Historical Note

Hermann Senator and albuminuria—forgotten pioneering work in the 19th century

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Dedicated to one of the pioneers of modern albuminuria research in diabetes, a close friend and teacher, Carl-Erik Mogensen (Aarhus/Denmark)

Abstract
Testing urinary albumin concentration by immune detection methods has recently turned out to be a highly rewarding procedure, as low level albumin excretion has turned out to be a powerful predictor of cardiovascular and renal risk in diabetic and nondiabetic patients. In the following we discuss a text dating back to the 19th century in order to make today’s nephrologists aware of the remarkable and prescient, but meanwhile completely forgotten investigations on urinary albumin excretion in individuals without primary kidney disease. The treatise of Hermann Senator convincingly disproved the then held dogma that albuminuria was always a sign of primary renal disease. These observations are all the more remarkable since he was forced to use relatively simple and not absolutely specific methods. He further provided an explanation of the renal handling of albumin which to a large extent is still valid today.

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In the following we discuss a text dating back to the 19th century in order to make today’s nephrologists aware of the remarkable and prescient, but meanwhile completely forgotten investigations on urinary albumin excretion in individuals without primary kidney disease. The treatise of Hermann Senator convincingly disproved the then held dogma that albuminuria was always a sign of primary renal disease. These observations are all the more remarkable since he was forced to use relatively simple and not absolutely specific methods. He further provided an explanation of the renal handling of albumin which to a large extent is still valid today.

Motto:

History teaches us that the views of modern times constantly revert to those points which were regarded by earlier observers as settled, and thus, particularly nowadays, when so few have leisure for the historical study of science, there is perhaps ample justification for bringing old notions within the intellectual view of a succeeding generation.

R. Virchow

Gesammelte Abhandlungen zur wissenschaftlichen Medizin 1856

From proteinuria in primary renal disease to albuminuria in individuals without renal disease

Proteinuria had been studied long before the era of modern medicine [1,2]. In 1648, Dekkers of Leyden observed that after addition of vinegar (acetic acid) urine coagulated in ‘wasting diseases’ without specifically relating this observation to the kidneys [3]. The first clear recognition and interpretation of proteinuria as a renal problem goes back to Domenico Cotugno (1736–1822) in Naples [4]. He studied the coagulation of various body fluids and in this context observed a soldier probably suffering from malaria with oedema undergoing massive diuresis. Cotugno stated, ‘coagulation would be seen if the material which flowed out were heated, which, as I anticipated, was proven by experiment. For with 2 pints of this urine exposed to the fire, when scarcely half evaporated, the remainder made a white mass, already loosely coagulated like egg albumin’. This ‘albuminuria’ was later noted amongst others in children with scarlatina, in febrile diseases and above all in patients with what we would call today primary kidney disease—most beautifully documented by Richard Bright (1789–1858) [5]. He was the first to systematically combine the presence of albuminuria with macroscopical anomalies of the kidneys in patients who we now know to have primary kidney disease. In the Gouldsonian lectures he made the following
statement: ‘in the natural and healthy condition of the urine little or no albumin is to be detected’—contrasting with what he found in patients with primary kidney disease: ‘I have never yet examined the body of a patient dying with dropsy attended with coagulable urine in whom some obvious derangement was not discovered in the kidneys’ [6].

Within a few years the link between proteinuria and kidney disease was widespread knowledge throughout Europe as illustrated by the subsequent books of Rayer in France [7] and Frerichs in Germany [8].

After some forerunners, such as the Dutch J. B. Stokvis [9], it was the seminal contribution of German physician Hermann Senator (1834–1911), a forgotten pioneer, to document the potential presence of albuminuria even in perfectly (or at least seemingly) healthy individuals. He put the notion firmly on the map that albumin may be found in subjects without primary kidney disease. In many respects the work of Senator has a modern ring; it gave farsighted, although not infallible, interpretations on the underlying pathophysiology and even provided a perspective of potential interventions. The first manuscript of Senator on albuminuria was published in 1882 (Die Albuminurie im gesunden und kranken Zustande) [10]. This publication was found to be so important that within 2 years it was translated into English by the Sydenham Society (Albuminuria in health and disease) (Figure 1 [11]). This translation was reviewed and revised by Senator himself [11, p. 153]. In this review, Senator requested the addition of two appendices of articles he had published in 1882 after the publication of the original German edition of his book. The appendices cover handling of albumin by the kidney [11, pp. 127–141] and treatment of patients with albuminuria [11, pp. 142–153]. The highlighting of these additions is important for two reasons. First, the original German text did not include any reference to treatment. Second, the discussion of how albumin is handled by the kidney (section ‘How is albumin handled by the kidney?’) is based on one of these appendices.

Later his manuscript was also translated into French [12]. Within 8 years the original monograph was followed by a second completely reworked edition (Die Albuminurie in physiologischer und klinischer Beziehung und ihre Behandlung, 2. gänzlich umgearbeitete Auflage) [13]. Given the recent interest in and explosive growth of evidence on low-grade albuminuria as a cardiovascular and renal risk factor [14–16], the results of such early work are of obvious historical importance. In that respect, it is remarkable that the motto Senator chose for his manuscript (derived from the work of Virchow [11, p. 1]) has later on become exemplary for his own work. We shall describe some selected aspects of his work which are still of interest today. These descriptions show us that indeed history teaches us that the views of modern times revert to those points which were regarded by earlier observers as settled.

**Biography of Hermann Senator**

Hermann Senator (Figure 2) was of Jewish descent [17] and born 1834 in Gnesen (Province Posen, today Poland). He received his medical training at the University of Berlin under the tutelage of the physiologist J. Müller and the internists J. L. Schönlein and L. Traube [18]. He obtained his MD by a thesis on liver disease and in 1868 a degree in Internal Medicine and Pharmacology at the Charité Hospital in Berlin in experimental and clinical medicine. He was also an expert in forensic medicine and widely acknowledged in this specialty as well. He published a total of some 200 original articles on clinical and experimental studies. According to contemporaries, his most appraised research was on fever and its treatment, on albuminuria in health and disease and on diseases of the kidneys [19]. In 1872, he was appointed co-editor of the prestigious Centralblatt für die Medizin. From 1888 to his retirement in 1909 he was the director of the outpatient clinic at the Charité Hospital. For more than 20 years, Senator was vice-president of the Berlin Medical Society, later to become president and honorary president. He died on 14 July 1911 in his 77th year.

**The past methods to detect protein/albumin in the urine**

Tests available then for measuring urinary protein were manifold [20]. The most commonly used method was
boiling and then adding nitric or acetic acid [11, p. 13]. Senator warned that this method was not very sensitive, and that not all protein coagulated by this procedure was indeed albumin. He advised therefore other techniques that had to be used in conjunction to exclude false positive tests due to non-albuminous substances [11, p. 14].

- Acidification of urine with acetic acid, and then adding potassium ferrocyanide.
- Addition of nitric acid to (non-warmed) urine, followed by boiling if any cloudiness resulted.
- Addition of a concentrated solution of sodium chloride or magnesium sulphate, to urine acidified by acetic or nitric acid.

Applying these techniques, he noticed that traces of albumin (<0.05%) could be detected in urine of apparently healthy humans as described below.

**The interpretation of Senator of his finding of albumin in the urine**

In the following, we give selected citations from the above book of Hermann Senator published by the Sydenham Society [11], with our comments on his opinions and findings in the light of today’s knowledge.

*How is albumin handled by the kidney?*

In one of the two appendices, Senator tried to answer the question how the kidney handles albumin (pp. 127–141). For his conclusions, relevant to the current accepted view on renal physiology (filtration, reabsorption, secretion), Senator deserves to be acknowledged. Despite the then popular theory by R. Heidenhain that the glomerular filtrate was the product of glandular-like secretion in the glomerulus, Senator remained convinced of the experimental findings of the great physiologist C. Ludwig documenting that the glomerular filtrate was primarily a transudate of blood plasma (pp. 127–138). Following the suggestion of J. Henle (Nachrichten von der G.A.Universität zu Göttingen 1863, p. 257) Senator concluded (p. 22) that ‘... the disturbance of the circulation in the Malpighian tufts is the cause of the albuminuria, but the ill effects of this disturbance are of less serious import upon the walls of the vessels than upon the epithelium which covers the vessels’. As a result, he attributed the retention of albumin under normal conditions to a property of this epithelium, in today’s parlance the podocytes.

(Today we agree that podocytes are a major barrier to the transit of albumin into the primary filtrate.)

Senator argued (p. 24), ‘We are therefore forced to assume that (albumin) is filtered through the Malpighian tufts, but in an extremely minute quantity, corresponding with its small capacity for filtration of albumin’ (an assumption in good agreement with current estimates of the filtration coefficient [21]) ‘because the escape of albumin from the Malpighian tuft is prevented by the epithelial investment of the vessels’ (p. 24). In this respect, he fundamentally differed from Ludwig and others at his time, who argued that the filtrate would be wholly free of albumin (p. 27). He furthermore gave detailed attention to the assumption that alterations in blood pressure may modulate the quantity of albumin leaving the glomerulus by modulating renal blood flow (pp 39–77).

Senator admitted that some reabsorption of proteins by the tubules is possible in principle (p 33), but he disagreed with the view of Litten (Litten, Frerich’s and Leyden’s Zeitschrift f. Klin.Med. I, pp. 177–178) that under pathological conditions the epithelium of the convoluted tubules may fail to remove albumin from the ‘transsuded secretion pressed through the loops of the glomeruli which in the normal condition contains albumin’.

(Today we know, however, that in the proximal tubule filtered albumin is taken back by cubulin and megalin mediated uptake and that reduced reabsorption may well increase the urinary excretion of proteins [22].)

Nevertheless, Senator was aware of the absence of data on this point and his caution against apodictic statements is almost a classic for medical research (p. 35): ‘An assumption certainly is not equivalent to a direct proof, but, in the absence of any such, it is perfectly justifiable as long as it cannot be shown that here is an error in the facts upon which it is based, ... and until we have direct proof of the contrary’.
Is some albumin potentially not captured by the then available technique?

Senator writes cautiously (p. 7) that ‘the term “albumin” is of limited significance, since it does not describe the excretion of one and the same albuminous substance; in addition, substances have recently been discovered in the urine which are deficient in the capacity of coagulation’ (i.e. heat coagulation). In this context, he points to peptones as potential degradation products of albumin (p. 8): ‘Not merely as a result of digestion, but likewise in consequence of...incipient putrefaction albumin undergoes modification...It is quite conceivable that in certain morbid conditions the ordinary albuminous substances...become so changed as to lose their coagulability on boiling and their capacity for precipitation upon the addition of certain acids and metals’.

(A fascinating note of caution the relevance of which is illustrated by the current work on modified non-immunoreactive albumin in the urine [23].)

Is albumin present in the urine of healthy individuals?

Senator stated (p. 15), ‘The question as to whether under normal conditions the urine does or does not contain albumin must always form the starting point for all investigations with regard to albuminuria. That this question should be raised at all may seem heretical...as it is regarded as long since disposed of and answered in a decidedly negative manner. However, in spite of...the doctrine that normal urine does not contain albumin, and that albuminuria is invariably a sign of disease, most recent observations...show that exceptions exist to the dogma...’. This change of opinion was caused by the demonstration that, without any renal disease, small quantities of albumin, formerly overlooked, could be found in urine (p. 16).

‘Improved methods of investigation and the discovery of delicate reactions have resulted in the discovery of albumin in very many instances, but in minute quantities, in the urine of perfectly healthy men, and this albumin, so far as it was possible to judge from these small quantities, differed in no respect from the albumin of the ordinary forms of albuminuria’.

He was well aware of the fact that no (demonstrable) albumin was not the proof of the absence of albuminuria. On repeated occasions, he made the point that albumin might well be found consistently if the method were sufficiently sensitive and therefore fought against the concept proposed by others of differentiating between ‘physiological’ and ‘pathological’ albuminuria (p. 21).

(This has recently been well documented by more specific methods.)

How frequently is albuminuria found in normal individuals?

Even more surprising are the figures he reports for the prevalence of trace albuminuria in healthy subjects (p. 18):

- 6 out of 119 healthy soldiers at rest and
- 19 out of 119 the same healthy soldiers after a march

- 24 out of 200 healthy persons undergoing life-insurance investigation
- 7 out of 61 healthy children
- 14 out of 32 healthy nurses.

(These figures are in reasonable agreement with some recent epidemiological studies in the general population assessing the prevalence of microalbuminuria using immune detection methodology, e.g. the PREVEND [24], HUNT [25] and NHANES studies [26].)

Only in passing he mentions an occasional finding of albuminuria in a diabetic patient. Of note, the methods available to Senator unfortunately precluded exact quantization of the amount of albumin present in the urine.

What is the variability of urinary albumin excretion?

Senator and three of his young colleagues carried out self-experiments measuring albumin in the urine at different times in the day and over prolonged periods of time, carefully discarding the first portion of urine to avoid admixture of semen or prostatic fluid. The presence of detectable albumin fluctuated considerably in the course of this investigation, but it was most frequently demonstrable in the morning hours and after a meal (p. 19).

(From his manuscript, it does not become clear what Senator’s explanation is why in some subjects he found more albuminuria in morning hours. It contrasts his own observations on exercise induced albuminuria. In retrospect, it might be that this was due to night-time urine concentration, making it easier to measure trace amounts of albuminuria.)

Which factors influence the appearance and intensity of albuminuria?

He reported that the frequency of demonstrable albuminuria in healthy individuals increased after ingestion of a meal:

- in 88 children from 3.6% before a meal to 19.3% after a meal
- in 32 soldiers from 15% before a meal to 40.6% after a meal.

Ancillary observations in patients with massive albuminuria and presumed kidney disease showed that albuminuria increased upon consumption of animal protein such as meat and eggs (p. 146). Furthermore, physical exercise significantly increased the amount of albumin excreted in the urine. He pointed to the potential value of these factors in the treatment of patients with chronic kidney disease (pp. 142–153).

What were the conclusions concerning underlying causes of and risk from albuminuria?

Senator admitted that he did not have the evidence, but suspected the cause was minor lesions of the kidney, but in the days before the availability of renal biopsy he obviously could not prove this assumption. Nevertheless, he concluded that such individuals should be followed to pick up potential deterioration in their health status. This notion was taken up by life insurance companies. In 1893, the Life...
Assurance Medical Officers Association was founded in England and at its opening symposium a paper was read on the significance of slight degrees of albuminuria and its possible consequences for life insurance companies [27]. The first prospective follow-up data were obtained even before the First World War, i.e. a century before HUNT [28], PREVEND [29] and others provided evidence that low-grade albuminuria is associated with higher risk for mortality. Barringer and Warren reported on the follow-up of subjects having undergone medical examination for life insurance companies [30]. Out of 396 subjects with albuminuria during their insurance health check, 70 were rechecked 10 years later. Of these 70 subjects, 22 had persistent albuminuria and 10 had suspected or proven chronic kidney disease with casts in the urine. The most relevant figure is that 25 had died against 16 expected from life insurance tables. The authors concluded that this was too small a sample to draw definite conclusions, but amazingly the risk increment is almost exactly to what has been observed in recent large-scale prospective studies, i.e. relative risk for all cause mortality in subjects with microalbuminuria [28,29].

What was the impact of Senator’s work? At the end one may pose the question: why was such important work so thoroughly forgotten although it had been so highly appreciated by the contemporaneous medical community [19,31,32]? One explanation might well be the difficulty of the measurement of albuminuria using the methods adopted by Senator, which required much attention to detail. The result was its substitution by the easier to perform nonreactive urinary albumin.

Conflict of interest statement. None declared.

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