Commentary

Rayer divided his history of albuminous nephritis into four parts, corresponding to the various combinations of the three hallmarks of the condition, i.e. diseased kidneys at autopsy, dropsy in life and a finding of albumin in the urine. The accounts take us from the earliest writings, through the Renaissance period to the pre-Bright era and then onwards to the more contemporary studies immediately post Bright, which were mainly conducted in Rayer's own department. The first part describes dropsy associated with diseased kidneys; the second part concerns the combination of albuminous urine and dropsy and also where urine low in urea and salts had been found; the third part brings the triad of albuminous urine, dropsy and renal lesions together. It is in this section that Bright's work is critically examined and questioned. In the final part Rayer outlines his main recommendations and conclusions.

In this commentary references have been omitted in favour of a Selected Bibliography that comprehensively covers the history of renal medicine, in particular the areas of controversy arising from Rayer's text. Fundamentally, Richard Bright described three types of nephritic kidneys at post mortem associated with albumin in the urine and clinical dropsy during life; his work provided a benchmark from which all further research on the subject would evolve. In the eyes of the medical world his description finally separated renal dropsy as a clinical entity from that of cardiac or hepatic dropsy. Nevertheless, he could not have anticipated the frenetic activity that his publication would engender, not only in the medical schools of England, but also in those of Scotland, Ireland and France. Thus, Bright's work provided not only the baseline, but also the stimulus, for his contemporaries, first to confirm the authenticity of his clinico-pathological triad, and then to add further, often egocentric comparative interpretations to his or their own findings. In fact, many of them did little to improve on Bright's classical description. In order to get the text in perspective it is worthwhile casting a backward glance at several important areas which could explain some of the often acrimonious polemical debates that arose amongst researchers into nephritis in the immediate post-Bright period. Two factors had an essential bearing on the diagnosis of nephritis: the first being the precise body of knowledge relating to clinical syndromes, renal pathology, renal function, urine and urinalysis available to physicians in the mid-nineteenth century, and the second being the prevalent demography of that age which was critically important given that the pattern of diseases then was completely different and could at times obscure correct diagnosis.

Both these points, plus the fact that diseases including dropsy were ineffectively treated and seen at a more advanced stage, make our modern assessment of the data fallible, even with the advantage of hindsight. Retrospectively, it is salutary to examine the pitfalls that might have been created by ignorance of up-to-date concepts available to present-day nephrologists and which led to misconceptions about what did or did not constitute nephritis at that time. As most of Bright's original patients died, he attributed an overly grim prognosis to renal dropsy. This finding was challenged at an early stage by his contemporaries and could be explained by the lack of young patients suffering from

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the more benign acute scarlatina nephritis in Bright's cohort. He modified his views with regard to mortality in his later studies. In fact it was Rayer who recognized and differentiated acute from chronic nephritis as he took a more clinical view of the disease than Bright, who had concentrated more on its pathological aspects. Longitudinal studies of disease were virtually unknown and therefore the perception of a disease such as nephritis having a prodromal stage, lead time, and a natural history measured by careful follow-up to recognize remissions, relapses, prognosis and sequelae was only just emerging.

Precise diagnosis had to await post-mortem examination, and that could only capture an instance in the evolution of the disease, a snapshot rather than a moving picture. Additionally, post-mortem changes must have added to the confusion. If the patient survived, the diagnosis of nephritis remained conjectural, and this fact alone created most of the debate. It would be another hundred years before serial renal biopsies would record the progressive histological changes of the various types of nephritis. An early death within days or weeks was very much the norm in patients at that time, often hastened by inappropriate depletion therapy such as bloodletting, diuretics and purging. Notwithstanding, one can only marvel at the simplicity and purity of Bright's classification achieved by painstaking study, perspicacity, and some degree of serendipity. The three types of kidney he described: the large red kidney of the acute nephritic syndrome, the large white kidney of the nephrotic syndrome and the small granular kidney of nephritis are very much as we encounter them today, albeit without the confirmatory histology of a renal biopsy.

We now know that the large white kidney was found to be infiltrated with amyloid, but this fact did not alter the basic concept of three types of kidney. It was not only simple, but also pure, because his classification was unadulterated by a mass of irrelevant renal pathology which blighted many of the studies that were to follow, including to some extent that of Rayer. It soon became apparent that many centres were using ''Bright's disease'' or ''maladie de Bright'' as a portmanteau term for almost any albuminuric patient, and some very odd and inappropriate pathologies were trapped in the same bag.

The epidemiology of the diseases that affected the population in the nineteenth century had a strong influence on the finding of albuminuria and, ipso facto, often led to an erroneous diagnosis of nephritis. Several common diseases of that period—mainly smallpox, tuberculosis, syphilis, gout, diabetes, amyloid disease from chronic infections, hydatid disease, scurvy, mercurial treatment, lead poisoning and others—had associated nephropathies accompanied by albuminuria. This was an age before the discovery of bacteria, but inevitably infections predominated, and any of those specific to the kidney or the genito-urinary tract could produce albuminuria: venereal disease with a urethral discharge was a potent source of albumin for example. In fact, many pathologies of the kidney and its appendages, such as cancer, calculi, cysts or hydronephrosis, could lead to a finding of albuminuria. The illnesses were not only often different, but also their natural histories frequently departed from the accepted modern pattern.

Additionally, the case mix of patients in the different studies described by Rayer resulted in heated discourse, as like was not always compared with like, for instance, as we have already stated, the bias created by predominantly post-scarlatina nephritis carried a more favourable prognosis than some other types of nephritis. Of course albuminuria was present not only in many diseases of the kidney and the genito-urinary system, but also could accompany febrile illness and congestive cardiac failure. We now know that the antibody

response to infection is the predominant pathogenic mechanism in nephritis, and this was indeed an age when infections were rife.

As far as renal function and its measurement was concerned it was not surprising that examination of the urine predominated as the yardstick and was one of the few indirect tests of a corresponding dysfunction. Although the balance between fluid intake and urinary output was recognized, confusion arose from low and high output renal failure. Quantitative studies, including weighing of twenty-four-hour urine collections and measurements of the specific gravity of blood and urine were employed. The reciprocal relationship between urea and albumin ratios of blood and urine of certain dropsical patients was known. However, most of these tests could not be replicated with sufficient accuracy to be used routinely in most of the comparative studies. Although it soon became obvious that dropsy need not develop, to sustain a diagnosis of nephritis the presence of albumen in the urine was the sine qua non. The quality of urine testing militated against this essential finding, however, as cloudy urine and false positives could be caused by the presence of urates, phosphates and certain foods, medicinal oils and herbs. Until the need for combining boiling with the addition of nitric acid was appreciated, the tests for albumin were not reliable. Finally, it is worth looking at both the clinical manifestations of nephritis today and some of the pathogenic mechanisms involved. Nephritis may be present in several ways, such as asymptomatic persistent proteinuria without oedema; the nephrotic syndrome; the acute nephritic syndrome; and nephrosclerosis, i.e. secondary hypertension. The latter could produce effects similar to the decline of renal function in progressive nephritis, including the full gamut of cardiac and cerebral complications and the protean manifestation of uraemia affecting every system of the body, either individually or collectively.

It would have been difficult in the nineteenth century to conceive that some renal dropsy patients might have normal renal function; that acute renal failure could result from so many different insults to the kidney, including nephritis, and that there existed a tubulo-interstitial type of nephritis which could lead to progressive fibrosis.

The many disparate mechanisms causing renal dropsy, such as hypoproteinaemic proteinuria of the nephrotic syndrome; the oedema of the acute nephritic syndrome precipitated by capillary leakage and a reduced renal function and urinary output of acute renal shutdown; the oedema of end-stage chronic nephritis attributed to reduced renal function and fluid overloading; and the back-flow oedema of acute or chronic obstructive nephropathy would all certainly have wrought some confusion amongst our predecessors.

The significance of renal disease inducing raised blood pressure and conversely the finding that advanced essential hypertension produced small smooth contracted kidneys almost identical to those of chronic nephritis would not have been appreciated. A further area of controversy was created because the latter group of patients might not always have albuminuria.

One of the most controversial areas, besides the hypertension story, was the appearance of albuminuric dropsy in the absence of any obvious renal disease at post mortem. We must assume that these cases were examples of minimal lesion nephritis or focal glomerulosclerosis without obvious macroscopic changes in the kidney.

The absence of albuminuria in a patient with small kidneys is still very puzzling and in fact to this day it is not clear whether, after an episode of acute nephritis, a patient passes

through an occult non-albuminuric phase in the progression towards an end stage contracted nephritic kidney. The bilateral small yet irregular kidneys of aseptic chronic pyelonephritis could also be mistaken for the small contracted appearance of chronic nephritis.

Some of the terminology used in the nineteenth century requires some explanation. The middle of that century was a nosographic hinterland as workers searched for a universal nephrological language. Several synonyms were used to signify dropsy or intracutaneous water as it was called then, such as anasarca, or leucophlegmasia. Most of the other terms are merely outdated and in the context, their meaning can be understood, such as ischuria, emulgent and oligotrophy. Two words have proved difficult to place, however. Alchatin would seem to be of Arabic origin and is generally thought to mean the loin or groin, or perhaps even a flux from either of these regions. Abotryoidal probably relates to granulation of the pyramidal region of the kidney.

With this wealth of background information let us now examine the text and explore some of the more interesting passages.

In part one there are several points worthy of comment. One is struck by the fact that the ancients were fully aware of the connection between kidney disease and dropsy, but that information seems to have been lost with the diuresis of time, only to be revealed again by subsequent generations. The study of the kidney seems to have attracted many of the great names in medicine such as Hippocrates, Boerhaave and others. This section is a mishmash of inconsistent descriptions with an over large number of reports mentioning only one kidney. Although ''openings'' or post mortems were not undertaken with any great frequency, it is still strange that the concept of bilateral involvement of the kidneys was not recognized by these early workers as an essential feature in dropsical patients. However, towards the end of this section Barbier, writing in 1827, corrects this impression by describing bilateral contracted kidneys. Similarly, the high instance of pain in the loin, fever and burning micturition suggests infection, supported further by mention of a lavatorial smell from the urine. Renal stones, probably also infected, are often cited, but presumably the description of bilateral calculous kidneys refers to hardness rather than stone-laden kidneys. Many cases of obstructive nephropathy are reported as a cause of dropsy and several of the contributions attempt to explain how dropsy is formed. Most of these suggested a hydrodynamic back-flow theory as this was the perceived mechanism that was in vogue then.

Serosity of the blood, tenuous or thin urine are mentioned, and indicate that some attempt was being made to explain both how the kidney filtered water off from serum and other ways in which dropsy could develop. Van Helmont, writing in the eighteenth century, seemed to have been prophetic when he attributed to the kidney the role of ''maker, achiever, performer and governor of true dropsy''. He also recognized that renal calculi did not produce dropsy. Equally, Van der Linden, a century before, had suggested that if the kidneys did not function ''waters flow back and infect the whole household''.

The reference to Renaissance writers indicates that Rayer assumed that his readers would know who they were; in France the greatest French physician of that period was Jean Fernel and Humanism was the governing belief, with many followers of whom the better known included Linacre, Paracelsus, Leonardo da Vinci, Vesalius, and Ambrose Paré.

It is interesting that several reports state that death occurs after about eight days of total anuria or ischuria as it was called then. This is a very accurate estimation. Hypertrophy of the kidney is reported both in the presence of a single congenital kidney and as a compensatory phenomenon following disease of one kidney. Several authors noted that the cerebro-spinal fluid could become uriniferous in nature and odour. The mention of Scottish medicine by J. P. Frank's students refers to the Brunonian School and theory named after the disputatious and disreputable Dr. John Brown.

Brown's theory, which held sway for a quarter of a century and encouraged much hot debate sometimes leading to violence, was based on whether a disease excited or depressed the body, so that the appropriate antidotal therapy could be given, i.e. suppression or stimulation respectively. It is said that his therapeutic ideas killed more people than the French Revolution and the Napoleonic wars combined.

Sauvages's account of ''anasarca urinosa'' is interesting as it clearly describes the back flow oedema of obstructive nephropathy. Rayer credits Barbier with the description not only of two small kidneys which were a quarter of the normal size, but also of the milky colour of serum or blood in nephritic patients. Rayer is at pains to emphasize the vagueness of many of the reports in this first section, but contends that the case for renal involvement as a cause of dropsy has been proven, although few of the descriptions relate to albuminous nephritis.

In part two, where patients with albuminous urine and abnormal kidneys are discussed, Cotugno is accredited with the first description of albumin in the urine in 1770, but Rayer surprisingly disagrees with his theory that albumin could leak through the kidney into the urine, in other words protein-losing nephritis. Many of the arguments are distorted by the inclusion of several examples of patients with diabetic nephropathy. However, one important finding in this context was that the more dilute the urine became the less albumin could be detected.

Wells's studies, which had been conducted in 1798 but not published until 1812, were carried out largely in patients with post-scarlatina nephritis and are described in detail. He emphasizes the importance of haematuria in the diagnosis and also the use of both heat and nitric acid to detect albumin. One of the most remarkable aspects of his studies was his experiments, in which he added both blood and serum in different proportions to urine in order to quantify urine testing from albumin; this was remarkably innovative.

Rayer notes that Fordyce was the first to describe the combination of renal lesions and coagulable urine. One of the most significant findings arose from the collaborative study in which Baillie and Brande compared the urine from patients with renal and liver dropsy. In 1807 they became the earliest to record the albumin and urea content of the urine in order to differentiate these two conditions.

Nysten, one of the earliest renal biochemists in France, notes frothiness of the urine as an indication of diseases of the kidney and Rayer recalls Hippocrates' aphorism describing bubbles in the urine of kidney patients. Even more fascinating is Nysten's description of the high urea content in a patient with acute peritonitis, which probably represents the first description of the hypercatabolic state of acute renal failure.

Chapotin's topographical studies of the inhabitants of the Île de France, now modern day Mauritius, are of great interest as they represent one of the first descriptions of nephropathy

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secondary to tropical infections, such as malaria. The only other possibility was that in an island community there may have been familial nephropathies and this is supported by the fact that the condition seemed benign, which might favour this latter proposition. There is a full description of Blackall's work in which Rayer disagrees with his policy of bloodletting relating to the phlogistic nature of nephritis. Blackall also noted the fibrinous state of the blood in renal patients.

Alison describes one interesting patient of Gregory's who survived nine years after an initial attack of dropsy and then died a year after a relapse; this is one of the earliest records of a reasonable period of follow-up of a patient with nephritis.

Rayer's admonishment of Crampton for not testing the urine in his studies of dropsy at Steeven's Hospital, Dublin, is amusing; even Bright sometimes omitted to test the urine in life and had to resort to sampling the bladder urine at post mortem. Most of the articles discussing the treatment of dropsy can be disregarded as the regimes were still based on the old fashioned precepts already discussed, for example sthenic versus asthenic. In fact Prout, not to be confused with Proust, strongly recommends discarding most therapies in dropsy as they are ineffective. Deservedly, Scudamore's seminal work on gout is mentioned as yet another example of a protein-losing nephropathy.

This part ends with comments on the work of Howship that show that Rayer was aware of the need to differentiate albuminous urine from that containing pus or mucus.

The third part is much the largest and occupies over half of the historical section. It is devoted to a great extent to more contemporary works, including those of Bright and his team. Rayer records that Bright describes, in addition to his three main types, a further two deranged conditions of the kidney, one in which the tubules are infected and blocked with small concretions—it is tempting to speculate that this was either an interstitial nephritis or possibly a medullary sponge kidney. Bright did not presume that his descriptions were sacrosanct or unimpeachable. He left the interpretations of some of these findings to others—this may have been a mistake because there is little doubt that Rayer, Christison, Martin Solon and others rose to the challenge and added several extra types. The reason might have been that Bright suggested that his three types represented a continuum in the progression of nephritis and his contemporaries were merely looking for the "missing links" in the pathway.

Rayer describes Christison's work in full as he was one of the first to confirm Bright's findings and more importantly was the earliest to record the presence of urea in the blood of nephritic patients. Rayer records Graves's criticism of Bright's work, which evolved around prognosis. It will be remembered that Bright's original cases were fatal, but it soon became obvious that one could survive following acute nephritis, particularly after an attack of scarlet fever. In addition it seems likely that some of the patients who recovered were suffering from the relatively benign minimal lesion nephritis. Bright did in fact suggest that a functional state of the kidney rather than a pathological one could allow albumin to leak into the urine in a manner similar to that found in minimal change nephritis.

Rayer rightly pays tribute to James Craufurd Gregory, who introduced four groups of nephritic patients based on a prognosis which brought a further realization that nephritis can exist without dropsy or death. In addition, this young doctor, who died prematurely, introduced the concept of normal controls when testing the urine in dropsy.

There then follows further evidence that patients could recover from dropsy and enjoy good health, thus supporting Rayer's recognition of the acute forms of the disease. The difficulties of separating cardiac dropsy from renal dropsy when the latter presents with pleurisy, pericarditis and peritonitis are outlined. Copland's attempt to classify nephritis into primary and secondary forms is laudable and he reiterates the finding of albuminous urine in children with eruptive fevers; but Rayer is doubtful about the wisdom and accuracy of both these statements. It is possible that the dropsical patient with clear urine whom Burrows of St. Bartholomew's Hospital showed to Bright, represented one of the earliest examples of hypertensive nephrosclerosis, the existence of which Bright had suspected. Anderson's efforts to categorize several diseases according to whether the urine is coagulable or non-coagulable represented progress and he also noted the association between nephritis and rheumatic fever which, like scarlatina, was common at that time. It is interesting that at this stage in the text Rayer distinguishes infections from affections of an inflammatory nature in the kidney. Osborne describes fibrinous blood in the renal vein with a caseous consistency suggestive of thrombosis, but Rayer had already described renal vein thrombosis and does not comment on the similarity. Corrigan describes two kidneys and speculates, as others had done, that they might represent successive stages of the same disease. Mateer's contribution inculpates anaemia of the kidney as a cause of dropsy and suggests that diuretics could reduce albumin loss—it can only be assumed that the diuretics were not mercury; a potent source of albuminuria. He proposed that in febrile diseases as the temperature settles albumin also disappears from the urine, in other words a "*crisis per urinas*" occurs; a rather novel yet possibly accurate proposition.

At this stage after commenting on Robert Willis's classification of albuminous urine depending on whether it was serous, oily or fatty, Rayer proudly presents the work of his own department. Like Bright, he had built a team of top-class young research workers, both doctors and students at l'hôpital de la Charité in Paris, and many of them defended their theses or dissertations on renal disease publicly, as was the practice in France at that time. A great deal of their work attempts to hive off the non-nephritic, yet renal, causes of albuminous urine.

Tissot's account of the renal changes found in pulmonary tuberculosis is suggestive of secondary amyloid and renal vein thrombosis. His insufflator test to detect albumin was ingenious if a little unreliable.

Sabatier, Rayer's intern, who sadly died at an early age, introduced a very plausible and modern explanation of how oedema forms in albuminous nephritis. He suggested that as a result of the decreased levels of albumin and the loss of drawing power in the blood there was a leakage of fluid into the tissues, which is very close to the present day theory of hypoproteinaemic oedema. Rayer is not impressed and compounds his error by indicating that the dropsy of acute post-scarlatina nephritis could not be explained by Sabatier's mechanism as it occurs before there is sufficient loss of albumin, which is perfectly true in that specific instance, but not in others. Desir extends Tissot's work in Rayer's department and excludes several other albuminuric diseases from the nephritic classification, including smallpox, venereal diseases, urinary infections, renal tumours, tuberculous kidney and hydronephrosis, and the sweet albuminous urine of diabetes.

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All this work is very creditable but would not have been necessary if Bright's classification had been adhered to in the first place. Rayer quotes Forget's letter to him and it is interesting that the latter uses the word albuminuria instead of albuminous nephritis. Yet another of Rayer's team, Genest, reiterates previous findings of the department without adding anything original to our understanding of dropsy. Guillemin describes septicaemia following paracentesis for ascites; a complication of which Bright was well aware. Bureau, another Rayer student, writing in 1837, brings the research full circle, almost to the stage that Bright's work had reached ten years previously.

Martin Solon's work, which closely followed that conducted in Rayer's department, caused the latter some concern and he took issue on several matters, devoting a disproportionate amount of space to the debate; the arguments are largely semantic revolving around the use of the word albuminuria. Martin Solon's classification of albuminuria seems admirable enough, apart from the fact that he describes five types. Nevertheless, he recognizes a sub-acute and latent form of the disease and is aware of the loin pain of acute nephritis. Rayer rightly criticizes the fact that there are small numbers in each group and in criticizing Martin Solon's work, he invokes the opinions and support of Littré, who accurately described the large red kidney with small red Malpighian corpuscles, i.e. glomeruli, the large white kidney and the small granular kidney, just as Bright did. Interestingly Littré rather dismisses the other types in Rayer's classification on the grounds that, as we suspected, they are meant to represent transitional stages, i.e. the missing links between the basic types. It is particularly fascinating that, like all the best studies on nephritis, Martin Solon followed the tradition of illustrating his book with kidney drawings just as Bright and Rayer had done and for that reason alone he deserves careful consideration.

The third part ends with Valentin's and Gluge's studies on the microscopic appearance of the kidney in nephritis, thus heralding the beginning of a new era that would ultimately lead to a histological classification of the condition.

In the fourth and final part, which comprises only a few paragraphs, Rayer outlines his conclusions and recommendations. He bemoans the fact that from ancient times his medical colleagues, although appraised of the manifestation of kidney disease, were unable to come to firm conclusions; the answers were there to see, but were overlooked. He noted the well-recognized phenomenon that each subsequent generation had to rediscover the basic criteria of any given disease. He reiterates that which is his main contribution to the natural history of nephritis, i.e. that acute and chronic forms exist and can be recognized by careful urinalysis. Rayer thus emphasises the importance of urine testing to distinguish acute from chronic forms of nephritis. He concludes by exhorting future nephrologists to follow-up their nephritic cases, not only in an attempt to prevent relapses but also for a better understanding of the underlying pathophysiological mechanisms of the condition.

Professor Gabriel Richet, the eminent Parisian nephrologist and medical historian, has extolled the virtues of his great French compatriot. His account provides a balanced critical study of the man and his work. Being neither hagiographic nor eulogistic, it simply outlines his major impact on the study of the kidney through meticulous note taking and

illustrations of the kidney at post-mortem examination, with his understanding of the subject complemented by his knowledge of the history of renal disease.

Indubitably, Rayer took another step along the pathway towards a fuller comprehension of nephritis in the immediate post-Bright era and he stands tall in the pantheon of pioneering renal physicians. Both Wells and Bright had recognized the defects in their work and had suggested that someone in the future would fill the gaps that they had left. To a certain extent Rayer fulfilled that role and his work deserves greater recognition in the English-speaking world of medicine.

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