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.

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Commentary: The birth of microalbuminuria: a milestone in the history of medicine

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Clinical scientists are rarely awarded the Nobel Prize for Medicine. Their legacy is provided by original observations that stand the test of time and gain insights into mechanisms of disease which may open the way to new treatment options. The article entitled ‘The concomitants of raised blood sugar: studies in newly-detected hyperglycaemics. II. Urinary albumin excretion, blood pressure and their relation to blood sugar levels’ by Keen and colleagues1 is one such example. The paper appeared in 1969 in the Guy's Hospital Reports, a journal first published in 1836 and managed by an editorial committee of Guy's Hospital which contained papers by staff and lecturers, including some of the great men of Guy's such as Richard Bright (who helped found the journal), Thomas Addison and Thomas Hodgkin. The journal ceased publication in 1974 because of increasing costs of production and its circulation, by modern standards, cannot have been wide. And yet the paper by Keen et al has become a classic and deserving of a reprint as a ‘historical article’ by the International Journal of Epidemiology. It deals with the relation of blood sugar (sic) levels and blood pressure with urinary albumin excretion in the Bedford Study, a survey that screened the population of Bedford for the prevalence of diabetes. The survey identified three diagnostic groups—normal controls, borderline diabetic patients (the equivalent of today's impaired glucose tolerance (IGT)) and diabetic patients—which form the subjects of this article.

In 1963, Keen and Chlouverakis had described a radioimmunoassay for measuring small concentrations of
albumin in the urine, well below the detection threshold of the then existing methods.\textsuperscript{5} The hope was that by improving the detection limit of albumin in the urine one would be able to diagnose early (and perhaps treat) diabetic renal disease, a condition in those days almost invariably fatal. Keen and colleagues applied this radio-immunoassay procedure to measure albumin in the urine following a 2-h oral glucose tolerance test in the three groups from the Bedford Diabetes Detection Survey. The paper by Keen H, Chlouverakis C, Fuller J and Jarrett RJ is important for four reasons.

The term micro-albuminuria (as a hyphenated word) first appears in the medical literature. In the original context it is used to mean small amounts of albumin in the urine. The term has been subsequently used to indicate small increases of albumin in the urine over and above the normal level of normalalbuminuria but below the level of clinical albuminuria detectable by ordinary dip-stick tests. It conventionally covers the range between 20 and 200\(\mu\)g/min. Microalbuminuria gained popularity after the publication in 1982 of a 14-year longitudinal study which showed that in type 1 diabetes microalbuminuria predicted an increased risk of renal disease and early mortality.\textsuperscript{6} The predictive power of microalbuminuria for renal and cardiovascular disease morbidity and mortality was subsequently confirmed in type 2 diabetes, arterial hypertension and in the general population.\textsuperscript{1,7} Publications on microalbuminuria soared to the level of more than one every other day. Both the term and the significance of microalbuminuria have been criticized. It has been argued that microalbuminuria is a misnomer. Micro is Greek for small in size and, etymologically, microalbuminuria would indicate a smaller albumin molecule in the urine. It has been suggested that the correct term should be oligoalbuminuria to mean small amounts of albumin in the urine. More recently, moderate albuminuria has been proposed as a term to replace microalbuminuria. Levels of microalbuminuria are variable and their relation with the severity of histological lesions, though significant, is weak. Isolated spot measurements of microalbuminuria may be misleading and less reliable than the rate of change of microalbuminuria, specifically a rise in albumin excretion rate, as indicators of progressive renal disease. Moreover some patients apparently can develop renal impairment without developing microalbuminuria.\textsuperscript{6–9} Despite these critiques (some of which are criticizable themselves; for instance, there is no proven early histological marker of progressive renal disease in diabetes), an overwhelming body of evidence indicates that a small increase of albumin in the urine above the normal range (and this is what microalbuminuria means) is one of the strongest predictive biomarkers of cardio-renal disease.\textsuperscript{10–12} The concept that raised albumin excretion rate flags early risk is here to stay. Of course the level of risk increases further as the albuminuria gets heavier, but this represents late phases of disease. Whether microalbuminuria, or for that matter albuminuria, is on the causal pathway for cardio-renal disease and is thus a surrogate for it, still remains an open question.\textsuperscript{13}

The use of a sensitive method to measure albumin in the urine allowed for the first time the description of the distribution of urine albumin excretion in the general population. It showed that in the control group the distribution was positively skewed, and that the percentage of individuals with higher excretion of albumin increased as the categories of glucose intolerance moved from normal to borderline diabetes to diabetes. The log-normal distribution of albumin excretion has been subsequently and consistently confirmed in much larger samples of the general population in many studies. It was also found that the relationship between albumin excretion and cardio-renal risk is a log-linear continuum across the whole range of albumin excretion.\textsuperscript{12,14} Clearly this advance in knowledge was made possible only because of the ability to measure microalbuminuria.

The degree of albumin excretion was found to be significantly correlated with the level of blood glucose and with that of systolic blood pressure. The authors assumed that the combination of hyperglycaemia and hypertension would result in an increase in the degree of albuminuria. They had no idea of the mechanism of this phenomenon. It was more than 10 years later that their assumption was proven correct.\textsuperscript{15} Direct micropuncture measurements of the glomerular capillary circulation showed that high blood glucose induced afferent arteriolar vasodilation, thus allowing the systemic blood pressure to be transmitted to the glomerular circulation (which is physiologically protected from systemic hypertension by afferent arteriolar vasoconstriction). This produced intraglomerular hypertension and disruption of the glomerular capillary barrier which resulted in increased albumin leakage. In subsequent years a large number of clinical studies also confirmed the importance and primacy of systolic hypertension as a promoter of progression of renal disease in diabetes.\textsuperscript{16–19} That hyperglycaemia may be causative of albuminuria, as the authors assumed, was also shown by a variety of clinical trials which demonstrated that intensive antihyperglycaemic therapy both reversed microalbuminuria\textsuperscript{16,17} and significantly reduced the risk of developing microalbuminuria and renal disease in newly diagnosed diabetic patients.\textsuperscript{22,23}

The authors took their observation to predict that ‘treatment of hypertension associated with diabetes may ameliorate or delay the onset of renal disease’. Again they were proven correct. For the following 30 years or so a number of controlled clinical trials showed that treatment of hypertension was crucial for renal protection in diabetes. In particular, antihypertensive agents which reduced intraglomerular pressure and albuminuria, which had resulted from the combination of hyperglycaemia and hypertension, proved particularly effective.\textsuperscript{24–26} Thus, the authors’
careful description of ‘simple’ cross-sectional, observational data and their brilliantly insightful interpretation of the results not only were consistently confirmed by experimental evidence, but also laid the foundation for and informed the work of the following 40 years.\(^2,7\) This has resulted in significant improvements in the prognosis of renal disease in diabetes. The authors’ names deservedly should be added to the list of the great men of Guy’s.

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