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A brief history of shock

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RECENTLY, 2 MIDDLE-AGED COUSINS were admitted to the Level I trauma center where I attend as a trauma surgeon. Each had been shot twice. Their wounds were similar; both suffered a single gunshot wound to the epigastrium and a second wound in the left flank. The first cousin (let us call him Joe), had a normal pulse and blood pressure and was oriented and composed; his skin was pink and dry. The second cousin (let us call him Frank) was hypotensive and tachycardic; he was apathetic and disoriented, although paramedics reported that he had been agitated and combative in the field just minutes before. His skin was pale and he was diaphoretic. There was 1 operating room immediately available and 1 that would be ready in 20 minutes. Frank was given priority. At surgery, he was found to have a bullet track passing through the left lobe of the liver, the gastric antrum, the pancreatic neck, and the splenic artery. There were ≥2 L of blood in his abdomen. Joe was found to have a bullet track that passed through the right lobe of the liver (nonbleeding) and through the hepatic flexure of colon. He had <500 mL of blood in his peritoneal cavity, and a moderate amount of free peritoneal fecal contamination. In both cases, the flank wounds were superficial. Both men recovered uneventfully. The answer to the question of which patient to operate upon first seems obvious: It does not require a trauma surgeon to recognize that the second man required immediate management. Why? Because Frank, unlike Joe, was in "shock."

A PubMed search for papers containing the key word "shock" yields >140,000 citations. The meaning of the term "shock" varies depending upon the context. My intention is to discuss the term as it is used in the surgical and trauma literature. In a setting of hemodynamic instability, this word is frequently used to indicate a syndrome of hypotension, tachycardia, and mental status change owing, presumably, to "inadequate tissue perfusion." Today we use the word shock to describe patients in extremis who suffer from a variety of distinct pathophysiologic processes, such as severe cardiac dysfunction or overwhelming infection that share insufficient tissue perfusion as a consequence.

The story of how this word came to be attached to these dramatic clinical syndromes and how our predecessors conceptualized the physiology of shock is a central theme of the past 300 years of surgical history. In this paper, I review the origin of the use of the word shock, and describe the evolution of the concept of shock from its first use in the surgical literature to the present. This is a story with hundreds of contributors. In the interest of economy, I have marked out a path that considers many, although not all. I limited the source material to English language literature, with 3 notable exceptions. There are other pathways through this topic, which feature other principal players. Please consider this *a* history rather than *the* history of this fascinating subject.

The *Oxford English Dictionary* (OED) devotes nearly 3 pages to the definition of shock.[1] The word itself may derive from the French *choc,* which was originally used to describe "an encounter between two charging hostile forces, jousters, etc."[2] The OED defines the medical usage of this word as:

> A sudden debilitating effect produced by overstimulation of nerve, intense pain, violent emotion, or the like; the condition of nervous exhaustion resulting from this. Now used more precisely for a condition whose principal characteristic is low blood volume.[1]

The OED credits Abernathy with using the word for the first time in 1804. However, the usually authoritative OED is incorrect on this last point: Shock first appeared in the English language medical

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literature in 1743 in a translation of a French treatise on gunshot wounds by Henri-François LeDran.[3]

THE GALENIC ERA

Before 1743, there is no record of the word shock used to describe a clinical syndrome. Certainly the syndrome itself existed. William Bradford Cannon credited Hippocrates with first use of the term "exemia" to describe patients in hypovolemic shock.[4] Cannon's aim was to replace the term "shock" with exemia, believing the latter more specific. My search of existing translations of Hippocratic corpus failed to locate this word. Nonetheless, the ancient physicians must have encountered patients in shock, even though little record of the syndrome or its treatment survives.

For the first 1,600 years of the modern era, medical thought was dominated by the works of Galen of Pergamon (CE 129–200).[5] Galen, who gained fame as a surgeon to gladiators,[6] was intimately familiar with hemorrhage,[7] and thus, one supposes, with hypovolemic shock. Despite this, he never mentions a constellation of signs and symptoms consistent with what we understand as shock. Ironically, whereas Galen made important contributions to the field of anatomy,[5,7,8] his notions that bodily functions were dependent on 4 humors—white bile, black bile, phlegm, and blood, each associated with a particular attribute: choleric, melancholic, phlegmatic and sanguine[6]—led him to the unfortunate conclusion that hemorrhage was among the conditions that benefited from bloodletting.[9] Galen did not invent therapeutic venotomy, but his advocacy of the treatment led many to adopt it in his name. It is sobering to contemplate the number of preventable deaths occurring over the span of the "Galenic Era" attributable to the belief that bleeding is a good therapy for hemorrhage.

Many of Galen's notions about human anatomy and physiology were erroneous. In the Galenic model, blood flowed outward in both the arteries and veins, having been created in the liver and vitalized by the lungs. Not until 1543 was Galenic anatomy corrected, when Andreas Vesalius published *De Humani Corporis Fabrica*. However, it remained for William Harvey to make the seminal discoveries that the understanding of shock required. In *Excercitatio de Motu Cordis et Sanquinis in Animalibus* (Anatomical exercises on the motion of the heart and blood in animals, often shortened to as "*De Motu Cordis*") published in 1628, Harvey made 2 important discoveries: First, blood flowed away from the heart in the arteries and returned in the veins, meaning that the blood circulated. Second, Harvey determined that the liver could not possibly manufacture the volumes of blood the Galenic model required. He did this by estimating the stroke volume of the heart, and extrapolating from this the volume of "cardiac output" per hour. Thus, Harvey established that the blood made a circuit, leaving and returning to the heart at regular intervals, and that there was a fixed, and presumably optimal, volume of blood circulating in the human body.[10] Harvey did not make a connection between the syndrome we recognize as shock and disordered blood volume; it would take 3 centuries for this to happen. However, it is with Harvey that our present understanding of shock began.

THE AGE OF ENLIGHTENMENT: HENRI-FRANÇOIS LEDRAN

The first use of the word "shock" to describe a trauma victim appears in the English translation of Henri-François LeDran's 1740 text, *Traité ou Reflexions Tire'es de la Pratique sur les Playes d'armes à feu*[3,11] (A treatise, or reflections, drawn from practice on gun-shot wounds[12]). A number of authorities assert that the term was a mistranslation of such words as *choc* and *secousse,* the French term meaning to jar or disturb.[13-20] However, neither of these words appeared in the 1740 French text. LeDran's meaning, and the intent of the translator, can be determined by reviewing the original text and the translation side by side. The word shock occurs 7 times in the English version: In 3 instances, it is used to translate the word *saisissement*; in another 3 instances, it is used to translate the word *commotion*, and in 1 case it is inserted for the French term, *coup. Saisissement* in modern usage is translated as "astonishment."[21] In the 18th century, the definition may have been more consistent with "fright" or "violent emotion."[22] The passage below, followed by the English translation, best demonstrates LeDran's intent:

> *Mais Quand même un blessé ne froit pas pléthorique, il suffit que le* ***saisissement & la commotion*** *qui accompagnent souvent les playes d'armes à feu, suspendent pour queques moments l'odre œconomique; ce qui est prouvé par les sincopes & autres accidents primatifs que nous avons dit arriver affez souvent. (p. 74)*

> (But though the patient be not previously laboring under a plethoric habit of the body, the **shock and agitation** which commonly follows gun-shot wound will be sufficient to suspend the laws of œconomy for a few moments: we have a proof of this from the syncopes and other symptoms we have said happen at least often enough.) (p. 48)

LeDran described a syndrome associated with gunshot wounds where victims are stunned and agitated as suspending the "laws of economy" (restless). We may infer from the choice of words such as "agitation" and "syncope" that the author and his translator believe they were observing a neurologic phenomenon. This is supported by a section following that quoted above:

> *Le* ***Saisissemant*** *dont le malade se sent quelquefois frappé à l'instant du coup & la commotion, peuvent avoir des suites funestes. (p. 93–4)*
>
> (The **shock** with which the patient sometimes finds himself, as it were, thunderstruck at the time of the blow, together with the commotion or agitation, may be followed by very fatal consequences.) (p. 62)

Careful review of both the French original and the English translation reveals that LeDran was describing the same phenomenon we see today. Men wounded by firearms were noted to be either agitated (*commotion*) or stunned (*saisissement*). Today, we recognize this behavior in settings other than gunshot wounds, but would use the word shock in the same way the English translator did. We can draw 2 conclusions about the birth of the word shock from this literature: First, usage in the English version seems to be a faithful and appropriate translation of the original French text. Second, Both LeDran and the English translator considered "shock" to be a neurologic response, which occurs as a sequela of gunshot wound alone. It was not construed as a result of the physics of gunshot wound.

Once introduced into the English medical nomenclature, the word shock did not immediately enter widespread usage. In fact, Samuel Cooper's voluminous surgical dictionary, published in 1822, had no entry devoted to shock.[23] He does discuss the fondness of "French Surgeons" for describing the symptom of "disorganization" as a consequence of gunshot wounds, and ascribes to Guthrie (below) the description of "constitutional alarm or shock" as a symptom indicating severe injury from gunshot wound.[23] In fact, it seems likely that the apocryphal history so often attached to the translation of the word shock from LeDran's work arises from Guthrie's dictionary. In 1859, when Theodore Bilroth published a comprehensive review of European gunshot wound studies then available, he used the word shock only in regard to the work of LeDran.[24]

At least 2 surgeons writing about gunshot wounds between LeDran's work in the 1740s and the mid 19th century use the word shock to describe a clinical syndrome. G. J. Guthrie, a British surgeon who served in the Spanish War of Independence (1808–1814), expanded the concept of shock to include both a stimulus resulting from trauma and a physiologic response to devastating injury in his *Treatise on Gunshot Wounds* (1827).[25] He chooses the word shock to describe the physics of wounding:

> When a thigh is destroyed by cannon-shot above or at its middle, the injury is very great, and the danger proportionate. The **shock** is frequently more than the constitution can bear, and the patient dies in a few minutes without much hœmorrhage.[25]

Yet, in the following passage, he also uses the word to connote the physical impact of wounding by cannon fire, and then uses it to describe a neurophysiologic response to wounding:

> if a man has the femoral artery fairly divided by a musket-ball, he will often bleed until he faints, but he will seldom or never die: but when this takes place from a cannon-shot, the patient will often die, whether he suffer amputation or not. Can this be accounted for in any other way, than from the general derangement caused by **the shock of the blow**, and the tearing away of parts? It is the double affect on the nervous and the sanguiferous systems, which I called **shock and alarm** and to which, in a case of this kind, many persons owe their lives, for without it they would bleed to death; with it the haemorrhage ceases. I do not believe, that, during the whole course of the Peninsular war, a tourniquet was applied in one case in ten where limbs were struck by cannon-shot' and when they were applied the greater number were useless. The time required to get the better of this state is various, and, where much blood is lost, the effect on the nervous system will be greatest.[25]

Twenty years later, the French surgeon Velpeau echoed Guthrie. In a *Lancet* article about managing the wounded during the Paris Revolution of 1848, Velpeau describes sequential physiologic decline after gunshot wound where the first stage is characterized by the "shock" of wounding.[26] This phenomenon is particularly severe with regard to the nervous system:

> The first is the period of stupor; this is the result of the sudden shock which the nervous system, and, in fact, the whole organism, experiences by the reception of the wound, the patient being mostly in a state of great excitement at the time. This period lasts generally from twenty four to thirty-six hours.[26]

Both Guthrie and Velpeau used the word shock to describe both the physics of wounding, particularly by firearms, and the neurophysiologic response to injury. In addition, they introduced a new concept regarding physiologic response to injury; both authors described the period following shock as "reaction," a time during which the patient is seen to respond to clinical treatments.

> At the first moment of injury, the operation should be performed, so that the shock to the nervous system may if possible be continuous, and opium with purgatives should be administered to allay it. As soon as the **reaction** becomes permanent, the surgeon must bring all his stores of observation and experience forth, for an erroneous decision is pregnant with danger either one way or the other with improvement.[25]

> [T]he second stage, which is the period of inflammatory **reaction**; this will appear towards the second or third day, and is analogous to the period of elimination in burns.[26]

For the first time, the term "reaction" was applied to a state that these physicians hoped the patient would attain after experiencing the shock that follows injury. If shock means a neurophysiologic response to injury, then "reaction" describes the physiologic recovery after shock. The surgeons of the next century expanded on this idea and used it to inform their treatment of the wounded.

THE AGE OF IGNORANCE: THE AMERICAN CIVIL WAR

Over 600,000 soldiers died during the Civil War (1861–1865); many more were wounded. Those caring for the injured did not learn much new about the physiology of shock, nor did they make much effort to study it. What they did learn was that the phenomenon of shock could be a response to more than just a gunshot wound. LeDran, Guthrie, and Velpeau were limited by their conviction that shock could only be a consequence of gunshot wound, but the surgeons of the Civil War recognized shock in casualties caused by different mechanisms, and realized that it could be a physiologic response to injury in general.

Dr Samuel Gross of Jefferson Medical College, a major figure in American surgery, published a manual for military surgeons in 1861.[27] Early in this work he noted the ease of diagnosing shock and focused on the neurologic findings:

> It is not necessary to describe minutely the symptoms of shock, as the nature of the case is apparent at first sight from the excessive pallor of the countenance, the weakened or absent pulse, the confused state of mind, the nausea or nausea and vomiting, and the excessive bodily prostration.[27]

He also recognized that shock is not solely a response to gunshot wound, and that it may result from a seemingly minor event:

> In many cases death is instantaneous owing to shock or shock and hemorrhage; in others it occurs gradually or without reaction, at a period of several hours …or days. Sometimes men are destroyed by shock, by, apparently the most insignificant injury, owing not to want of courage but to some idiosyncrasy.[27]

Professor Julian J. Chisolm, from South Carolina, made similar observations about the nature of shock in his 1863 manual for the military surgeons of the Confederacy.[28] He, too, recognized that shock can result from any form of injury, not just gunshot wound. He expanded the understanding of the concept by drawing attention to the idea that shock is a neurologic syndrome:

> **nervous shock** accompanies the most serious wounds, it may often be met with the most trivial injuries. It is recognized by the sufferer becoming cold, faint and pale with the surface bedewed with cold sweat; the pulse is small and flickering, there is anxiety, mental depression and at times incoherence of speech. Often this shock is very transient when accompanying simple wounds. A drink of water and a few encouraging words may be sufficient to dispel it.[28]

Both Gross and Chisolm further defined shock in terms of "nervous depression."[27,28] The therapies they recommended were intended to stimulate the patient to a state of "reaction." Both men prescribed stimulants such as alcohol, ammonia, hartshorn (ammonium carbonate), and turpentine. They also recommended remedies such as sinapisms (mustard plasters), "frictions," and cataplasms (poultices of hot clay). Finally, both agreed on the importance of wrapping the patient in blankets. Betraying the persistence of Galenic thought, Chisolm also recommended that the combat surgeon treat casualties suffering from internal hemorrhage by performing urgent venotomy to bleed the patient and "save him from immediate death."[28]

The standard for clinical management of shock in the field during the Civil War was perhaps best exemplified by the treatment of Confederate General Thomas (Stonewall) Jackson, as reported by

his surgeon, Hunter Holmes Maguire.[29] Educated in Philadelphia, Maguire was one of the most respected surgeons on either side of the war.[30] Jackson had been wounded in the left axillary artery, among other places, and was clearly suffering from hypovolemic shock. Maguire's treatment included early and frequent pre-operative administration of alcohol and coffee, both intended as stimulants. He also wrapped Jackson in blankets and allowed 2 hours for "reaction" to occur. After this period of resuscitation, he amputated the general's left arm. Interestingly, Maguire did not use the word shock to describe the general's condition in any of the 3 accounts he published of Jackson's death.[29,31,32]

In the hundreds of pages of *Medical and Surgical History of the War of the Rebellion*, there is surprisingly little use of the word shock.[33,34] One short section entitled "The Mysteries of Shock" states that autopsy reports on combat casualties exhibit "a remarkable absence of any comments on the obscure subject of shock."[33] Apparently, the word "shock" was not in common use by physicians working on the front in 1865; a decade later it could still be labeled an "obscure subject."

It was the publication of Edwin Morris's *A Practical Treatise on Shock* in 1868 that seems to have led to the common use of the term shock to describe a clinical syndrome.[35] Morris, a physician at the Union Infirmary, London (now known as the Greenwich District Hospital) reviewed everything that had been written to date about the use of the word shock starting with Guthrie's *Treatise*. Morris further develops the theme of shock as neurologic syndrome:

> The brain and spinal cord, the very center of this nervous power, is the medium through which the animal system receives powerful impressions, produced by mental or physical causes: and to understand shock and its consequences, it is absolutely necessary that we should have a thorough knowledge of the physical properties and functions of the nerves themselves.[35]

His work seems to have had a wide readership, and is cited by leading clinicians who use the term shock as a matter of course.[20]

THE BEGINNINGS OF UNDERSTANDING: THE LATE 19TH CENTURY

The concept of shock as a "nervous" condition gained more currency after the Civil War. This may be due in part to the influence of the work of the great French physiologist, Claude Bernard.[36] Bernard, who characterized the autonomic nervous system and demonstrated its effect on the cardiovascular system, did not comment specifically on shock. However, his careful experimental method, including the first accurate measurement of blood pressure in the laboratory, gave currency to the concept that the central nervous system, via the autonomic outflow, was responsible for adjustment and maintenance of the blood pressure and systemic perfusion.[37]

In 1866, the surgeon Thomas Buzzard formulated a classification system for "shock to the nervous system" based on his experience caring for victims of railway accidents and "other violence."[38] He proposed a continuum of pathology ranging from the most severe, in which death is rapid, to a chronic condition suggestive of posttraumatic stress disorder, with the assumed neurologic basis of shock remaining the unifying principle.

Thirteen years later, Mansell-Moullin devoted an entire book to the subject. *On the Pathology of Shock* expanded on the idea that shock was primarily a nervous phenomenon.[39] (By this time, the sphygmomanometer had been invented, thus allowing for the addition of hypotension to the list of the signs of shock.) According to Mansell-Moullin, the hypotension associated with shock is "primarily due to the power of inhibition which is one of the inherent properties of the nerve centers."[39] He was particularly suspicious of the splanchnic nerves, and identified splanchnic vasodilation as a major cause of shock. This theory was supported by the work of the German physiologist, Goltz, who demonstrated that frogs suspended by the nose and struck on the mesentery developed shock, presumably due to a mesenteric nervous reflex.[40]

In addition to crediting mesenteric nervous elements, Mansell-Moullin believed that the forebrain was a factor in the production of shock. "Excessive emotion"[39] could modulate the physiologic response to injury as well. Another 19th-century surgeon and medical educator, Ireland's Edward Mapother (1835–1908), added an ethnic twist to this theory by suggesting that those of Saxon heritage had superior "power to endure shock" than the Germans, the French and, in particular, the "more nervous" Celts.[41] Underlying Mapother's theory was the belief, born more of literature review than experimentation, that "Shock paralyzed the dilator nerves" leading to "contraction of the arterioles."[41] This view was to find a number of adherents in the 20 years preceding the First World War (WWI).

Mapother's theory of shock as a function of pathologic vasoconstriction was subsequently

amplified by Malcomb,[42] who believed spasm of the superficial arterioles was the central pathology in shock. Interestingly, Malcomb advocated both saline infusion, a new therapy at that time, and older remedies such as "application of rubifactants such as mustard" and rubbing the lips of patients in shock. Like most investigators of the time, Malcomb did not draw his theories from experimental work; instead, he relied on clinical observations.

THE AGE OF REASON, 1890–1925

Before WWI, 2 theories of shock emerged that, unlike the "vasoconstrictor theory," were derived from work in the laboratory. Dr George Crile, the well-known American surgeon, reporting on experiments in dogs, found that vasoconstriction occurred after both hemorrhage and burn trauma.[43] He concluded that vasomotor changes resulting from nervous stimulation played an important role in the pathophysiology of shock through a process he termed "anoci-association."[44] This theory, which subsequently grew into an effort to describe a diverse spectrum of pathology,[45] posited that shock is due to excessive activity in visceral efferent nerves, which creates a state of visceral vasodilation that results in hypotension. Crile's theory was derived from laboratory work demonstrating that manipulation of visceral and sensory motor nerves could produce shock-like states in a variety of animal models.[46-48] Crile believed that sensory afferent stimulation and expectation of noxious stimuli by the higher centers of the brain were the key factors in shock. Adequate sedation and anesthesia were essential to avoiding shock.[45]

Although most did not subscribe to the theory of anoci-association, some arrived at the theory that an early phase of arteriolar vasoconstriction in shock was eventually superseded by "depressor impulses" resulting in arteriolar vasodilation, followed by dilation of the portal and 'other internal' veins in which blood volume then fatally pooled.[49] This theory of nervous vasomotor collapse seems to have had relatively wide acceptance in the period before WWI.[50] The notion that the profound hypotension of shock was due to "missing blood" pooled in the splanchnic vascular bed was to drive much of the thinking on shock in the first half of the 20th century.[51]

A second experimental model of shock appeared in the first decade of the 20th century based on the work of Yale University physiologist Yandell Henderson.* He observed that animals suffering from hemorrhage had lower than normal partial pressures of carbon dioxide in their blood.[52] Yandell Henderson knew that hypocarbia resulted from tachypnea, and surmised that pathologic hyperventilation was an important factor in shock.[52-55] He called this the "acapneic theory."

Henry Janeway and Ephraim Ewing, at Bellevue Hospital in New York, suggested that there might have been a relationship between hypocarbia (acapnia) and splanchnic vasodilation. After extensive experimentation with dogs, they came to believe that hypocarbia associated with shock created a pathologic accumulation of blood in the veins of the mesentery, resulting in "missing blood."[56] This work attempted to combine the splanchnic vasodilation envisioned by Crile and the hypocarbia measured by Henderson into a common thread: Reflexive hyperventilation after severe injury resulted in hypocarbia which then promoted splanchnic vasodilation. Blood pooling in the splanchnic vessels was effectively removed from circulation, resulting in progressive shock. Other proponents of the "missing blood" hypothesis, most notably Carl Wiggers, doubted hypocarbia was a fundamental cause of shock,[51] and looked for other reasons for blood to seem to be missing from the circulatory system in shock.

WWI provided an opportunity to investigate shock in a rigorous and scientific fashion. A number of investigators traveled to the Western Front, then returned to the laboratory to test hypotheses regarding the physiology of shock generated on the battlefield. William T. Porter, based on his experience with casualties, particularly those with long bone injuries, believed that fat embolism was the cause of traumatic shock.[57] He subsequently conducted experiments in which he injected olive oil, cotton seed oil, cod liver oil, and cream into the jugular veins of various small mammals.[58] The animals in these experiments developed hemodynamic collapse, an observation that supported, and, in his mind, validated, his "fat embolism theory" of shock.

E. M. Cowell, of the British Special Investigations Committee of the Medical Research Committee, introduced the concept of "wound shock" based on his experience on the battlefields of France.[59] Cowell believed that it was the wound itself that was the primary stimulus leading to the physiology of shock; he assumed that the etiologic agents were as yet unidentified toxins liberated from wounded tissue. Cowell further divided shock into 2 separate phenomena: Primary shock, where a casualty is

*One should not confuse this Henderson with Harvard University's Lawrence J. Henderson who, in 1908, described the famous blood buffering properties of the bicarbonate/carbonic acid system universally known as the Henderson-Hasselbach equation.

found to be hemodynamically unstable on arrival at the aid station, and secondary shock, where a casualty with previously normal vital signs deteriorates after reaching medical attention. The notion that shock was primarily a neurologic condition persisted: Cowell states, "the conditions of excitement, cold, thirst, fatigue and possibly loss of sleep become important pre-wound factors in the initiation of wound shock."[59]

When the Americans joined the war effort in 1918, the British and American forces established a joint commission to study battlefield shock led by William Bayliss of University College, London, and Walter Cannon of the Massachusetts General Hospital.[14] Both men wrote book-length treatises on the subject of shock, which nicely summarized the variety of contemporary theories and the evidence for or against each based on observation of combat casualties; both argued against the "acapneic theory" of shock.

Cannon measured "alkali reserve" in experimental dogs and cats, and grasped, as Yandell Henderson had not, that the hypocarbia and tachypnea seen in shock were evidence of the presence of the bicarbonate buffer system.[4,60] He rejected most of the existing theories in favor of a modified version of the "missing blood" theory. He tried to rename hypovolemic shock using the Hippocratic term *exemia*, because he believed that there was pooling of blood within the body in response to shock, which resulted in a marked reduction in circulating blood volume.[4,60] Cannon supported this theory with evidence of a discrepancy between the red blood cell counts in capillary specimens and those in venous blood specimens in combat casualties.[4] Capillary specimens were found to have higher counts, indicating hemoconcentration and pooling in the capillary space.[61]

Intravenous saline infusion had been used as early as 1831 for the treatment of hypovolemia owing to cholera.[62] It was first used to manage shock by Jennings in 1882,[63] followed by Robson in England and Matas in New Orleans in the 1890s.[64,65] Nonetheless, it was not until WWI that intravenous therapy was widely used for treatment of shock.

Both Cannon and Bayliss reported on the efficacy of a number of intravenous solutions including synthetic colloid solutions based on gum acacia[4] and gum arabic.[66] Cannon's famous warning against early aggressive fluid resuscitation—"If the pressure is raised before the surgeon is ready to check any bleeding that may take place, blood that is sorely needed may be lost"[67]—remained a caveat largely ignored until the past decade. Cannon rejected the Galenic notion that bleeding is an effective treatment of shock. Ironically, his 1923 *opus* on traumatic shock concluded with the recommendation for a novel 3-blanket wrap as the most efficacious treatment of traumatic shock.[4] In this regard, he had not progressed much beyond the resuscitation techniques offered by Maguire in the Civil War. Nonetheless, Cannon was the first to recognize that reduction in blood volume plays a role in the production of traumatic shock.[61]

By the end of WWI, what was now called "wound shock" in England and "traumatic shock" in the United States, was considered a 2-stage phenomenon: Primary shock, which occurred immediately after wounding, was largely a neurologic phenomenon; secondary shock developed later due to toxins elaborated by the wound itself.[68] Hypotension and decreased tissue perfusion seen in secondary shock were believed to result from pooling of blood in certain capillary beds, resulting in the phenomenon of "missing blood." For the next 25 years, researchers would search for both the missing blood and the causative toxins. This research ultimately yielded concepts now considered fundamental to the understanding and treatment of shock.

THE MODERN ERA: BLALOCK'S EPIPHANY

Although better known for his groundbreaking work in cardiac surgery, Alfred Blalock is also responsible for the present heuristic approach to the subject of shock. In 1927, Blalock presented a theory of shock as a disorder of blood volume.[69] Beginning with "10 common causes" of clinical shock, he developed laboratory models to aid his search for a unifying principle. Searching for either toxins or lost blood, he tried to induce shock in experimental animals in a standardized model using crushing injuries to the extremity.[70] In this work, Blalock repeated 1 of Cannon's experiments supporting the missing blood theory. Where Cannon had compared the weights of the experimental and control limbs amputated through the proximal thigh, Blalock precisely divided the pelvis and lumbar spine. Blalock found the added weight of the crushed limb accounted for all observed hypovolemia. He concluded there was no missing blood or fluid at all.

In additional experiments, Blalock systematically excluded central nervous system injury as a cause of shock.[71] Not satisfied, he concluded that a number of pathologic states could be explained with a simple model founded on an assessment of the state of the blood volume. What emerged

was a classification system, first published in 1934, that grouped different pathologies together under the central theme of disordered blood volume.[72] Like Cannon before him, Blalock sought to replace the word "shock" with a better term: He favored "acute circulatory failure." Like Cannon, he was unsuccessful in renaming the syndrome, but unlike Cannon, Blalock established a durable conceptual framework that linked hypovolemia with other etiologies for shock.

Blalock's original framework identified 5 distinct physiologic settings for shock: (1) hematogenic shock (hypovolemic); (2) neurogenic shock; (3) vasogenic shock (including both anaphylactic and septic shock); (4) cardiogenic shock; and (5) "unclassified conditions." He soon discarded unclassified conditions, leaving the 4-part classification of shock that is now standard fare for every medical student.[73] Alfred Blalock would write at least 44 papers the topic of shock between 1927 and 1942,[74] shedding more light on this subject than anyone before or since.

Perhaps Blalock's greatest contribution to the subject, however, was to consider the various physiologies responsible for shock under a simple construct: Shock results from "a decrease in the ratio of the blood volume in circulation to the capacity of the vascular tree."[75] This characterization, focusing on the "effective blood volume,"[75] allows the 4 physiologies to be understood together using a simple yet profound ratio.

Blalock's categorization of shock was not universally accepted until recently. The alternate rubric of primary and secondary shock, first advanced by Porter, persisted in surgical thought well into the 1960s.[76] Blalock's work refuting the missing blood theory did not find a large number of adherents. In fact, in his surgical text on the topic of shock a decade later, Blalock himself seemed uncertain on this topic, presenting many of the theories of shock listed by Cannon, with supporting or refuting data, but making no definitive statement regarding the root physiology of hypovolemic shock.[75]

POSTMODERNISM: CELLULAR PHYSIOLOGY OF SHOCK 1945–1965

Those searching for the whereabouts of the "missing blood" included Carl Wiggers. Born in 1883, Wiggers devoted his life to the study of cardiovascular physiology and shock.[77] His first paper on the topic of hemorrhagic shock was published in 1914[78]; in 1945 he published a groundbreaking paper on the fluid dynamics of hypovolemic shock. Using a model subsequently known as the "Wiggers' Preparation," he demonstrated that dogs, bled to a state of severe prolonged hypotension, died despite infusion of the same volume of blood that had been lost.[79] This model was subsequently expanded by Wiggers' son Harold.[80-82]

In 1949, a doctoral candidate at Columbia University named Monica Reynolds substituted large volumes of isotonic crystalloid solution for blood in a dog hemorrhage model.[83] Reynolds found that animals who received 2 cc of saline for every cc of shed blood could be resuscitated from profound shock with crystalloid alone. It remained for G. Tom Shires, using a Wiggers' preparation 15 years later, to determine that adding large volumes of lactated Ringer's solution to the shed blood resuscitation dramatically improved the survival of dogs bled to profound shock—from 0% to 80%.[84] Shires finally seemed to determine the location of the "missing blood" that researchers had been searching for since the turn of the century. Fluid loss in excess of that shed seemed to be disappearing, not into the extravascular space, as had been supposed, but into the intracellular space. Shires reached the surprising conclusion that both the extracellular and intravascular space contracted in hemorrhagic shock. This finding was subsequently explained by sophisticated work in a primate model where measurements of cell membrane potential changes during a "Wiggers' experiment" suggested that there was a net gain in intracellular water owing to changes in sodium pump.[85] John Dillon, also working with a dog model, confirmed the superiority of resuscitation from hemorrhagic shock with a partial replacement of shed blood combined with large volumes of lactated Ringer's solution, although this work contradicted Shires' in that there was no evidence of intracellular accumulation of sodium in this very carefully controlled series of experiments.[86] Shires' assertion that disordered transmembrane sodium transport was at the root of the perplexing physiology of hypovolemic shock remained in standard textbooks of surgery into the 1990s.

Work on shock after a burn injury was progressing concurrent with this hypovolemic shock research. In 1944, Cope and Moore[87] published a compelling series of experiments in dogs demonstrating increased capillary permeability at the site of full-thickness skin burns but, interestingly, not from distant tissues.[87] Subsequent work, done largely on survivors of the Coconut Grove Nightclub fire in 1942, confirmed that in humans "a relentless expansion of the interstitial fluid volume takes place" after a burn, and that this expansion was directly proportional to the area burned.[88] Interestingly, Cope warned against "overzealous

therapy," which may "exaggerate the extracellular space expansion."[88]

By the early 1970s, it was widely understood that successful resuscitation of burn patients required very large volumes of crystalloid.[89] Furthermore, it was understood that this volume requirement resulted from the huge parasitic expansion of the extracellular space.[90] Support for liberal crystalloid resuscitation in burns reached its apogee with the publication of the so-called Parkland formula in 1974 and persists to the present day.[91,92] During the latter half of the 20th century, there was a belief that laboratory burn models could serve as an excellent model for trauma resuscitation. The work cited, which suggests that both types of injury (burns and trauma) resulted in obligate expansion of the extracellular space, has been used to reinforce the idea that trauma patients are also best managed with large volumes of crystalloid.

REACHING THE NEW MILLENNIUM: 1990–PRESENT

Informed by research demonstrating that infusion of large volumes of crystalloid solution improved survival of experimental animals subjected to large blood loss, and perhaps influenced by the high-volume resuscitation now known to be effective in burn care, clinicians adopted aggressive volume resuscitation strategies. Injured patients received volumes of resuscitation fluid in ratios of ≥3:1 to estimated blood loss. By the early 1990s, some researchers had begun to wonder if early fluid resuscitation actually improved outcomes in hypovolemic patients.[93] Indeed, in 1994, Bickell et al[94] demonstrated that delay in resuscitation of hypotensive trauma patients suffering from penetrating wounds results in superior survival. This finding seemed to confirm Cannon's 1924 observation that delayed and even limited resuscitation increases survival rates in patients with hypovolemic shock.[95] Data from the laboratory confirm that crystalloid resuscitation is harmful at a cellular level.[96,97] Recent experience in the care of combat casualties has resulted in the concept of "damage control resuscitation" where restoration of circulating blood volume is often delayed until definitive control of bleeding is possible.[98] This approach focuses equally on restoration of red cell mass and coagulation factors and eschews crystalloid infusion.

Research on the physiologic mechanism of the shock syndrome has led to insights too numerous to list here. However, a few recent reports deserve mention. Work at the molecular level has illuminated the role of histone acetylation in shock, suggesting novel resuscitation strategies involving manipulation of DNA transcription.[99] Recent work by Navy researchers suggests that in the most severe form of hypovolemic shock, hemodynamic collapse may be worsened by the Bezold-Jarisch reflex, a central nervous system reflex.[100] Further, genetic polymorphisms in the autonomic nervous system have recently been shown to affect mortality in trauma patients.[101] No one has yet found these genetic traits overrepresented in any particular ethnic group, including the "Celts," but one must wonder nonetheless whether Mapother and his contemporaries were as far wrong as they once seemed to be.

Perhaps the most lasting lesson to be learned from the study of the history of shock is the difficulty in arriving at a single definition. Cannon himself proposed abandoning the word in favor of *exemia*, a term he could define precisely as a state resulting from loss of blood.[4] Blalock's thinking about definitions for shock evolved over more than a decade from a state of "diminished blood volume"[69] to a more modern notion of "inadequate tissue perfusion."[72] Yet to Blalock we owe our modern typology of shock, which turns out to be an excellent conceptual framework, although it does not help us to define this syndrome any more clearly.

After the World War II, Edward Churchill, trying to reconcile the differences in definition of shock as used by American and British medical officers, theorized that differences between the 2 allies arose from distinctions in frames of reference rather than differences in understanding.[102] The British focus on symptoms led to a typology quite different from that of the more physiologically oriented Americans. In the end, though, combat casualties died in the same way for the same reasons regardless country of origin. With regard to "shock," Churchill advised, "It is misleading when invested with a connotation of specificity that does not exist in reality."[102] Sadly, in the 60 years since these words that illuminate the pathophysiology of this syndrome, were published, little progress has been made in defining it. It might be that the more poetic definitions of prior eras are, in fact, better at capturing the sense of "shock" than are phrases that parse notions of tissue perfusion.

Samuel Gross implied as much in his 1882 warning about the insidiousness of shock: "[A] more careful examination soon serves to show that deep mischief is lurking in the system; that the machinery of life has been rudely unhinged."[103] However imprecise, this definition hints at the systematic derangement, now understood as multiple organ system failure, that "lurks" within the shock patient. In 1895, John Collins Warren described a

multiply injured patient who was "staring at the surgeon with an expression of complete indifference as to his condition."[104] Strikingly, Warren described shock as "this momentary pause in the act of death."[104] Evocative descriptions such as these provide us with as much practical insight into the phenomenon of shock as any scientific model.

In conclusion, several weeks after the 2 cousins were shot, a young man was brought to the emergency department after having been struck by a motor vehicle. He was grossly intoxicated, and had a dramatic open fracture of his forearm. Nursing notes describe him as "belligerent." It was presumed his behavior was due to his drunkenness and he was intubated and chemically paralyzed on this basis. A focused abdominal sonogram was "negative" and on the strength of this, brief episodes of hypotension were explained away. Seventy minutes after arrival he was taken to the CT scanner, where he was found to have a massive hemoperitoneum with a large jet of contrast seen arising from an injury to the splenic hilum. He was rushed to surgery for splenectomy. His hospital course was prolonged by respiratory failure, probably aggravated by the prolonged shock he experienced on admission. I am certain that all the physicians who cared for this patient were able to define shock as a syndrome of inadequate tissue perfusion: The problem was that none was able to recognize it.

Even with all of the advantages of modern medicine, shock remains a clinical challenge. Our understanding of the physiology of this syndrome far exceeds that of our predecessors, yet perhaps in our focus on "disordered perfusion" we miss its behavioral manifestations. Perhaps we can learn from Gross and Canon that it may be better to be able to recognize shock than define it. This review does, however, allow us to draw a number of definitive conclusions about the history of shock. The term "shock" has been used to describe hemodynamically unstable patients since at least 1743. The origin of the term results from a faithful translation of Henri Francois LeDran's treatise on gunshot wounds. For the first 150 years of its use, the term "shock" implied a neurologic response to injury. Common usage of the term "shock" began after the American Civil War, probably as a result of the publication of Morris's Practical *Treatise on Shock*. Success with crystalloid burn resuscitation methods in the 1960s and 1970s may have contributed to the inappropriately large volume crystalloid resuscitation strategies common in non-burn trauma during the 1970s and 1980s. Notions about the physiology of shock have changed over years and continue to evolve, but the clinical syndrome itself has not changed. Patients whose behavior "suspends the laws of economy" can be found in the resuscitation areas of any major trauma center. Because concise physiologic definition of this syndrome has proven so elusive, historical descriptions can be surprisingly useful and informative.

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