

Arnold Bloom's legacy today: the art of medicine in an evidence-based world

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The 13th Arnold Bloom Lecture was delivered by Professor Ken Shaw at the Diabetes UK Annual Professional Conference, London ExCel Centre, 30 March 2011

Ken Shaw was Senior Registrar to Arnold Bloom at the Whittington Hospital, London, 1973–1974

The name of Arnold Bloom is recorded on the Diabetes UK Roll of Honour which aims to acknowledge people who have played an exceptional role in the history of diabetes

Introduction

Preclinical undergraduate education at Cambridge, sadly now approaching some 50 years distant past, provided a formative experience of the then ongoing vigorous and at times vitriolic debate between what was described as the 'Two Cultures'¹ – the notion that society was split between the sciences and the humanities, argued respectively on the one hand, by Chief Government Scientific Officer CP Snow, and on the other hand, by Downing College English Literature Don FR Leavis. The concept of this contrived divide has provided an enduring fascination, none more so than that derived from the practice of medicine which, despite the increasing drive towards evidence-based clinical management, is still greatly determined by the vagaries and vicissitudes of human nature. We frequently adopt polarised perspectives – take contrasting points of view – but in reality clinical medicine is much more often a compromise. The Downing College motto, *Querere Verum* ('to seek the truth'), somehow directs us to keep an open mind on the way we think and the way we behave.

Ten years on, I had the privilege of working with Arnold Bloom, an exceptional clinical scientist with an astute clinical acumen. Inspirational and charismatic, Arnold Bloom embodied the art of medicine with meticulous observation and scientific application. For much of his professional career, the big debate was whether diabetes control and long-term diabetic complications were related or not. Many proponents argued for 'laissez-faire' as others did to the contrary. In more recent times, this debate may be more refined as we rightly demand good evidence for what we prescribe, but this evidence may yet be uncertain and often conflicting. Scientific analysis and personal judgement are a balance still required if the desirable aim of individualised care is to be achieved.²

Arnold Bloom

At the 1980 spring meeting of the British Diabetic Association, Arnold Bloom chaired the 10th RD Lawrence memorial lecture, which was delivered by Dr Robert Tattersall who in turn, referring to Lawrence's own earlier 1949 Banting lecture, quoted: 'the good clinician must strive to direct a life of normal efficiency and happiness to suit the patient's habits, desires and temperament.'

Clearly, the concept of individualised care is not a new recognition. Two years later (1982), Arnold Bloom himself delivered the 33rd Banting lecture which he based on his pioneering project work, sponsored by the British Diabetic Association, developing a UK register of all newly diagnosed children with diabetes.³ Initiated in 1972, over 2000 cases were notified within the first two years of registration, providing original observations on epidemiology, genetics and causation of childhood diabetes. Much was new knowledge at the time: a seasonal variation of onset with peaks in spring and autumn, a bimodal age distribution with a primary peak at 11 years and a secondary peak at around five years, and a remarkable high incidence of simultaneous onset in siblings. Even a north-south geographical gradient was reported, more cases being identified in the southern regions. With a £1.00 per reported case incentive (to the doctor!) blood samples were taken for analysis at the Epsom Public Health Laboratory, from which study the finding of raised Cocksachie B virus antibodies added to developing awareness that viral infection might play an important part in the pathogenesis of young-onset diabetes, anticipating today's emerging interest in enteroviruses and possible link with diabetes. In his captivating style, Arnold Bloom generated considerable interest into why some children develop diabetes, identifying key issues still much debated today: the combination of genetic susceptibility,

early viral exposure and subsequent autoimmune damage, all posing potential pathways for eventual cure.

Arnold Bloom published extensively. His clarity of communication made him a popular author of publications directed to patients and their families: *'Diabetes Explained'*⁴ ('It is unreasonable to expect anyone to accept restrictions without understanding the reasons for them'); *'Life with Diabetes'*⁵ ('Diabetes is a condition which can best be coped with when the patient and the doctor work together as a team').

However, it is Arnold Bloom's clinical research contribution to the medical literature that is of special note. His 1958 *BMJ* paper⁶ on 'Oral Treatment of Diabetes' records a huge milestone innovation in therapy, while illustrating how much of today's understanding of diabetes was by no means so clear-cut then as it is now, and that only by careful scientific observation is so much more known today concerning the nature of diabetes. At that time, different types of diabetes had not been clearly defined, only varying levels of severity. If diet had failed, patients were treated with insulin. Of the 40 patients admitted to hospital for study, it is not surprising that a number rapidly became ketotic on withdrawal of insulin, but in fact some two-thirds responded well to alternative treatment with the novel oral agent D.B.I. (phenformin) achieving a significant fall in blood glucose levels.

Recognising that insulin and phenformin were likely to have different modes of action, Arnold Bloom went on to study⁷ the effects of both therapies in combination with each other, observing a 20% reduction in overall insulin dosage with less variability of individual glucose levels, again remarkably prescient of the present usage of insulin and metformin. Summarising his observations,⁸ Arnold Bloom concluded that phenformin was not a substitute for insulin ('Tablets are not Talismans'), but was particularly helpful for the overweight person. Relapse rates were lowest with older patients (the majority under 30 years of age needed insulin while only 10% over 50 years relapsed on phenformin).

Although the classification of diabetes into types 1 and 2 diabetes was



Arnold Bloom (left) and Ken Shaw at the British Diabetic Association Medical and Scientific Meeting, Oxford 1985. (Image reproduced by courtesy of Praful Thaker who took the photograph)

not to be defined for some years ahead, these early research findings indicated distinct, differing levels of responsiveness and thereby differing patient characteristics, independent of simple duration of diabetes alone, clearly signalling the heterogeneity of diabetes itself.

Ward rounds at the Whittington Hospital

Life within Arnold Bloom's team was very much a learning exercise in true apprenticeship style, stimulating an absorbing interest in diabetes and an enduring empathy for people living with diabetes. Ward rounds provided tremendous teaching opportunities and when some unusual outcome was observed, publication was encouraged, even providing an early experience of the risks of putting 'one's head above the parapet' ('Alberti small dose intramuscular insulin regimen fails to improve diabetic ketoacidosis in an elderly man with diabetes!⁹). Participation in clinical trials of new oral hypoglycaemic agents provided further insight into individual variability of responsiveness. In what these days would be described as a phase 3 clinical study, we found that of patients with newly diagnosed 'maturity-onset' diabetes treated with gliclazide, then a very new sulphonylurea on the therapeutic block, 80% achieved a good or excellent response but 20% did not.¹⁰ Suspecting non-compliance with tablets might be the

explanation for the latter, we were surprised to find poor responders often had the highest measured blood gliclazide levels. What determines this differing responsiveness? – certainly not poor compliance in these cases. Perhaps, one day, pharmacogenomics will become routinely available to help determine the most appropriate drug treatment for individual patients.

One of the most satisfying studies undertaken was a quality of life assessment of patients attending the Whittington Hospital Diabetic Clinic.¹¹ Using a self-administered questionnaire, we found that people with diabetes reported a raft of different symptoms at almost double the frequency of those without diabetes derived from a matched population in general practice. Diabetes is the great magnifier – apart from the more typical osmotic symptoms, unsteadiness of gait, shortness of breath, poor mental concentration and slow walking pace were all much more common. Almost 60% complained of sleepiness by day, but there again so did 40% of the population without diabetes! We appear to be a generally tired nation and diabetes doesn't help. A separate study looking at side effects of therapy¹² identified differing complaint rates with age, the young clearly feeling better on insulin; the elderly less so. Tablets, rather than insulin, were better tolerated by older patients, and perhaps that was to be expected.

These last two studies, in collaboration with the Department of Epidemiology at the London School of Hygiene & Tropical Medicine, had the added bonus of much appreciated critical appraisal from the 'father of clinical epidemiology', Geoffrey Rose. It was Rose who raised the debate comparing the respective benefits of treating the population as opposed to the individual.¹³ He commented that by taking the population approach and controlling the causes of incidence, there was large potential for the population as a whole, but only small benefit to the individual. In contrast, by taking the individual approach, identifying those susceptible and at 'high-risk', the strategy was appropriate for the individual but of limited potential to the population.

Although Rose's observations were primarily addressed within the context of cholesterol and coronary heart disease, the principles equally apply to the treatment of diabetes. The substantial reduction in microangiopathic complications over the last three decades has resulted from a complexity of reasons. The setting of specific metabolic targets with the dissemination of overall clinical practice guidelines has indeed confirmed the benefit of a strategic approach for the diabetes population as a whole. However, meta-analyses of various therapeutic interventions may show only small, despite statistically significant, benefit for the whole population but fail to identify which individuals are likely to do best with a specific treatment. With current protocol-based prescribing some individuals will benefit, but others may be inappropriately treated, while others have unrealistic expectations of benefit or may indeed be put at risk of side effect without benefit. A model of identifying high risk individuals and determining appropriate personalised therapy is still much needed. But how can those at higher risk be identified?

Portsmouth microalbuminuria prospective cohort study in T1D

By the early 1980s it had become increasingly evident, for whatever reasons, that the clinical consequences of diabetes differed considerably between individuals and that there was an identified need to try and determine those at greatest risk

to allow a more selective management strategy. We were interested to ascertain what factors were associated with the risk of developing diabetic complications and whether individual risk could be formulated. With this objective in mind, a longitudinal cohort study of 172 patients with type 1 diabetes (T1D) was initiated, specifically addressing issues related to early diabetic nephropathy.¹⁴ Characterised at baseline by a mean age of 31 years, average diabetes duration of 15 years, normotensive and without macroproteinuria, 18% of patients had sustained microalbuminuria (albumin excretion rate [AER] >30µg/min; albumin:creatinine ratio [ACR] >3): 12% had intermittent microalbuminuria and 70% remained negative. The evidence base for therapeutic intervention not being established at this time, this cohort study was primarily observational in nature, seeking to identify early determinants of developing nephropathy and subsequent implications to associated co-morbidities and mortality.

At a four years' review,¹⁵ specifically looking at those patients (6.8%) who had progressed to macroalbuminuria (AER >300; ACR >3), the strongest predictors of progression were found to be baseline ACR (mean ACR 17 for those that progressed) and HbA_{1c} level. In fact, a modest rise of ACR (from mean 0.8 to 2.6) was observed for the whole cohort with a continuous relationship between urinary albumin excretion at baseline and four-year follow up. A 10-year review¹⁶ addressed the important subgroup of those who had progressed to microalbuminuria (8.2%) having been negative at baseline. Again, the strongest association with progression related to increased baseline HbA_{1c} level in all cases without exception, but in contrast many with equally high HbA_{1c} levels when the study commenced had shown no indication of progression 10 years later. Clearly, poor glycaemic control was identified as a significant risk factor, but it alone could not explain the observed variability in outcome.

Recognising this disparity of clinical outcome and that such might in part be determined by differing genetic susceptibility, the immunogenetic profile of the cohort of 172

individuals was determined studying the major histocompatibility complex class I antigens.¹⁷ Independent of metabolic control, expression of HLA-A2 antigen was associated with a two-fold increase in progression from negative to microalbuminuria status and was present in all those who developed macroalbuminuria, suggesting that immunogenetic factors are indeed important in the development of diabetic nephropathy.

A longer-term review¹⁸ at 14 years' follow up allowed important, clinically relevant observations to be made in terms of associated morbidity and mortality. Sadly, an inevitable attrition rate had been recorded with 19% of the original cohort having died, on average with three years longer duration of diabetes and being six years older, but nonetheless still prematurely at a mean age of 55 years. The causes of death were diverse, only one-third relating to cardiovascular disease, and with deaths from infection and cancer being equally prominent. Significant predictors of total mortality in this cohort of patients with T1D included urine ACR, serum creatinine and the presence of retinopathy. Factors determining risk of coronary heart disease within the cohort were separately considered, combining data from those known to have died from a cardiovascular event with others, still surviving, identified by validated clinical assessment. Duration of diabetes proved the strongest predictor of cardiovascular morbidity or death, but abnormal lipid metabolism was also significant, less so for total cholesterol but primarily in respect of HDL cholesterol, LDL cholesterol and in particular apolipoprotein B. Systolic hypertension, preceding clinical onset of coronary heart disease, increased the risk by 3.5-fold in men and by 2.5 in women.

These observations on a relatively young cohort of established T1D confirmed significant variability between individuals, but the reasons for this are not sufficiently clear-cut to allow a more selective focus on patients with microalbuminuria alone. Although two-thirds of the cohort were negative on repeat measurement at the commencement of the study, a small proportion did progress over 10 years and so negative status does not itself allow subsequent monitoring to be

relaxed. On the other hand, it is still only a small proportion of those with microalbuminuria who – even without specific therapeutic intervention as during the early part of this study – went on to develop advanced nephropathy. Following our later policy of ACE inhibitor treatment, progression to end-stage renal failure was virtually eliminated. Finding likely genetic differences in susceptibility raises the fascinating concept of genomic medicine whereby complication risk can be predicted and individualised treatment determined.

It is evident that the presence, and in particular the severity, of microalbuminuria in established T1D does potentially predict risk of progressive nephropathy, but it does not clearly define individual risk as such. Microalbuminuria is a significant predictor of premature mortality risk, but it is a surrogate marker and so far there is no direct evidence that reducing microalbuminuria *per se* affects longevity. The finding that the total mortality included 40% non-vascular deaths is consistent with other recently reported data,¹⁹ but it is presently uncertain whether this reflects increased incidence or reduced survival from such other causes, particularly cancer. Interestingly, in respect of predicting coronary artery disease, dyslipidaemia and systolic hypertension appeared more important than microalbuminuria, confirming the need for multifactorial treatments. Thus, with our overall goal of seeking clear-cut indicators of individual risk, we have been unable to determine with sufficient discrimination a single focus alone on patients with microalbuminuria, but nonetheless the powerful risk relationship with poor glycaemic control stands out, remaining an essential component of diabetes management.

The legacy of Arnold Bloom

Arnold Bloom understood the need to underpin best clinical practice with meticulous observation and robust research, but he also recognised the essential contribution of wisdom derived from experience – combining science with the art of medicine. The older generation remembers with affection his wonderful way with words, enlivening the Medical and Scientific

'In the present state of our knowledge, it seems reasonable to attempt to keep the blood sugars as near normal as possible, though not at the cost of provoking frequent hypoglycaemic reactions. The diet should be regular and wholesome but the patient should not be made unhappy with impracticable restrictions. The evidence does not warrant a procrustean attitude, nor is it fair to imply that the onset of degenerative complications is due to shortcomings in the patient's adherence to the regime imposed.'

Box 1. An example of Arnold Bloom's commonsense advice. The extract shown here is from his article on 'The management of diabetes and its complications' published in 1968²⁰

Section of the British Diabetic Association, entertaining but always educational. His commonsense advice is easily exemplified from his writings (see Box 1).²⁰

Getting the balance right in those days was indeed a compromise between undesirable hyperglycaemia and unacceptable hypoglycaemia. However, from his own contemporary clinic observations, Arnold Bloom registered the higher incidence of severe complications of diabetes in those with the highest blood glucose levels,²¹ at a time when the relationship was far less certain and the evidence base, from studies such as the DCCT and the UK Prospective Diabetes Study, was yet to be established for many years to come.

In so many ways the present world of diabetes care has changed enormously since those earlier days. The incidence of severe long-term complications of diabetes has progressively lessened, actually in advance of the evidence base, as a result of a variety of clinical and therapeutic innovations with which Arnold Bloom would surely have marvelled. Yet, diabetes is a human disorder and as such subject to the capriciousness of human behaviour. Arnold Bloom understood the human factor extremely well. Today's world rightly demands rigorous, scientifically determined direction on best clinical practice, but maintaining the individual, human perspective remains as important now as it was then. Combining the compassionate art of medicine with the demands of emerging new knowledge remains a

paramount lesson from the past and a legacy entirely apt for the present.

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