continue) in Tanzania and Cameroon. All such projects depend on engaging the right people on the ground, and here Kaushik Ramaiya and Jean-Claude Mbanya, having spent time in Newcastle, have been key collaborators, not just in the projects but in senior positions in IDF regionally and globally. Many other researchers have been involved of course, familiar names now in the diabetes epidemiology and care field, with perhaps one of the more important and least recognized being Donald McLarty. George possibly took his cues from Harry Keen's Whitehall and Bedford studies and Paul Zimmet's work in Mauritius, and a key component was always to base policy on measured disease impact and hence on high-quality epidemiological findings. George already knew the importance of science to the development of diabetes care from his biochemical/insulin work discussed above—the attitude of "get the data and then apply it" was implemented in rural Africa.

George once professed that there was nothing he liked better than lecturing about diabetes. He certainly did his complement internationally, talking on a wide series of topics. Of course he was also involved in organizing meetings globally other than for IDF/EASD, and a notable series was held under the auspices of Nobuo Sakamoto's unit in Nagoya, working with Nigishi Hotta.

Meanwhile, Back in Europe, and Diabetes Guidelines

In 1977 George joined the Executive Council of the EASD, becoming its secretary in the early 1980s (and therefore was responsible for the content of the annual EASD meeting) and president for the 1992–1995 triennium. Along the way he took on the editorship of *Diabetologia*, reading and editing every published article personally in detail and leaving his assistant editor (your current author) to pick up the myriad changes implemented or not by anxious authors in successful revisions. A *Diabetes Care* editorial celebrated George's approach (18). He also founded, as secretary, the EASD Study Group on Artificial Insulin Delivery Systems, Pancreas and Islet Transplantation, giving it (in a typically irreverent touch) the acronym AIDSPIT. He never attended one of its annual meetings, but they continue to this day.

Of even more impact, certainly in the last 10 years, was the first of the European diabetes guidelines. The first document, correctly entitled "a consensus view," grew from a meeting organized by George Alberti and Arnold Gries in Berlin in 1987, with the "blessing" of IDF Europe. This evolved into a more comprehensive Desktop Guide for the Management of Non-insulin-dependent Diabetes Mellitus in 1989. A number of features are notable: no systematic literature review was used, and both were highly influenced by the authors' views and notably those of a small executive group. One company (Boehringer Mannheim) provided the funding. But the reception was good, just at a time when the IDF/WHO (Europe) St. Vincent Declaration was having significant international impact, and so a further iteration followed in 1993 under its auspices and with a wider consultative group (19). Though sometimes a poor finisher, George Alberti did not rest there, however, and moved on to a more evidence-based approach (though not systematic) for the Desktop Guide to Type 2 Diabetes Mellitus (with a sister for type 1 diabetes) in 1998–1999 (20). These guidelines can be seen as setting the scene for the guidelines, position statements, and consensus views developed and still evolving in the decades since, some of which are now truly evidence-based and free of commercial funding.

And Back in the U.K.

Back in Newcastle, George moved from Clinical Biochemisty to the chair of Medicine in 1985, with a brief sojourn in Nashville with Alan Cherrington where he studied biochemical effects of catecholamines on Alan's dog model. George did actually do medical ward rounds for unselected admissions in Newcastle for a while, but his junior staffs' views on his abilities are not recorded. He then became dean of the Medical Faculty.

Alongside these activities George Alberti remained active in U.K. diabetes, in particular through roles in the British Diabetic Association (now Diabetes UK), notably in its Medical and Scientific Section (indeed from 1974), then Research Committee, then Council, then as chair of the organization in 2009. While it hardly seems possible, given the wealth of other activities, he at the same time was active in the Royal College of Physicians (of London), being a member and then chair of their Diabetes and Endocrinology Committee before being elected president of the College, the highest position for any physician in the U.K., in 1997. This drove interests more broadly than diabetes, though the Africa projects remained important to him; notably while at the College he pushed forward policies over specialty training for medical graduates, gaining friends and enemies. Other contributions were to the U.K. Medical Research Council and the U.K. General Medical Council, the latter responsible for standards of medical practice.

He retired from Newcastle University in 2002. But "retirement" has not been quiet. As noted above contributions to international activities continued. A national role in the reconfiguration of emergency medical services saw George giving continued advice to U.K. ministers of health (he was on government committees from 1976), and his charisma and communication skills enabled him to explain the modern medical advantages of fewer, more distant but more highly skilled services to gatherings of concerned local people. A notable national contribution was the chairing of a U.K. national working party on the health care response to violence against women and children, a document which has raised and directed attention in the area ever since (21). The Imperial College London provided an academic anchor for a while, while the hospital local to his London residence (King's College Hospital) found itself with a new and active chairman, returning the compliment more recently by rescuing George's health from a serious illness.

Inevitably the London-based activities drew George away from Newcastle. Additional enticements were his love of the

George and Stephanie hiking in the English Lake District

hills of the Lake District of northwest England, where he has a country retreat, and of Stephanie Amiel, whom he married in 1998. Their joint enjoyment of opera as well as that of diabetes helped. He also admits to spending a certain amount of time gardening and chopping wood, being an avid reader of classical crime fiction, and having an addiction to peanut brittle. His three sons (from his first marriage) also dispersed geographically and academically, now being an academic GP (family doctor) in Middlesbrough, professor of Cultural Anthropology at Framingham (MA), and keeper of Science and Technology at the National Museum of Scotland, Edinburgh. George also has 10 grandchildren, though none live nearby.

George was knighted in the year 2000 for his dedication to the field of diabetes. Sir K. George M.M. Alberti may refer to himself as laid back and irreverent, but there is nothing irreverent about the footprint he has made in the field of diabetes. His campaign for change in management and urgent care, his biochemical/insulin work, and his research in the treatment of diabetic ketoacidosis has greatly benefited the many millions of those with diabetes.

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