The Rise and Fall of Acute Tubular Necrosis – An exercise in medical semiotics

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ABSTRACT

Ideas require words for their expression and words are sharp instruments, potentially dangerous if used unwisely. Inappropriate selection of words to convey a concept can powerfully inhibit progress that otherwise may have flowed unrestrained had superior linguistics prevailed. The syndrome associated with systemic manifestations in patients who experience rapid increases in serum creatinine concentrations provides an excellent example of this. Observers have used many terms over centuries to describe this condition, with one of them, 'acute tubular necrosis' (commonly 'ATN'), providing a particular example.

Graham Bull, A.M. Joekes and K.G. Lowe introduced this phrase in 1950 to escape from previous inadequate terminology bedevilling a then recently redescribed condition. They envisaged a unifying pathogenetic mechanism that would underlie all cases. Enthusiastic to improve therapy, they relied heavily on observations made by others to justify their novel terminology. Many adopted it: it gained huge traction and current textbooks continue to employ it. Yet as early as 1962 investigators such as Ernest Finckh had demonstrated quite unequivocally that it seriously failed the task assigned to it. Other unsatisfactory terms such as 'acute renal failure' of 1951 have come and persisted somewhat uncomfortably alongside it until challenged by 'acute kidney injury' in 2007, yet even this has weaknesses.

The present communication reviews the linguistic history of this field over the past 75 years, the backgrounds of some of the people involved, and the importance to the scientific enterprise of care in choice of vocabulary.

KEYWORDS: Acute tubular necrosis, Acute kidney injury, Acute renal failure

Introduction

Sudden cessation of renal function often has catastrophic clinical consequences. It must always have occurred since typical precipitants of it have existed for millennia. Even though physicians have observed patients and documented their findings over all those years a succinct description of the condition failed to impact broadly upon medical consciousness until the mid-20th century. It then took the mass destruction that accompanied ruthless bombing of civilians during World War II, together with astute conceptualisation by a few physicians, to create a composite awareness within the medical community that such a phenomenon does indeed often occur under appropriate circumstances, and to generate terminology that gained wide traction with which to describe it.

The pathway of knowledge about this condition that led from ancient times through to the 1940s was tortuous, at least in part because of the disorganised terminology that clinicians used to describe it. Garabed Eknoyan presented a comprehensive overview of this to a previous meeting of the International Association for the History of Nephrology (1). He outlined the plethora of words that various authors had used, together with their approximate dates of adoption. They ranged from ischuria renalis (1760) to renal inadequacy (1879) followed by hysterical ischuria (1888), acute Bright's disease (1888), vasomortoric nephrosis (1917), war nephritis (1917), toxic tubular nephritis (1918), toxic degenerative nephrosis (1923), toxic nephritis (1923), necrotizing nephrosis (1923), acute tubular nephrosis (1923), traumatic nephritis (1937), acute haematogenous interstitial nephritis (1938), acute toxic nephrosis (1938), transfusion kidney (1940), crush syndrome (1941), pressure ischaemia (1941), traumatic anuria (1942), compressive syndrome (1942), crush kidney syndrome (1944), traumatic uraemia (1945), lower nephron nephrosis (1946), haemoglobinuric nephrosis (1947), shock kidney (1948), acute uraemia (1949), and eventually acute renal failure (1951). The great American nephro-physiologist, Homer Smith (1895-1962), was probably responsible for introducing that last term and for propelling it into prime position for everyday use until 2007 when yet another iteration occurred: *acute kidney injury* (2). *Acute renal failure* however had a competing phrase that emerged at about the same time as it and that addressed much the same phenomenon: *acute tubular necrosis*. The latter achieved considerable traction among clinicians and indeed continues even now in occasional use, but it soon met with some well-justified criticism. The purpose of the present communication is to examine the historical background of *acute tubular necrosis*, its rise to prominence, debates about its nature, and its gradual fall from grace.

The historical background

Richard Bright's (1789-1858) publication in 1827 of his *Reports of Medical Cases* focussed attention on diseases of the kidneys, and thereby publicised renal disease as a fertile field for medical research (3). His proposals encouraged study of the mechanisms of damage to the kidneys, and the development of diagnostic criteria by which to group individual cases. The earliest challenges that investigators faced arose at several levels—clinical, biochemical, histological, and philosophical—and nowhere were they more pertinent than in situations where renal function deteriorated rapidly. The clinical challenge was to correlate changes in the urine with concurrent manifestations occurring in other organ systems, all with apparently diverse antecedent triggers. Biochemically, the initial challenge revolved around understanding the metabolism of urea, but soon moved on to addressing the roles of other nitrogenous and non-nitrogenous substances based upon their levels in the urine and the blood. The histological challenge was to improve techniques by which to examine tissue, surmount the limits imposed by the availability only of autopsy material, and to

interpret the changes observed. Philosophically, many observers sought to identify unifying pathogenetic explanations for similar manifestations in patients where the causes of those manifestations clearly differed.

Clinicians placed major diagnostic significance on identification of abnormalities in the urine during the first century after Bright. Albuminuria and haematuria in particular focussed attention upon the likelihood of renal disease. The description of urinary casts in 1844 by Friedrich Henle (1809-1885), following the latter's landmark description of epithelial cells elsewhere in the body seven years earlier, created yet another diagnostic dimension (4). Observers distinguished blood casts as well as epithelial, hyaline, granular, fatty, hard, and waxy ones. Protracted debates arose over their differential significance (5). A consensus however evolved by the turn of the century about the implications of the epithelial ones: they implied desquamation of the lining of the renal tubules, suggesting that disease had damaged these. Changes in the volume of the urine, especially anuria, also attracted diagnostic attention but interpretation of this was difficult: reduced volume could occur in many situations, often quite physiological, so only complete anuria accompanied by other systemic manifestations of disease provided a reliable indication that the kidneys were suffering. Oedema was clearly significant, but distinguishing between cardiac or hepatic or renal disease to explain its genesis, and in the renal situation explaining its association sometimes with proteinuria but sometimes not, created a great diagnostic dilemma. Indeed the prominent concurrence with urinary abnormalities of manifestations in other organ systems—of symptoms such as anorexia and vomiting, of breathlessness, convulsions, coma, rashes and itch, of profound weakness, and many more—created great confusion. Added to all of this was the wide range of apparently antecedent conditions that sometimes presaged the development of renal disease: exposure to cold, or to extreme heat; infections such as scarlet fever, small pox, chicken pox, measles, malaria (with blackwater fever as a particular example), typhoid, erysipelas, or pneumonia; chemicals that included alcohol and several then fashionable drugs such as turpentine, phosphorus and mercury; and diverse other conditions, even burns. All these issues posed intellectual challenges for clinicians to interpret.

The biochemical underpinning of acute renal impairment developed equally slowly. Hillaire Rouelle (1718-1779), working in Paris, first identified urea in 1773 when he extracted from urine a soapy material that dissolved in alcohol (6). Antoine de Fourcroy (1755-1809), Louis Vauquelin (1763-1829) and William Cruikshank (1745-1800) soon followed, leading to the naming of the substance as *urée*. Jean Prévost (1790-1850) and Jean Dumas (1800-1884) in Geneva provided the first evidence in 1821 of its accumulation in acute renal impairment when they demonstrated its rapid rise in the blood of animals subjected to bilateral nephrectomy (7). This in turn led to the proposal of the term *urémie* in 1847 by Pierre Piorry (1794-1879) to describe a key chemical manifestation of renal failure (8). Suggestive as was his work, great controversy persisted throughout the 19th century over the clinical measurement and role of urea in human disease, with many researchers denying its significance. The introduction in the early 20th century of improved methods of venesection, followed by the development of micro-analytic techniques, allowed the measurement of serum urea in patients suffering from apparent renal disease to enter routine clinical use. Then creatinine emerged: Max von Pettterkofer (1818-1901) in Munich discovered it in the urine in 1844 and Jacob Volhard (1834-1819) synthesised it in 1862, but it was not until 1926 that Poul Rehberg (1895-1985) suggested using its rate of excretion as a measure of renal function (9). Although uric acid retention in renal failure was identified early (uric acid was discovered in 1776, renal retention identified in 1848) awareness that perturbed levels of various other inorganic chemicals could occur in renal failure developed only slowly. Some prominent examples were of phosphorus (discovered 1669, retention in renal failure identified 1913), hydrogen (discovered 1766, uraemic acidosis described 1887, pathological significance speculated 1912),

sodium (discovered 1810, toxicity of salt in renal failure proposed 1909), and potassium (discovered 1810, clinical significance recognised 1949). A biochemical underpinning for the diagnosis of acute renal impairment thus only emerged in the mid-20th century.

Developments in pathology were equally tardy. The latter half of the 19th century saw the progressive development of histological techniques as microscopes improved, and as workers devised appropriate sectioning and staining processes to facilitate ever more detailed examination of tissue. The unavailability in everyday practice of tissue from living patients however severely limited research. Interpretations depended upon autopsy material obtained at a variable time after morbid events had affected the kidneys. The clinicians responsible for the original introduction in 1951 of a technique by which percutaneously to biopsy kidneys anticipated that this would be of greatest value for the investigation of patients suffering from acute anuria (10). Previously to that observers had described a wide range of microscopic changes, the clinical correlations and implications of which for long gained little consensual acceptance. An account of acute renal impairment published at the turn of the century had mentioned changes in the glomeruli (a capsulitis with associated haemorrhages, and proliferation of cells within the capillary tufts), interstitium (inflammatory exudates especially adjacent to glomeruli), and tubules (an opaque appearance of their epithelial cells with swelling, and granularity of these; and with casts and other material blocking the tubules) (5). Histological discussion during the early years of the 20th century led to the drawing of an important distinction between renal diseases that appeared to be primarily of an inflammatory nature (designated as forms of *nephritis*) from those of a degenerative nature (designated as forms of *nephrosis*) (11). Physicians then subdivided nephroses into larval, necrotizing, chronic, and amyloid forms. Those designated as *larval* had albuminuria without apparent deterioration in renal function, and with a generally good prognosis. Those designated as *necrotizing*, in contrast, typically followed mercury poisoning, although also could complicate infectious diseases. If anuric, their prognosis was considered poor; with autopsy examination revealing large kidneys that microscopically had necrosis of the tubular epithelium, especially in the proximal tubules, cloudy swelling and vacuolar degeneration of remaining cells, desquamation, and some cellular calcification.

The philosophical impediment arose from an apparent fixation on the part of many clinicians that a single explanation must exist for the development of similar manifestations associated with the sudden impairment of renal function despite causes differing markedly between individual patients. Commentators appeared to overlook the fact that such an exercise involved bending observable facts to conform to the artificial construct that became known as *acute renal failure*.

These several factors—clinical, biochemical, pathological and philosophical— bedevilled understanding of the field of acute renal impairment throughout the century that preceded the events during World War II that permanently changed understanding of it.

The rise of *acute tubular necrosis*

The World War II battle that brought acute renal impairment to prominence was the bombing of London that occurred in late 1940. Collapsing buildings generated many civilian casualties. Observations on crush injuries led Eric Bywaters (1910-2003) and his colleagues to describe a series of cases of acute renal impairment in which release of myoglobin from damaged muscles (rhabdomyolosis) explained the mechanism of the consequent renal impairment (12). This was far from the first report of acute renal impairment or indeed of complications following crushing, but it focused attention on sudden cessation of renal function in a way that had not previously existed. It provided a clear sequence of causation leading to a persuasive pathogenetic mechanism that in

turn led to a distinct and highly threatening clinical picture.

Understanding crush syndrome fortuitously accompanied another medical development that had occurred during the war: namely the construction by Willem Kolff in The Netherlands of an artificial kidney machine with which he successfully dialysed a series of patients who suffered from renal failure. The cessation of hostilities allowed Kolff to promote his invention internationally, with the result that he took a dialysis machine to the Postgraduate Medical School at Hammersmith Hospital in London for Bywaters and his colleagues to use. The exercise was, unfortunately, far from successful in that the ten non-glomerulonephritic acute renal failure patients whom they treated had an 80 percent mortality rate (13). Bywaters' particular interest was in the musculo-skeletal aspects of crush injuries so a few years later he passed over treatment of the renal aspects to an enterprising young renal physician and physiologist, Graham Bull.

Graham Macgregor Bull (1918-1987), a University of Cape Town medical graduate, had previously undertaken several renal research projects. A South African Council for Scientific and Industrial Research Travelling Fellowship had taken him to London in 1947 where the British Post Graduate Medical School at Hammersmith appointed him as a lecturer attached to its renal service (14). He participated in March 1948 in the treatment of a young woman who had become anuric after suffering from toxaemia of pregnancy, complicated by a concealed accidental haemorrhage that occurred associated with delivery of a stillborn child. She received three successful dialysis sessions together with dietary and fluid treatment, however she remained anuric. Recovery was considered impossible, her treatment was withdrawn, she died, and an autopsy showed renal cortical necrosis (15).

This case led Bull to develop some guidelines for the treatment of anuric patients, documented in a highly influential article published in *The Lancet* in 1949 (16). It divided patients with more than four days' anuria, but excluding ones with pre- or post-renal causes, into three groups: 'lower nephron nephrosis' (due to mismatched blood transfusion, crush syndrome, intravascular haemolysis, abortion, or protracted 'shock'), toxic nephrosis (such as from mercury, carbon tetrachloride, or phenol poisoning), and acute nephritis. It excluded patients who suffered from malignant hypertension, bilateral cortical necrosis, or subacute nephritis as they were likely to die. It advocated therapy based on a conservative approach by prospectively preventing further deterioration rather than by interventional dialysis after deterioration had occurred. This method involved fluid restriction (less than 1000mL per day), avoidance of electrolyte (sodium, potassium and bicarbonate) administration, and suppression of exogenous and endogenous nitrogen metabolism. It reflected the views of the Dutch academic clinician, JGG Borst (1902-1975) whose approach Bull modified by inserting into patients a permanently indwelling naso-gastric tube through which to feed a high glucose and fatty peanut oil diet containing no nitrogen. Seven out of eleven patients with lower nephron or toxic (mainly mercury) nephrosis whom he treated in this way survived, leading to the conclusion that 'If the conservative management is instituted sufficiently early without previous overhydration, diuresis can be confidently anticipated in anuria due to any recoverable renal lesion'. A subsequent editorial in the *British Medical Journal* supported Bull's conservative approach, arguing against dialysis as too risky to undertake ('It seems clear that until artificial kidneys become safer they have no place in the treatment of acute renal failure'), and blaming previous medical mismanagement as the principal cause of the traditional view that anuria had a poor prognosis (17).

Bull and his colleagues published a further paper in 1950 entitled 'Renal function studies in acute tubular necrosis', pioneering the term *acute tubular necrosis* as a replacement for *lower nephron nephrosis* (18*)*. They described 34 anuric individuals, none of whom had evidence of acute nephritis, malignant hypertension, urinary obstruction, or gross infection. They tested how well

some of these could concentrate urine, conserve sodium chloride, excrete para-amino-hippurate, and reabsorb glucose; and they measured their renal plasma flow, renal oxygen consumption, glomerular filtration rate, and cardiac output. The renal disease appeared to run a similar course in all patients regardless of aetiology—passing through phases of onset, anuria or severe oliguria, early diuresis, and late diuresis (but the latter two phases only in survivors). They provided minimal histological information beyond stating that tubular damage existed in all cases and commenting that 'Anatomically the characteristic lesion is a necrosis and subsequent regeneration of the renal tubular epithelium'. This, to them, underpinned a unifying mechanism. The pathologist with whom they worked, J. Henry Dible (1889-1971) later wrote that in the tubules 'There was evidence of cellular necrosis' and that this appeared to affect the whole nephron (19). Bull and Dible went on to provide a more detailed histological description when they reviewed the topic three years later, claiming that tubular cell death was the cytological hallmark of the condition, whilst accepting that in the mildest forms cellular dysfunction rather than death might predominate. They also considered that a preliminary circulatory assault was the harbinger of secondary cellular necrosis (20).

Acute tubular necrosis soon became popular as a descriptor of acute impairment of renal function, existing alongside and rivalling *acute renal failure*, a term whose origin paralleled it. Clinicians on both sides of the Atlantic adopted it (21-24). Bull, after becoming Professor of Medicine at Queen's University in Belfast in 1952, built a major nephrological reputation by publishing further articles about, and lecturing on, the management of renal failure. He summarised his ideas about pathogenesis when his colleagues and he wrote in 1955 about pathological studies that showed 'In the mildest cases of renal damage there were only protein precipitate and protein casts in the tubular lumina. There then followed a series of increasingly severe degenerative changes in the tubular epithelium (which we call "acute tubular necrosis") and, finally, renal cortical necrosis, rated in order of increasing severity as focal, minor, patchy, and gross (25).'

Dissatisfaction with *acute tubular necrosis*

Perceived unsatisfactory overtones in the term *lower nephron nephrosis* had triggered the proposal of *acute tubular necrosis* as a preferable name for acute deterioration in renal function when it occurred in at least certain groups of patients. It was however not long before concerns arose in the minds of some observers about the appropriateness of the latter. The choice of the word *necrosis* was largely responsible for these. Authors had used this word in the English language since 1665 to indicate death of part of a person's body (26). The condition under consideration caused anuria often followed by polyuria and complete recovery. If the anuria was due to death of the tubular cells, and if death was absolute as everyone considers it to be, how could the kidneys recover and go through a polyuric subsequent phase? The claim that necrotic tissue could regenerate appeared to be a logical impossibility. The available histological examinations of the kidneys of anuric patients, furthermore, often showed no evidence of necrosis, but merely much milder changes, if indeed any at all. Additionally, when necrosis did appear it was often quite patchy, yet the anuria was complete. In summary, malfunction of the kidneys correlated poorly with necrotic histological features in them, yet the name applied to the condition indicated necrosis as its prime characteristic.

The fall of acute tubular necrosis

Two pathologists, Ernest Finckh (1924-2009) and Simon Sevitt (1914-1988), working a decade after the original proposal of the concept, publically challenged the simple notion that acute tubular

necrosis provided a satisfactory mechanistic explanation for the development of acute impairment of renal function in most affected patients.

Finckh, an Australian, had won a Nuffield Dominion Travelling Fellowship in 1956 that enabled him to work for a year in the Morbid Anatomy Department (Pathology Department) at University College Hospital, London. His project there was to study acute haemolytic crises induced in rats by the subcutaneous injection of glycerol. He returned to Sydney the following year and extended those experiments to examine effects on the kidneys. A controlled trial that he carried out on rats injected with subcutaneous glycerol produced unequivocal necrosis of the proximal convoluted tubules on histological examination, but demonstrated that the animals had significantly increased urinary volumes, rather than anuria, until well after the necrosis had developed. A similar trial carried out on unilaterally nephrectomised rats showed that temporary clamping of the artery supplying the remaining kidney produced similar results: tubular necrosis, but polyuria rather than oliguria or anuria (27). This suggested that the anuria was not a consequence of the tubular necrosis. He then followed this up by performing autopsies on 28 patients who had died with oliguric acute renal failure and on control patients who had died with no evidence of renal disease (28). He found that morphological changes in the renal failure patients were usually only slight, that they were sometimes entirely absent, and that they were only occasionally pronounced; that the control patients showed similar changes to those seen in the renal failure patients, albeit less frequently; and that none of the morphological changes in the renal failure patients correlated with clinical features in a way that would be expected if they were responsible for the renal failure. These findings again challenged the established concepts and led him to propose a hypothesis—published in an article in *The Lancet* in 1962—that, rather than demonstrable structural damage to the kidneys being the main factor in the pathogenesis of oliguria and uraemia, a functional vasomotor disturbance within the kidneys was primarily responsible, occurring for example in the initial stage of hypotensive shock and persisting into the oliguric and diuretic phases (29).

Sevitt, an Irishman working in Birmingham in England, addressed the same issue at about the same time as Finckh. He was troubled by the inability of a theory of acute tubular necrosis to explain non-oliguric cases of acute impairment of renal function, of the absence of glycosuria when severe damage to the proximal tubules was supposed to have occurred, and of the urinary sodium and potassium excretory patterns that were contrary to anticipated if tubular damage was the prime mechanism. He argued in consequence for an alternative explanation, the central theme of which was that a persistent and often irreversible fall in glomerular filtration rate lay at the heart of the problem (30).

A wealth of further investigations by many researchers over the following half-century followed these attacks upon the orthodox explanations. Information progressively emerged to suggest that each of the many identified causes of acute renal impairment was likely to have its individual mechanism, but also that often multiple mechanisms interacted in each individual patient. The situation was far more complex than had originally appeared to Graham Bull when he proposed his single unifying mechanism. The disadvantage that he had faced appeared in retrospect to have recapitulated the historical problem faced by generations of clinicians prior to him who had addressed the same problem: difficulties at the clinical, the biochemical, the histological and the philosophical levels. Clinically, he and those around him recognised the occurrence of acute renal impairment by the presence of anuria, not discerning that non-oliguric forms could occur; also working before the relationships of many of the symptoms and other manifestations to the disease process had been clarified. Biochemically, the lack of availability of routine, repeated and automated testing of chemical levels in the serum and urine stymied management of patients. Histologically, coping with a lack of biopsy material to provide information at progressive stages of the disease process; and a lack of controlled trials on significant numbers of patients to validate

individual observations. Philosophically, an assumption that a single mechanism would suffice to explain the process in all cases, rather than a recognition that each case was a unique example of disease and would probably have individual characteristics at a pathogenetic level of diagnosis, just as it had at a clinical level.

And into the future

Soiled as it now is, the term *acute tubular necrosis* persists in the contemporary medical vocabulary. It appears in the chapters on acute impairment of renal function of many textbooks. Remarkably, the authors of these volumes commonly stigmatise it whilst continuing to use it. Comments appear such as:

'The term *tubular necrosis* is a misnomer because the alterations are not limited to the tubular structures and true cellular necrosis in human ATN is often minimal. However the term *acute tubular necrosis* is commonly used in the clinical setting. To make things even more confusing, the terms *acute tubular necrosis*, *acute renal failure* and *acute kidney injury* are frequently used interchangeably in the literature…' (31).

Although in clinical practice the term *acute tubular necrosis* (ATN) is often used synonymously with AKI, these terms should not be used interchangeably. Although ATN is the most common form of intrinsic AKI, particularly in critically ill patients, it represents only one of multiple causes of AKI' (32).

'While renal dysfunction due to acute tubular cell injury is still often referred to clinically as "acute tubular necrosis," the changes found on pathological examination are generally more subtle. Indeed, as we shall see, "acute tubular injury' is a more suitable term for this most common form of ARF' (33).

But is indeed *injury* a preferable term by which to describe acute impairment of renal function? *Injury*carries a clear overtone of physical damage to, of structural interference with, the kidneys. It therefore poses a structural term to convey the meaning of a syndrome of malfunction. It recapitulates the same problem that *acute tubular necrosis* faced: describing a physiological process in anatomical words. One might wonder therefore whether *AKI* might be better translated as the abbreviation for *acute kidney impairment* (or even *ARI*: *acute renal insufficiency*, to mirror the French terminology) rather than commencing yet a further round of scientifically unsound terminology for this long-suffering disease.

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