Commentary: Professor Harry Keen, clinician, epidemiologist, diabetologist, basic scientist and defender of the UK National Health Service

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Harry Keen is arguably the grandfather of diabetes epidemiology, establishing himself at a time when neither specialty was regarded as either interesting or important. He was born in 1925 and qualified in medicine from St Mary’s Hospital Medical School in 1948, shortly before the inauguration of the National Health Service, for which he acquired and retained a strong loyalty. After house jobs and National Service, he embarked on his formative years at St Mary’s under Professor George Pickering, who remained a strong influence. Harry began clinical research at King’s College Hospital, where Pickering had arranged for him to study hypertension in diabetes in the clinic headed by R.D. Lawrence, the second of Harry’s mentors. In 1960–61 he spent a fruitful year with James B. Field in the National Institutes of Health, where he was introduced to the fascinations of laboratory research, including bioassays for insulin and preliminary attempts to isolate islets of Langerhans. He returned to London to join the Department of Experimental Medicine under Professor John Butterfield. Here he was introduced to the epidemiology via the planning and execution of the pioneering Bedford Study, later to be followed by participation in the Whitehall Study (now Whitehall 1) originated by Donald Reid and Geoffrey Rose. These studies provided, inter alia, much valuable information about the relations between cardiovascular disease, diabetes and glucose intolerance. The prospective elements of these studies provided much of the data which led to a new definition and classification of diabetes. Indeed, Harry chaired the World Health Organization (WHO) Expert Committee which pronounced on these matters in 1980 and also the WHO Study Group which modified the original proposals in 1985. Largely due to his initiative, a further involvement with WHO led to the Multinational Study of Vascular Disease in Diabetes, a notable example of international scientific collaboration.

Along with the epidemiology, Harry continued with clinical and laboratory research (see below). John Parsons at Mill Hill had started treating patients with hypoparathyroidism with subcutaneous infusions of parathyroid hormone, and Harry immediately saw the potential in type 1 diabetes. With John Pickup he set up a research programme which eventually resulted in the present day widespread use of continuous insulin infusion therapy.

At Guy’s, Harry headed a diabetes unit which not only provided a successful clinical service—he was one of the pioneers of the use of specialist nurses—but was also a busy research scene.

He was also active in other ways within the hospital. Following the initiation of clinical directorates in 1985, he became the first Director of Clinical Services for Medicine, having previously been chair of the Division of Medicine. As an example of his formidable energy he was, at the same time, active in several other spheres—WHO, the British Diabetic Association (now Diabetes UK), International Diabetes Federation, National Institutes of Health and the Department of Health [Chair, Committee on Medical Aspects (COMA)].

In 1989 there was a White Paper on NHS reform. Like many others, Harry saw most of the proposals as damaging to the NHS and he played a leading role in opposition. He later became chair of the NHS Support Federation, which has campaigned in support of the founding principles of the NHS, not least, more recently, in relation to the Lansley legislation.

I have mentioned Harry’s formidable energy, which is obvious from the above. I hope I have conveyed his unusually multifarious activities. More difficult to portray is Harry the personality: always engaging, optimistic, ready to engage in civilized dispute (we did not always agree!) and congenitally incapable of saying ‘No’ to a request for a piece of his time.
Given that Bright,1 physician to Guy’s Hospital, had first described the association between renal disease and albuminuria, it seems appropriate that Harry Keen developed an interest in the association between diabetes and albuminuria when he became a lecturer in the Department of Medicine at Guy’s. I remember him returning from a British Diabetic Association Scientific meeting enthused by a presentation given by Nick Hales and Philip Randle, concerning a new, simplified immunoassay for insulin. Harry and Costis Chlouverakis, then a research assistant in the Department, immediately set to work to develop a similar assay for urinary albumin, with fairly rapid success.

From the late 1940s, particularly in the USA, there was considerable interest and activity in screening for what is now called type 2 diabetes. Clive Sharp, then the Medical Officer for Health for the town of Bedford, was a screening enthusiast and approached Professor John Butterfield at Guy’s for help in screening the local population. Butterfield assigned Harry Keen and Roy Acheson, then Reader in Sociology at Guy’s, the task of designing the project. They felt that a research project, rather than a simple survey, would be more appropriate for a University Department. An obvious subject would be to use the data in an attempt to throw light on an evidence base for the glycaemic criteria for diagnosing diabetes, for, at the time, different criteria were used between and even within countries, all of them quite arbitrary. The standard oral glucose tolerance test in Britain at that time used a 50-g glucose load. Keen and Acheson therefore asked a number of physicians what level of blood glucose 2 h after the load they would regard as definitely normal and also what level they would regard as definitely abnormal. The consensus levels were 120 mg/dl and 200 mg/dl, respectively. For the purposes of the survey, these values were to be used to identify individuals as probably normal or diabetic; values in between would be labelled ‘borderline diabetic’. In the eventual survey, the initial screening procedure comprised a test for glycosuria in urine specimens passed after a carbohydrate-loaded breakfast. Subsequently a capillary blood glucose level was measured in the glycosuric individuals 2 h after a 50-g oral glucose load. In addition, full standard oral glucose tolerance tests were performed on a random sample of the cooperating population.

Following the survey it was decided to look at a number of potentially related variables in relation to the range of glycaemia.2,3 In the report by Keen et al. these were age, sex, weight/height ratio, blood pressure and urinary albumin excretion. In the light of subsequent research, findings of interest were the shift to the right in the distribution of urinary albumin excretion, in the newly diagnosed diabetics particularly and in the borderline diabetics, and the positive association of systolic blood pressure and albumin excretion only in the diabetics. Also noteworthy is the lack of association between body weight/height (ponderal index was used in this study, body mass index not yet having achieved popularity) and albumin excretion. However, it must be remembered that these were the early 1960s, well before the era of the very fat.

About this time, Ruth Osterby in Denmark was studying electron microscopic preparations of renal basement membranes from renal biopsies in diabetic subjects. Harry arranged a cooperative study where his then registrar—Dr Ron Hill—would carry out physiological studies in Guy’s diabetic clinic patients, both with type 1 and type 2 diabetes, including urinary albumin excretion; in some renal biopsies would be done and samples submitted to Ruth Osterby so that comparisons could be made between structure and function. However, because Ron Hill obtained a consultant post before doing many (any) biopsies, the planned study was aborted. Some 14 years later, I obtained the data on the participants from Ron Hill and, with colleagues, managed to trace the life/death status of nearly all the participants. I gave the data to Giancarlo Viberti to analyse without, as I recall, any great expectation, so well remember his expression of delight when he turned up with the results. In both type 1 and type 2 diabetics there was a clear association between increased albumin excretion and all-cause mortality and in type 1 diabetics also with the development of clinical proteinuria.4,3 These associations appeared to be independent of blood pressure measurements. Similar data were published around the same time by Carl Erik Mogensen.6

Since these early reports, the relationships between chronic renal disease, albuminuria, blood pressure and, in particular, cardiovascular disease have been extensively studied in much larger population groups.7 Data, derived from cohort studies, from more than 1.4 million individuals, have been analysed in two meta-analyses. Chronic renal disease [defined using estimated glomerular filtration rate (GFR)] had a non-linear relationship with cardiovascular disease but, by contrast, the association with albuminuria had no threshold effect even after adjustment for other risk variables. The meta-analyses also clearly showed that the associations between albuminuria, chronic renal disease and cardiovascular disease were independent of both hypertension and diabetes mellitus.

As I mentioned earlier, the population we studied in Bedford was, by present standards, relatively lean. Today, obesity (BMI >30) is increasingly common. Studies on obese individuals with the variables included in the so-called metabolic syndrome show increased frequencies of raised albumin excretion and/or reduced estimated GFR in the absence of diabetes or hypertension.8

Although albuminuria is now well established as a risk factor for cardiovascular disease, despite a great deal of research its role in pathophysiology remains speculative and to date there is no established therapeutic indication.7
Finally, to return to Richard Bright, not only did he show the association of renal disease and albuminuria, but he also established the concept of the renal origin of cardiovascular disease. So it has been a long story, yet to be completed.

Conflict of interest: None declared.

References

1 Bright R. Cases and observations illustrative of renal disease accompanied with the secretion of albuminous urine. Guy’s Hospital Trans 1836;1:338–79.