

Emergence of the Concept of Acute Kidney Injury

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Acute kidney injury (AKI), a recently defined clinical entity, is an ailment that has afflicted humans from time immemorial. Its emergence as a disease follows by 50 years that of acute renal failure (ARF) after the Second World War. The medical model of ARF emerged as studies of the kidney in traumatic shock unraveled the pathophysiology of the disease and focused on its treatment with hemodialysis. ARF was reframed as AKI, based on the model that had been developed for chronic kidney disease, to incorporate the accrued epidemiologic data and present it as a public health model of disease that is potentially preventable and treatable at earlier stages of the disease.

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The subject of this issue, acute kidney injury (AKI), is barely a few years old. In fact, there has never been a time that humankind has not suffered from AKI. It is the evolution and changes in our framing of diseases and diagnostic terminology that accounts for its emergence only recently as a clinical entity of major interest.¹ As an ailment, AKI has afflicted humans from time immemorial because of trauma sustained by our earliest ancestors in their quest for survival as hunters and gatherers. As such, and as with other diseases, AKI predates medicine; its historical roots are buried in the misty beginnings of priestly medicine, which emerged as illnesses began to be separated from other kinds of suffering. When recorded medicine began in antiquity, it was the abnormal symptoms and external signs with which patients presented that formed the framework of the diagnostic taxonomy of what was then considered a disease. Dominant among those presenting symptoms were pain and changes in excretion. So far as diseases of the kidney, this translated into the

pain of urolithiasis and either increased or suppressed urine excretion.² Over time, increased urine output (polyuria) was termed diabetes in the 2nd century BCE and emerged as a diagnostic entity by the 2nd century CE.³ By contrast, that of suppressed urine output (oliguria) went unnamed and linked to the obstruction of urolithiasis that usually presented with pain. Nevertheless, by the time medicine matured and for the centuries that followed, suppressed urine output also came to be considered an ominous prognostic sign in several other diseases.^{4,5}

That past is real. Imposing an order on its subsequent evolution, which history does, is treacherous. An account of the story of acute renal failure (ARF), which preceded AKI as a diagnostic term by half a century, has been the subject of a previous article.⁴ The present article examines their temporal emergence within the broader context of the major conceptual and technical developments in medicine over the past century. Of necessity, some of the story told here will be repetitive to that of the previous report on ARF but is now interpreted within the evolution of our understanding of the renal complications of traumatic shock. It has been said that “no complete history of acute renal failure as a concept has yet been written.”⁶ That platitude is a truism, which applies to history in general, for historiography is a progressive subject that builds on past accounts as new evidence is uncovered. As such, the present article is by no means a complete history but a step in

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reconstructing the emergence of the concepts of ARF and AKI.

Broadly, this is the story of the emergence of the concept of traumatic shock (Fig 1), which laid the groundwork within which the medical model of ARF as a disease developed. The medical model of disease emerged in the past century as the pathophysiology of diseases was unraveled and specific treatments became available.^{7,8} It is this model that framed ARF as a disease and dominated its progress over the past 50 years. The medical model did not include epidemiology and public health in its framing of a disease. By contrast, the recent statistical approach of evidence-based medicine emphasizes the epidemiologic perspective of disease as a public health model.⁸ It is this epidemiologic perspective of disease as a public health problem that accounts for the recent reframing of ARF as AKI of an age-old ailment that had actually plagued humankind from time immemorial.^{1,4}

Beginnings: A Disease Waiting To Be Recognized

Historically, Galen (119-200) provides the clearest differential diagnosis of suppressed urine output based on the presence or absence of a distended bladder on physical examination.⁹ The causes of an empty bladder Galen lists include kidney stones, bloody urine (eg, stone, malignancy, and glomerulonephritis), tissue fragments (eg, papillary necrosis and malignancy), and kidney infection. For the purposes of this article, it is the latter cause, kidney infection, which is pertinent. Although the notion of contagion was appreciated in antiquity, the use of the descriptive term “infection” precedes the recognition of invading infectious organisms as a cause of disease by more than 16 centuries. Rather, the past use of “infection” in medicine is akin to that of its first use in English in the 13th and 14th centuries as “a process of affecting injuriously; corrupted or diseased condition.”¹⁰ In the 18th century, Giovanni Batista Morgagni (1682-1771) provided what may be considered the first organ-based classification of suppressed urine (ischuria) into ischuria vesicalis, ischuria ureterica, ischuria urethralis, and ischuria renalis.⁴ The “kidney infection” of Galen, the “ischuria renalis” of Morgagni, and the subsequent use of “nephritis” (a term introduced in the 16th century to mean “inflammation of the kidneys”¹⁰) are the inclusive but wastebasket terms, often used interchangeably, that provided the framework within which diseases of the kidney in general, and those of ARF and AKI in particular, were grouped, described, and studied well into the 19th century.¹¹⁻¹³



Figure 1. Resuscitation of the child freed from the rubble of a collapsed building. Fresco by Giotto (1266–1336). Location: S. Francesco, Assisi, Italy.

It is within this terminology (ischuria renalis, inflammation of the kidneys, and nephritis) that a reasonable, although not fully differentiated, description of the clinical course of ARF begins to be reported in the Age of Enlightenment. William Cullen (1710-1790), in his *First Lines of the Practice of Physic* (1777-1784) chapter on “Nephritis and Inflammation of the Kidneys” devoted mostly to urolithiasis, mentions in passing decreased urine output caused by “external trauma, heavy exercise, and puerperal fever.”¹¹ A clearer clinical picture of ARF surfaced in the 19th century, beginning with its description by William Heberden (1710-1801) in his *Commentaries on the History and Cure of Diseases* (1802) chapter on “Ischuria,” as “a total suppression has lasted seven days, and yet the patient has recovered. It has been fatal as early as the fourth day. But in general those patients, who could not be cured, have sunk under the malady on the sixth or seventh day.”¹² A more detailed description is provided by John Abercrombie (1780-1844) in an 1821 article titled “Observations on Ischuria Renalis” as “the disease seems, in general to come suddenly. The peculiar symptom is

a sudden diminution of secretion of urine, which soon amounts to a complete suspension of it. The affliction is probably first considered as retention; but the catheter being employed, the bladder is found to be empty...after several days the patient begins to talk incoherently, and shows a tendency to stupor. This increases gradually to perfect coma, which in a few days is fatal. The occurrence of coma may be expected about the fourth or fifth day from the time when the secretion of urine becomes suspended."¹³

Shortly thereafter, Richard Bright (1789-1858) described his eponymous disease of albuminuric end-stage kidneys in 1827, which was soon followed by its classification into acute and chronic forms of Bright's disease.⁴ By the turn of the 20th century, acute Bright's disease became the taxonomic classification under which ARF was generally classified and discussed. In his *Textbook of Medicine* (1909), William Osler (1849-1918) mentions "trauma, toxic agents, exertion, and pregnancy" as causes of acute Bright's disease.¹⁴ In the discussion that follows, Osler refers to the work of Francis Delafield (1841-1915) who in an 1888 report titled "Acute Bright's Disease" provides what can be considered an accurate description of the microscopic pathology of ARF, classified as "parenchymatous degeneration of the kidneys": "the acute morbid process which seems to belong to the epithelium of the tubes...the changes in the cells are a simple swelling of cell body, especially of its network, causing it to look larger and more opaque and to take on irregular shapes; and infiltration of cell bodies with granules of fat; a death of cells, which may take the form of coagulation necrosis, or of disintegration and crumbling of the cell bodies; a formation within the tubes of myelin globules, apparently derived from the epithelium; and a growth of new cells, to take the place of the desquamated epithelium. All these changes are most marked in the convoluted tubes."¹⁵

Just about the time that the microscopic features of acute tubular injury were being identified and described as a single entity (acute parenchymatous degeneration), the gross pathological appearance of the kidneys reported by Bright were classified as "nephritis" and "nephrosis."^{16,17} As a result, the character-

istic lesions described by Delafield and others were now relegated to the new classification of "nephrosis" and resurfaced as diverse and rather disparate pathological diagnostic terms (vasometric nephrosis, necrotizing nephrosis, acute toxic nephrosis, hemoglobinuric nephrosis, and lower nephron nephrosis) and clinically discussed under the broad rubric of Bright's disease well into the 1940s.^{4,18}

Thus, by the dawn of the 20th century, a reasonable description of the clinical course and pathology of ARF were reported and several of its causes recognized, but its taxonomy remained dubious and rather confusing. This was the period of ascendancy of the neurosciences and study of nerve function, whereby the kidney was considered to be under the control of the brain and its actions increased, altered, or suspended by cerebral causes.¹⁹ Accordingly, decreased urine output was attributed to flaccidity of the kidneys and their suppressed secretion due to "spasm." An extreme example of this is shown in the work of a founder of neurology, Jean-Martin Charcot (1825-1893), who described "hysterical ischuria" as "a symptom probably due to spasm of the renal vessels, and is comparable to the arrest of the secretion which occurs in an animal when the abdomen is opened."²⁰ It is on this background then that studies of traumatic shock during the major military conflicts of the 20th century provided the setting in which changes in nosology, diagnosis, and therapy led to the emergence of the concept of ARF.^{4,21}

Foundations: Military Medicine and Traumatic Shock

From the 17th century onward, military physicians had described a posttraumatic syndrome characterized by clammy skin (at times dubbed "death-sweat"), pallor, marked physical prostration, collapse, and depressed bodily functions, which were attributed to an exhaustion of nerve forces immediately after trauma (Fig 1). Older writers referred to this sudden collapse and progressive deterioration, from which some recovered, as "petite morte" (little death) in French and "scheintod" (apparent death) in German.^{21,22}

S. Weir Mitchell (1829-1914), who studied nerve injury in wounded union soldiers during

the American Civil War (1861-1865), sums up the condition, as “we have nothing to separate the wounds of great nerves from those involving only muscular or bony parts This state of shock so well known to surgeons, is simply a reflex effect of injury...”²³ Kidney function was considered to be “suspended in common with other functions and restored with them should reaction occur.” Oliguria and anuria were noted but not fully explored. However, advances in clinical chemistry already were beginning to have an impact on the urinary findings of such cases as is evident in an 1879 report: “By renal inadequacy I mean that state of kidney, in which it is unable, without material diminution of quantity, to produce urine containing the average amount of solids and of specific gravity greater than 1.014. The deficiency of solids chiefly affects the urea and uric acid. Whatever diminished secretion...invariably within a short time aggravated the patient’s suffering.”²⁴ The subsequent meticulous analytic studies of Otto Folin (1867-1934) on the chemical composition of the urine were instrumental in laying the foundation of what followed in the study of urinary abnormalities of traumatic shock.^{25,26}

The First World War provided a new setting for the study of posttraumatic shock that was to change its focus to the then increasing appreciation of the peripheral circulation,²⁷ primarily through the work of a physiologist Walter Cannon (1871-1945).²⁸ Previous reports of traumatic shock had noted the weak, thready, and irregular pulse in shock cases. A fall in perfusion pressure as a result of shock was implied and attributed to exhaustion of the vasomotor center, which in the prevailing parlance of neurology was termed “vasomotor paralysis.” Actual changes in perfusion pressure were not documented or recorded.²² By the time of World War I, the sphygmomanometer had become clinically available but was sparsely used. Cannon used the sphygmomanometer to record changes in blood pressure in the cases he studied and documented that failure of the peripheral circulation was central to the development of traumatic shock that could not be accounted for solely on the basis of blood loss. He proposed that the decreased blood pressure and consequent reduced blood flow to the kidneys accounted for the diminished secretion of

urine.²⁸ Simultaneously, analytic studies on the urine of such cases began to provide new information on the observed suppression of urine secretion. Notable among them are those of the 1913 Nobel Laureate Charles Richet (1850-1935), who in a study of the relationship of the quantity of urine and its total nitrogen and urea content to outcome in 26 severely wounded soldiers reported that there was a significant decrease at baseline in urine volume and composition, with continued depression in those who died, but an improvement in those who recovered.²⁹ The prevailing concept then was that in trauma urine function is profoundly disturbed, the urine dilute, low in volume, and diminished in total nitrogen and urea content.²⁸⁻³⁰

In his *Traumatic Shock* (1923),³⁰ Cannon further notes the changes in blood composition as an accumulation of nonprotein nitrogen that starts promptly after wounding, is at its height on the next day, and gradually returns to normal values, with the constituent most conspicuously high in amount being creatinine that was increased proportionately more than that of urea. In conditions that led to death, these abnormalities were higher at baseline and sustained a gradually persistent rise. He concludes that the diminution of kidney activity might be involved to account for the elevated nonprotein nitrogen in the blood.³⁰ That the kidneys are injured in traumatic shock was further documented by the description of the structural changes that accompany the functional and chemical abnormalities, which were being described concurrently.^{31,32}

Emergence: ARF Enters the Diagnostic Taxonomy

The period between the 2 world wars saw an increasing number of traumatic shock cases as a result of work-related accidents in the new industrial setting of the time, especially those of life-threatening car and train accidents. And, because more operative procedures were being performed, postsurgical shock emerged as a clinical subject of investigation. In addition, changes of kidney function began to be noted and reported in cases of severe diarrhea, transfusion reactions, and toxin exposure.⁴ Whereas all described in variable

detail some of the clinical, biochemical, and structural features of the posttraumatic shock kidney described during World War I, they did so in articles published in various specialty journals, each under different names that were not appreciated as a single disease until the years that followed the Second World War.⁴

What set the stage for pulling it all together were the experimental studies between the 2 world wars that elucidated kidney function and introduced new methods for its study. Notable among the several contributors to the field is a pharmacologist who had collaborated in the studies of traumatic shock during World War I, A. N. Richards (1876-1966), who upon his return to the United States embarked on a series of micropuncture studies of kidney function that established the filtration-reabsorption functions of the nephron.^{33,34} Another is Jean R. Oliver (1889-1976) whose microdissection studies of toxic and ischemic models of acute kidney injury were fundamental to the subsequent elucidation of the pathogenesis of ARF.³⁵ And, of course, the clearance concept of Homer Smith (1895-1962) provided the basis for studies of kidney function in health and disease as well as his introduction of the term acute renal failure.^{36,37}

Thus, by the time that the kidney injury of crush victims during the London Blitz of World War II was first reported in 1941,³⁸ the understanding and tools to study kidney function were much more sophisticated than they had ever been in the past. As a result, the clinical and experimental studies of the acutely injured kidney during and shortly after World War II expanded exponentially. Although disparate names continued to be applied³⁹ ultimately, the use of ARF prevailed and came to serve as the banner around which all subsequent reports rallied, thereby overcoming the disparate nomenclature that had confused and confounded the information that had accrued in the past.

Evolution: ARF Becomes AKI

What determined postwar progress in the field was the demonstration of reversibility and now the available treatment for ARF. Without aggrandizing the role of any single contributor to this progress, special credit is



Figure 2. (Left to right) George E. Schreiner, Willem J. Kolff, and John P. Merrill, 1979 (photograph by Eli A. Friedman, MD).

due to 3 individuals (Fig 2): Willem J. Kolff (born 1911), who introduced the artificial kidney⁶; John P. Merrill (1917-1984), who described the clinical course, treatment, and reversibility of ARF;⁴⁰ and George E. Schreiner (born 1922), who promulgated the treatment and promoted the study of ARF.⁴¹ Thus, by the 1950s, the medical model of ARF was well entrenched as a defined, understood, and treated disease.

What prompted the recent emergence of AKI was the definition of chronic kidney disease (CKD) and its public health model in the Kidney Disease Outcomes Quality Initiative guidelines for the evaluation, classification, and stratification of CKD.⁴² By defining CKD as kidney damage for at least 3 months, these guidelines set the stage for that of potentially reversible kidney injury of less than 3 months duration as a separate entity and provided a model on which it could be developed.⁴³ In fact, the subsequent evolution to ARF to AKI mirrors that of the evolution of end-stage renal disease to CKD. End-stage renal disease as a medical model of disease had focused therefore on its treatment with dialysis. By the same token, ARF, which as a medical model of disease had focused principally on its treatment with dialysis, was now reframed as AKI to incorporate epidemiologic data and present it as a public health problem that is potentially preventable and treatable at earlier stages of the disease.^{1,43} The widespread acceptance of AKI and the impressive progress made since

its entry into medical taxonomy is reflected in the articles of the present issue of *Advances in Chronic Kidney Disease*.

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