The History and Evolution of Circulatory Shock

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KEYWORDS

• History • Shock • Hypovolemic • Cardiogenic • Distributive

Claudius Galen, the famous second-century Greek physician, taught that there were two kinds of blood. ''Nutritive blood'' was formed in the liver from ingested food. This blood was carried by the veins to all parts of the body to be consumed as fuel. ''Vital blood'' was produced by the heart, traveled through the arteries, and carried ''vital spirits.'' Recirculation of blood via a cardiac pumping mechanism was not part of his conceptual framework. This view of the cardiovascular system was accepted as doctrine for millennia. William Harvey (1578–1657),[1] the court physician to King Charles I and King James I, in his 1628 treatise, ''Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus,''[2] questioned Galen's concepts and set the path to the modern understanding of cardiovascular physiology and hemodynamics. He described how the heart functions as a pump to maintain the recirculation of blood in the arteries and veins. Harvey stated, ''The blood in the animal body moves around in a circle continuously, and that the action or function of the heart is to accomplish this by pumping. This is the only reason for the motion and beat of the heart.'' Understanding the basics of circulation was the first step in understanding shock.

The history of shock starts with traumatic injury and much of the history of shock relates to the history of traumatic shock. A ''posttraumatic syndrome'' was recognized by the early Greeks, including Hippocrates and Galen. It was not until the 1740s, however, that that the term, *shock*, came into clinical use. In the late 1700s, Woolcomb, Hunter, and Latta, among others, provided clinical descriptions of shock and death caused by shock. The question of why a wounded soldier who had modest visible blood

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losses would succumb was not always clear.[3] The idea that soldiers could die from a mysterious, indefinable condition, later termed ''shock'', a process not synonymous with hemorrhage, was a novel concept.

A French surgeon, Henri Francois LeDran (1685–1770), in ''A Treatise of Reflections Drawn from Experience with Gunshot Wounds'' (1731), coined the word, *choc*, to indicate a severe impact or jolt that often led to death. Review of the original article, however, reveals that his use of the term was in reference to the original injury itself (as in a jolt or blow [ie, the initial physical injury]), not to a posttraumatic syndrome. The British physician Clarke's mistranslation of LeDran's term introduced the term, ''shock'', to the English language to indicate the sudden deterioration of a patient's condition with major trauma and wounds. The term was initially used to denote any state characterized by physical collapse.

The English surgeon, George James Guthrie,[4] was the first to use the word to specifically denote physiologic instability in 1815. Edwin A. Morris,[5] however, who began to popularize the term, using it in his 1867 Civil War text, ''A Practical Treatise on Shock After Operations and Injuries.'' He defined it as ''a peculiar effect on the animal system, produced by violent injuries of any cause, or from violent mental emotions.'' Before Morris popularized the term, ''shock'', a variety of colorful terminology often was used to describe the phenomenon, including ''sudden vital depression,'' ''great nervous depression,'' and ''final sinking of vitality.''

TECHNOLOGY

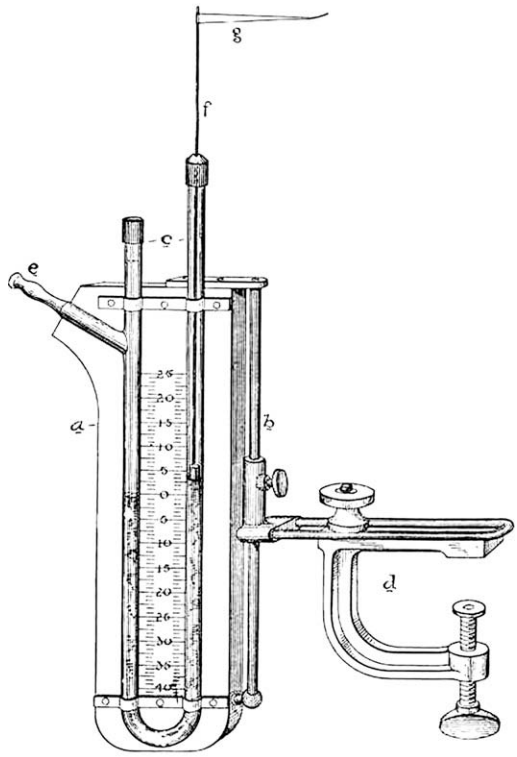
There have been several technologic advancements that have assisted physicians and scientists in understanding and treating shock. Among them, two monitoring methods stand out: the ability to measure blood pressure with the sphygmomanometer and the ability to measure cardiac output (CO) and filling pressures using a balloon-tipped, flow-directed pulmonary artery catheter. To a great extent, these devices have been the used as basis of the development of the defining characteristics of shock.

Sphygmomanometer

The first known records of blood pressure measurements were obtained by Stephen Hales[6] (1677–1761), a member of the British clergy who had no formal training in medicine and who measured the blood pressure of a horse in 1706 at Cambridge. In 1733, he published the book, *Haemastaticks*, in which he described his technique of inserting a brass tube into the femoral artery of a horse and connecting it to vertical glass tube. Arterial blood rose to a level of over 8 feet in the glass tube. After putting the tube into a vein, the blood rose only inches. This led to the discovery that blood circulated because of a pressure gradient between the arteries and veins. Hales[7] used the same technique to perform the first right and left heart catheterizations in a mammal. In 1828, J.L.M. Poiseuille, the French physiologist and mathematician, reduced Hales' bulky apparatus by having blood push against a reservoir of a substance heavier than blood (ie, mercury). Normal blood pressure would support a column of mercury no more than 200 mm high.[7,8] In 1847, Carl Ludwig modified the Poiseuille instrument by attaching a pen to a float on top of the mercury column that traced fluctuations of pressure on a revolving drum.[7,8] This was called a kymograph and became popular for keeping a permanent record of the pressure fluctuations. Karl Vierordt[9,10] designed a sphygmograph that drew pulse tracings without penetrating an artery but did not directly measure blood pressure, a predecessor to the modern sphygmomanometer. His device measured blood pressure noninvasively by using the principle that blood

pressure was equivalent to the amount of force required to obliterate the pulse. The instrument required that physicians pile up weights over an artery until the pulse tracing ceased, impractical for clinical use. Fortunately, S.S. von Basch[11] subsequently developed the first relatively accurate clinical sphygmomanometer in 1881 and in 1896, Scipione Riva-Rocci[12] introduced the now familiar instrument that collapses vessels by means of an inflatable cuff which became generally adopted in 1903 after some additional modifications (**Fig. 1**).

In the early days of shock research, it was not clear which parameter (pulse rate, pulse strength, level of consciousness, skin temperature, and so forth) was the most relevant for the diagnosis and monitoring of shock. Lockhart Mummery and George Washington Crile[8,13] (a famous surgeon-scientist in the 1800s and one of the founders of the Cleveland Clinic in 1920), proposed that low blood pressure was the central and defining feature of shock. Crile, one of the first experimental physiologists to systematically study shock, produced the seminal treatise, ''An Experimental Research into Surgical Shock,'' in 1899.[14] In this volume, he discussed his 138 animal experiments causing shock by means that had been observed in humans: laceration or incision, crush injury, manipulation of organs during operations, scalding, electrical injury, and gunshot wounds. He measured arterial and venous blood pressures, respiration, and heart rate. He also tested many remedies then used to combat shock, including cocaine and atropine.[8,14] Respected physicians and physiologists of that



Mercurial manometer with graduated scale.

Fig. 1. Mercury sphygmomanometer (circa 1905).

era, including Harvey Cushing (the father of modern neurosurgery), Lockhart Mummery, Henry W. Cook, John B. Briggs, and Theodore C. Janeway, assisted Crile in winning acceptance of the importance of blood pressure monitoring in critical illness.[8,13,15]

Although invasive arterial blood pressure monitoring in the critically ill has become the standard of practice in recent decades, the importance of the development of noninvasive blood pressure assessment for defining shock at the turn of the century has never been surpassed.

Cardiac Output Assessment and the Pulmonary Artery Catheter

Although Hales is credited with the first right and left heart catheterizations in 1711, the Frenchmen, Bernard, a physician (in 1844), and Chauveau and Marey, a veterinarian and physician, respectively (in 1861), produced the first tracings of the right and left ventricles (both groups of studies in horses) (**Fig. 2**).[7,16–18] Human catheterization was to follow. In the early twentieth century, medical dogma suggested that the introduction of a catheter into a human heart would uniformly result in immediate death. Despite this, Bleichroder and colleagues[19] performed right heart catheterization on themselves in 1905 while trying to find ways to deliver medical therapy closer to target organs. No contemporaneous tracings or radiographs were taken, however, and the work faded into obscurity. In the summer of 1929, a 25-year-old surgical resident, Werner Forssmann (1904–1979), working in a hospital in Berlin, Germany, introduced a ureteral catheter into his left basilic vein and threaded it up 30 cm (against the explicit instructions of his surgical chairman). Obtaining a radiograph, he saw that the catheter had reached his shoulder.[7,20,21] He then advanced the catheter to 60 cm and found that it was in the right ventricular cavity. The radiograph taken was the first documented evidence of right heart catheterization in a human (**Fig. 3**). The historical significance of this event has been well documented. A notable but little noticed element in this episode, however, is the fact that, to perform the procedures required (including venous cutdown), Forssmann had to restrain and tie down the surgical nurse, Gerda

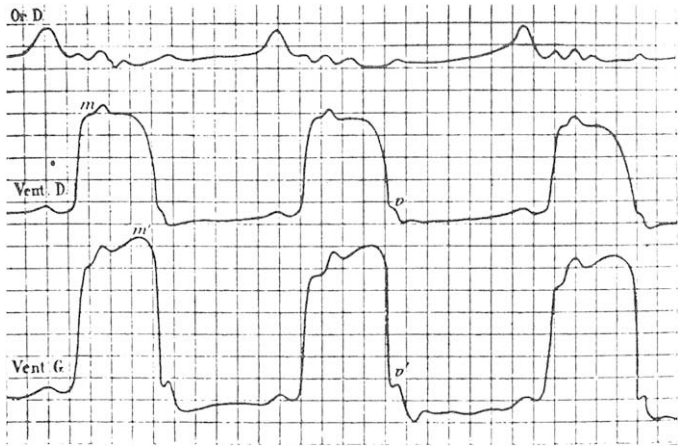


Fig. 2. Tracings of one of the earliest cardiac catheterizations (horse) by Chauveau and Marey (1863). Right atrium (*top*), right ventricle (*middle*); and, left ventricle (*bottom*). (*From* Chauveau JBA, Marey EJ. Appareils et experiences cardiographiques: demonstration nouvelle du mecanisme des mouvements deu coeur par l'emploi des instruments enregistreurs a indications continues. Mem Acad Med 1863;26:268–319.)

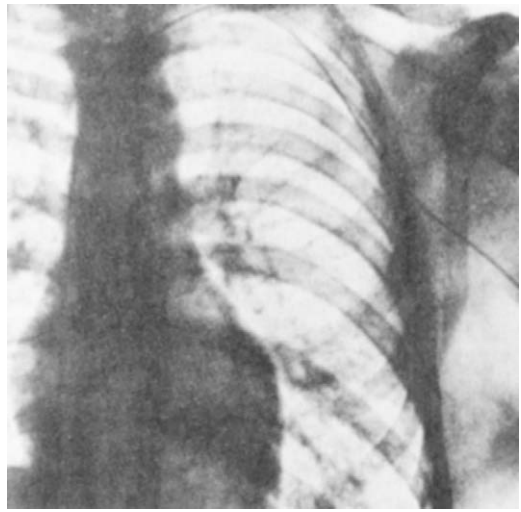


Fig. 3. Original radiograph of Forssmann's placement of a catheter into his right atrium. (*From* Forssmann W. The catheterization of the right side of the heart. Klin Wochenschr 1929;8[2085]:2087. With kind permission from Springer Science+Business Media.)

Ditzen, charged with supervision of the operating room during the procedure.[7,21] In the 1940s, Andre Cournand (**Fig. 4**) (1895–1988) and Dickinson Richards (1895–1973)[22–25] obtained right heart and pulmonary artery pressures of normal individuals and of patients who had heart failure. The studies done of right heart catheterization earned Cournand and Forssmann the Nobel Prize in Medicine and Physiology in 1956.[7,26]

Although the techniques for vascular catheterization were developing, there also were significant success in measuring human CO. A scientific basis for noninvasively measuring CO based on blood and lung oxygen concentrations dates back to Fick[27] in 1870. Indirect measurements of CO were made by Grisham and Masters[28] using pulse wave analysis in 1941 and by Starr and Wood[29] using ballistocardiographic methods in 1943. It was the work of Hamilton in 1929, however, who adapted Stewart's[30,31] indicator dye technique for human application that opened the door to the first clinically relevant studies of CO. Cournand and colleagues[24] used the technique to assess CO in traumatic shock during World War II whereas the first attempts to measure CO in myocardial infarction (using indocyanine green dye dilution) was described in 1951 by Gilbert and colleagues[32] and Freis and colleagues.[33] The first use of this technique for assessment of the hemodynamics of septic shock also is credited to Gilbert and colleague[34] during the 1950s.

The work by these early investigators and scientists eventually culminated in the development of the flow-directed, balloon-tipped, thermodilution CO-capable pulmonary artery catheter. Even though this catheter's creation is attributed to H.J.C. Swan (1922–2005) and William Ganz (1919–present), several earlier investigators provided the immediate groundwork for this development. Charles Dotter, who later gained acclaim as the inventor of angioplasty, described the first balloon-tipped pulmonary artery catheter in 1951 whereas Lategola described a soft (but not balloon-tipped) flow-directed pulmonary artery catheter in 1953.[7,35–37] Both catheters were able to obtain pulmonary artery occlusion pressures in animals but did not have thermomodilution capability. R.D. Bradley[38] was the first to describe the use of a miniature flow-directed pulmonary artery catheter in critically ill patients in 1964. The first thermodilution-derived CO catheter

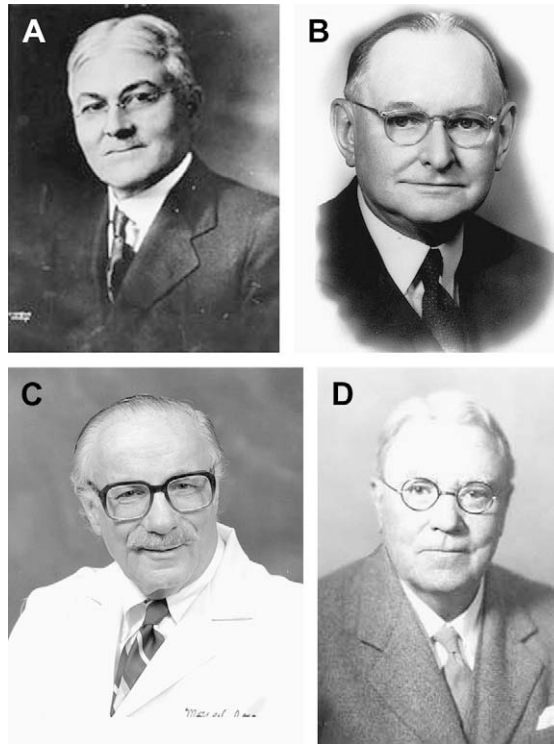


Fig. 4. Major figures in shock research during the nineteenth and twentieth centuries: (*A*) George Washington Crile (1864–1943), (*B*) Carl Wiggers (1883–1962), (*C*) Max Harry Weil (1927–present) (*Courtesy of* The American Physiological Society, Bethesda, MD; with permission.), and (*D*) Walter B. Cannon (1871–1945).

was described by Fegler[39] in anesthetized animals in 1954 but not until 14 years later did Bradley, in collaboration with M.A. Branthwaite,[40] describe the assessment of CO by thermal dilution in humans using a thermistor mounted on the tip of his earlier catheter device. Absent a balloon tip, this device did not "float" in the circulation and thus could not readily traverse the pulmonic valve into the pulmonary artery or provide a pulmonary artery occlusion pressure to estimate left ventricular end-diastolic pressure.

The eponymously named modern, balloon-tipped, flow-directed catheter now in ICUs throughout the world, was developed by Swan and Ganz. As the story goes, Swan's conception of the flow-directed pulmonary artery catheter occurred "in a brief moment of enlightenment during an outing with his children in Santa Monica."[41] Swan is reported to have noted that among many sedentary boats, a boat with a spinnaker sail catching the wind was flying by the others. Swan apparently hypothesized that a balloon attached to the end of a highly flexible catheter might, like a sail, facilitate the safe passage of the catheter into the pulmonary artery. Lategola and Rahn[37] also used the sail analogy ("As the catheter is slowly advanced into the jugular vein, the partially inflated balloon, *acting like a sail*, is swept into the right heart by the blood flow.") [*emphasis added*] in their published work almost 2 decades earlier. Ganz[42–44] initially conducted the experiments with the balloon-tipped, thermodilution-capable catheter in dogs and found that the catheter floated through the right heart into the

pulmonary artery and wedged itself in a small pulmonary arterial branch. The use of this device was documented in 1970 in *The New England Journal of Medicine*.[42] The Swan-Ganz catheter has since had a central role in shock research and in clinical ICU practice.

DEFINITIONS

Definitions of shock have paralleled the prevalent concepts regarding pathophysiology, which in turn often correlated with advancements in technology used to assess the condition. In the 1700s and 1800s, there was no understanding of pathophysiology. Definitions of shock essentially were descriptive in nature. Travers (1826) provided what might be the first etiologic definition of shock as "species of functional concussion…The influence of the brain over the organ of circulation is deranged or suspended." In 1867 Furneaux Jordan,[45] a British surgeon, described a patient who had shock: "…as pale, as motionless, as indifferent to the outward world as if the injury had already terminated in death. The pallor of the skin has the sickly white hue which only bloodless human skin is capable of presenting. The ruddiness of the lips is gone…The surface of the body is everywhere cold to the touch…Small drops of moisture lie on the skin, especially on the forehead….It is commonly said that the action of the heart is accelerated; it is certainly enfeebled, the pulse being irregular and intermittent….Most inspirations are shallow and of varying degrees of rapidity." In 1895, John Collins Warren[46] described shock as a "momentary pause in the act of death" characterized by an "imperceptible" or "weak, thread-like" pulse and a "cold, clammy sweat." In 1876, Samuel Gross described shock as a "manifestation of the rude unhinging of the machinery of life."[47]

In the early 1900s, after the introduction of the sphygmomanometer, hypotension was used to define shock. The belief held by notable physicians of the time (in particular the influential Crile) (see **Fig. 4**), that shock was the result of a disorder of the nervous system, led to definitions focused on "nervous collapse." Surgeons[48] defined shock as a bodily reaction to the wound: "severe…injuries…are followed by a train of phenomena known as shock, or a general perturbation of the nervous system." In the 1930s and 1940s, as it became clearer that blood volume was a central issue in traumatic shock, the definitions incorporated these beliefs. Alfred Blalock (see **Fig. 4**)[49] wrote, "shock is a peripheral circulatory failure resulting from a discrepancy in the size of the vascular bed and the volume of the intravascular fluid." Carl Wiggers (see **Fig. 4**),[50] in the 1950s, suggested that "shock is a syndrome that results from a depression of many functions, but in which reduction of the effective circulating blood volume is of basic importance, and in which impairment of the circulation steadily progresses until it eventuates in a state of irreversible circulatory failure." With this definition, Wiggers introduced the critical concept that shock could become irreversible, the underpinning of the golden hour concept that underlies so much shock research and therapy today. With the understanding that other disease processes (besides trauma) could cause shock, Simeone,[51] in the 1960s, defined shock as "a clinical condition characterized by signs and symptoms, which arise when the cardiac output is insufficient to fill the arterial tree with blood, under sufficient pressure to provide organs and tissues with adequate blood flow." Given further advancements, Kumar and Parrillo[52] have defined shock as the "state in which profound and widespread reduction of *effective* tissue perfusion leads first to reversible, and then if prolonged, to irreversible cellular injury." There can be no doubt future definitions of shock will continue to evolve as new insights develop.

CLASSIFICATION

Like the definitions, the classification systems for shock have evolved over time. In the early eighteenth century, shock was intrinsically related to trauma. There were initially no distinctions made between hemorrhagic shock and traumatic shock. The idea of a shock syndrome without trauma did not exist. By the mid- to late 1800s, physicians noted that some wounded soldiers who did not have shock at the outset of injury developed a secondary shock, or "wound" shock.[3,53] In retrospect, many of these cases likely were related to posttraumatic hypovolemia resulting from tissue edema or infection, but at the time the cause was entirely unclear. Sepsis as a distinct cause of shock initially was proposed by Laennec (1831)[54] and subsequently supported by Boise (1897).[55] In 1934, Fishberg and colleagues[56] introduced the concept of primary cardiogenic shock resulting from myocardial infarction.

In the early 1900s, as the scientific community came to realize that there were other forms of shock not primarily related to trauma, a broader classification system emerged. Blalock suggested a four-group classification system: (1) oligemic (ie, hypovolemic)-type (primary decline in blood volume), (2) neurogenic (primary loss of vascular tone), (3) vasogenic (primary arteriolar and capillary dilatation), and (4) cardiogenic.[57–59] With continued research into the causes of shock, a more elaborate classification system arose. In 1967, Weil[60] (see **Fig. 4**) proposed seven categories of shock: hypovolemic, cardiogenic, bacteremic (ie, septic), hypersensitivity (ie, anaphylactic), neurogenic, obstructive, and endocrine. Weil[61] later proposed a reclassification of shock grouping the seven previous categories into a simpler scheme with only four categories: hypovolemic, cardiogenic, distributive, and obstructive. Hinshaw and Cox[62] delineated the hemodynamic profiles of these forms of shock in 1972. They described (1) hypovolemic shock, resulting from a decreased circulating blood volume in relation to the total vascular capacity and characterized by a reduction of diastolic filling pressures and volumes; (2) cardiogenic shock, related to cardiac pump failure resulting from loss of myocardial contractility or functional myocardium or structural or mechanical failure of the cardiac anatomy and characterized by elevations of diastolic filling pressures and volumes; (3) extracardiac obstructive shock, involving obstruction to flow in the cardiovascular circuit and characterized by impairment of diastolic filling or excessive afterload; and (4) distributive shock, caused by loss of vasomotor control resulting in arteriolar and venular dilation and (after resuscitation with fluids) characterized by increased CO with decreased systemic vascular resistance (SVR). This four-category classification system, suggested by Weil and Shubin and whose hemodynamic profiles were described by Hinshaw and Cox, is the basis of the broad classification system used today.

HISTORY OF SHOCK RESEARCH

This review discusses some of the highlights in the development of the understanding of hypovolemic shock, particularly as a consequence of trauma; cardiogenic shock resulting from acute myocardial infarction (AMI); and distributive (ie, septic) shock. The study of shock for many years was the study of victims of injury (as a result of war, accident, or surgery). This review, therefore, has a larger section on the development of ideas related to traumatic/hypovolemic shock than other areas.

Hypovolemic/Traumatic Shock

Nervous system dysfunction

The predominant pathophysiologic theory regarding the genesis of shock from approximately the mid-1800s to World War I was that of nervous system dysfunction.

As nerves were the only anatomic structures believed ubiquitous throughout the body,[8] clinicians and investigators concluded that only a disorder of the nervous system could account for the variety of clinical signs and symptoms encountered with shock. Crile was the most prominent advocate of this theory. Bernard, Brown-Sequard, Goltz, Mitchell, Fischer, and G.H. Groeningen were among the other well-known clinicians and physiologists advancing this position. Their view is reflected in the emphasis on psychologic influences in many of the early shock definitions. James C. Mumford,[63] for example, observed in 1891 that shock could follow ''violent mental emotion'' in addition to a variety of physical ailments. In 1817, John Hunter (a British surgeon)[64] proposed that entire body ''sympathized'' with wounded part whereas Astley Cooper,[65] a British surgeon, in 1928 said there was ''irritation,'' leading to ''the remote effects of injury.'' In 1827, Guthrie[66] stated that after any wound, there was a general ''constitutional alarm'' that harmed organs distant from the site of injury. Frank E. Bunts[8] in 1891 stated, ''While some difference of opinion exists as to what proportion of the nervous system is primarily affected, yet most are agreed, I believe, that shock is the result of a sudden violent impression upon some part of the nervous system, acting not alone, as some would have us believe, upon the heart but upon the entire blood vascular system.''

There were several reasons why nervous system dysfunction won early uncritical acceptance as the cause of the clinical manifestations of shock. First, several nervous system findings, such as altered state of consciousness, anxiety, and muscular weakness, are manifested by patients who have shock. Second, many surgeons believed, as noted by Bunts, that individual psychologic differences influenced severity of shock with worse outcomes in those who had excessive fear toward operation than those who approached operation more calmly.[8] Similarly, William Gibson[67] in 1824 suggested that psychologic condition may have been the reason that similar wounds in different people produced widely varying reactions. These observations and the knowledge that people could faint on hearing bad news or on witnessing an unpleasant event provided further support to the notion that shock was a nervous system disorder. Third, given the understanding of human physiology at the time, other mechanisms by which an injury in one part of body could affect distant sites or how so many different injuries could produce the single clinical picture of shock were not readily apparent.[8] As a consequence, the concept of nervous system failure as the cause of shock became widely accepted despite the paucity of direct evidence.

By the mid–nineteenth century, a body of knowledge began to emerge indicating that the heart and vasculature were under nervous control.[8,68] This insight set the stage for the scientific theories that followed proposing a physiologic basis for the proposition that physical injury could lead to nervous dysfunction-induced shock.

In 1861, Friedrich Leopold Goltz[69,70] made a connection between nerves and the heart. Goltz performed an experiment in which he repeatedly tapped the abdomen of a frog. This caused ''overstimulation'' of the vagus nerve resulting in cardiac asystole with pooling blood in the splanchnic veins. The underlying idea was that exhaustion of the stimulatory nerves resulted in shock in these experimental animals. Based on the work of Goltz, Hermann Fischer,[71] in 1870, argued that wound injury produced a reflex paralysis of the vasomotor nerves, especially to the splanchnic vessels leading to pooling of blood in the abdominal vessels. These theories quickly were adopted by clinicians of the era. In 1864, Mitchell and colleagues[72] made the connection between vasomotor nerves and injuries causing shock in the text, ''Gunshot Wounds and Other Injury of Nerves:'' ''Recalling the fact that irritation of the vasomotor nerves is capable of producing contraction of the blood vessels, [some have] inferred that when an external nerve is violently or permanently excited, it may be able to produce

contraction of the capillary vessels of the nerve centers and thus give rise to paralysis….We suppose, first, the existence of an exterior nerve lesion, secondly a consequent irritation of the vasomotor nerves in a limited part of the spine; contraction of its capillaries, anemia, nutritive changes, and [shock].'' At the turn of the century, Samuel Meltzer put a different spin on the nature of nervous dysfunction in shock. The clinically minded Meltzer, observed that many organs, including the heart, are regulated by two sets of nerves, one which excites and one which inhibits, and argued that the general depression seen in shock might be the result not of the exhaustion of excitatory nerves but rather of the predominance of inhibitory nerve activity. Providing an experimental example, Meltzer[73,74] noted that the normally rhythmic contractions of intestinal peristalsis ceased immediately when he cut the skin of an animal. As no time elapsed in which excitatory nerves could become exhausted, Meltzer concluded that inhibitor nerves produced the inactivity. He suggested a similar explanation for all the depressed bodily functions in shock.

Given the competing theories of the time, it is no surprise that the clinical terms frequently used to describe this ''nervous dysfunction'' of shock included ''over-stimulation,'' ''paralysis,'' ''under-stimulation,'' and ''depression.''[8,75] The use of these contradictory terms was reflective of the fact that no clear consensus existed on whether or not nervous system activity required support or suppression. Based on the varying views of the nature of nervous dysfunction as the source of shock, drugs used to combat shock included stimulants and depressants, depending on which type of injury to the nerves was suspected. Strychnine, a stimulant producing convulsions and widely used as a tonic, was William Halstead's[8] therapeutic mainstay. Some surgeons suggested goading the nervous system with electric current. For those who believed the nervous system was overstimulated from wound injury, a patient's nerves could be rested with alcohol, opium, or sleep.[8,76]

Crile was one of the earliest investigators to systematically study shock. He originally was a major proponent of the theory of vasomotor exhaustion initially proposed by Goltz[69,70] and modified by Groeningen[8] to suggest ''exhaustion'' occurred in the brainstem. Many of Crile's early experiments in the late 1800s involved incising the flesh of an unanesthetized animal (presumably cutting cutaneous nerves) and assessing the blood pressure response. Crile found that immediately after the initial incision, there was a reflex fluctuation of blood pressure believed the normal response of the animal to interruption of a sensory nerve. Later in the experiment, after hours of manipulation and with the animal in shock, further incisions failed to elicit any further reflex fluctuation. This was interpreted by Crile as evidence of exhaustion of the vasomotor center after repeated insults to the animal. He believed that once the vasomotor center was exhausted and failed, large vessels would relax, blood pressure would fall precipitously, and blood would pool in the great veins. This would lead to reduced venous return to the heart, which would cause it to beat erratically leading to clinical shock.[8] In 1899, ''An Experimental Research into Surgical Shock'' by Crile[14] suggested that local anesthesia might reduce shock by preventing damaging impulses from reaching the brainstem. In 1901, in ''An Experimental and Clinical Research into Certain Problems relating to Surgical Operations,'' Crile recommended cocaine for its ability to block reflex fluctuations in blood pressure.[8] Continuing to believe that nervous impulses were responsible for the lowered blood pressure and shock, he claimed that cocaine hindered ''the passing of such afferent impulses, thereby preventing effects upon the respiration, the heart, or the vasomotor mechanism – ie, shock.''[8]

During his subsequent studies, Crile tested, alone and in combination, strychnine, alcohol, digitalis, saline solutions, adrenalin, nitrates, and a rubber pressure suit. In test after test, only adrenalin, saline solution, and the pressure suit consistently raised

pressure.[8] Notably, Crile's pressure suit was the progenitor of the later flight suits used for fighter pilots and astronauts to combat the impact of high g-force maneuvers and of medical antishock trousers. Based on his own work, Crile[77] recommended that surgeons use limited amounts of saline solution and adrenaline to raise blood pressure for management of traumatic shock (an approach that has found a place in modern practice).

In view of the later data that Crile published, other investigators began to question whether or not vasomotor exhaustion existed or played a role in the pathogenesis of shock; however, controversy on this issue persisted for decades from the late 1800s to World War I. Several experiments in the early 1900s helped put the question of ''nervous failure'' of vasomotor responsiveness as a cause of shock to rest. A key experiment overlooked by Crile and other advocates of the theory of vasomotor paralysis was performed by Henry H. Janeway[78] in 1914. Janeway surmised that if the theory of vasomotor exhaustion was correct, then shock should be able to be induced by simply overstimulating major nerves in an animal not in shock. This critical experiment failed to reproduce shock and, along with other key studies, that showed an absence of medullary damage in shock[79] helped convince investigators that the nervous system dysfunction was a manifestation rather than a cause of the syndrome. Despite these results, the final studies on the question of ''nervous dysfunction'' as a cause of shock did not occur until 1956.[80,81]

Circulating volume loss

The primary competing hypothesis to nervous system dysfunction as the cause of shock was loss of circulating blood volume. Overt hemorrhage generally was conceded to cause shock but the relationship of decreased circulating blood volume to shock absent overt hemorrhage was uncertain. The earliest insights regarding the potential role of fluid deficiency in shock dates back to the attempts by Thomas Latta[82] in 1832 to resuscitate shock due to cholera-induced volume loss with intravenous fluids. This idea generally was ignored until Goltz[70] suggested that death from hemorrhage was the result of loss of intravascular volume rather than red blood cells 32 years later. By the late 1880s to 1890s, the observation had been made that intravenous fluid replacement of lost blood could cure patients who were hypotensive and in shock from overt hemorrhage,[83–85] although this therapy would not become the standard of care for decades.

Despite this, the importance of giving fluid in shock states other than those associated with overt hemorrhage was not appreciated, perhaps because the nervous system dysfunction theory of shock was pervasive at that time. Further, the understanding of cardiac hemodynamics was in its infancy and it was not understood that even if there was venous pooling in abdominal veins, fluid infusion still could increase venous return, forward flow, and blood pressure. In the early 1900s through World War I, the central importance of fluid administration to treat dehydration and hypovolemia began to emerge. Therapy of shock typically might have included normal salt solution (rectally and subcutaneously) and strychnine (1/60 g) along with best rest and passive warming. In some cases, fluid (water) was given orally or rectally.[3,8,86] It was only in most urgent cases that intravenous route was believed necessary.

In the early 1900s, efforts were made to examine circulating blood volume and demonstrate that blood volume was decreased in nonhemorrhagic traumatic shock. Yandell Henderson and coworkers[87] first suggested in 1908 that a decrease in venous return and CO was responsible for the decline in arterial blood pressure in traumatic shock. Unfortunately, they have rarely received credit for this insight because the proposal was embedded in the ''acapnia'' theory of shock (ie, that low levels of carbon

dioxide were responsible for hypotension). Given the study design, these experiments likely represent the first examination of what would become known as obstructive shock. Henderson's model of shock required overventilation of his animals to create positive intrathoracic pressure resulting in decreased venous return. At the time, Henderson believed that it was hypocapnia-mediated venous pooling that caused the shock in the model.

In 1915, Keith and coworkers[88,89] aand Robertson and Bock[90] at John Hopkins developed and used a crude technique to measure blood volume in the field by injecting the dye, vital red, which is retained intravascularly in the plasma compartment. In their series of war-related clinical studies, the concentration of dye in the blood was measured several minutes after initial injection. From the concentration of dye in the sample, they were able to calculate the volume of blood in the body.[88,89] They found that if blood volume was approximately 75% or greater of the expected value, the blood pressure was essentially normal. If the blood volume was decreased to 65% to75% of normal, then the systolic blood pressure was 70 to 80 mm Hg and the patient showed evidence of clinical shock. If the blood volume was 50% to 60% of normal, then many patients were very ill and almost pulseless. In making these observations, they concluded that the decrease in blood volume clearly produced shock and that severity of hypotension correlated with the degree of blood loss. Effective circulating blood volume was a central factor in the pathogenesis of traumatic shock. This work was reinforced by the early animals studies of the famous cardiovascular physiologist, Wiggers,[91] who was able to demonstrate that traumatic ''surgical'' shock was most akin to severe hemorrhage in the marked decrease in blood and central venous pressure. This series of studies by Keith was a remarkable achievement that presaged Wiggers'[92,93] work on the nature of irreversible shock in his canine hemorrhagic shock model almost 25 years later.

Knowing that decreased effective volume was important, investigators then needed to determine where plasma volume was redistributed in traumatic shock patients who were not obviously bleeding. One hypothesis was that blood pooled in the abdominal veins during shock and essentially became unable to contribute to circulating blood volume (termed, *intravascular hemorrhage*), an extension of the theories of Goltz[70] and later supported by Crile.[94] The idea that a patient in shock ''bled'' into his own abdominal veins, however, primarily stemmed from Fischer's[71] animal experiments in 1870. The initial explanation for the dilated abdominal veins was based on the theory of vasomotor exhaustion where, with progression of injury, the abdominal veins would dilate and accumulate blood taking it away from the periphery and leading to the cold, pale appearance of the patient or experimental animal in shock. Given the experiments suggesting that the vasomotor center was still active in shock, however, blood vessels would be expected to be constricted, as observed in the studies refuting the vasomotor theory of shock.[78,79,95] The concept of abdominal pooling of blood volume persisted. Walter B. Cannon (see **Fig. 4**), a well known physician and physiologist, proposed early in his career that in traumatic shock blood was stagnant in engorged veins between two sets of constricted blood vessels: intestinal arterioles on one side, portal and hepatic vessels of the liver on the other. He also suggested that vasomotor nerves to these constricted vessels were responsible for the pooling of blood. The goal of therapy was to open the constricted vessels or to constrict the dilated vessels holding the trapped blood to move blood back into circulation.[50]

Crile[77] expanded on his idea of intestinal sequestration of blood volume in his 1907 article, ''Hemorrhage and Transfusion.'' This proposed phenomenon, so dominant in the medical literature of the time, however, likely was the unique result of producing shock by manipulating the intestines violently. Henry Janeway's[78] method of inducing

experimental shock, although different from Crile's, also caused blood to collect in intestinal veins. Janeway produced shock by placing a band around the inferior vena cava, which backed the blood up into the large veins. In this model, what was interpreted by Janeway as "abdominal vein hemorrhage" causing shock today would be interpreted as reduced return of blood to the heart and a subsequently diminished right heart output. The belief that blood volume pooled in intestinal veins during shock continued to be widespread in the early years of the 20th century.

Frank Charles Mann[96,97] significantly advanced the understanding of shock physiology by suggesting that the blood in the abdominal compartment actually left the veins, oozing into the surrounding tissues. He suggested, "the cause of shock is the tremendous loss of red cells and fluid from the blood, due to the reaction of the great delicate vascular splanchnic area to irritation—an acute inflammation of the peritoneum, due to trauma and exposure to the air and changes of temperature." Mann set out to measure the volume of blood lost from the circulation. To estimate the loss, Mann compared the volume of blood he could drain from the total circulatory system before and after shock induction. In a normal animal, Mann found that he could drain 76% of the blood from the body. He concluded that in normal animals, 24% of the blood was "in the tissues," presumably not subject to draining. But from animals in shock, Mann[98] could drain only 39% of the blood, leaving 61% "in the tissues," not circulating. The difference between 61% and 24% was the volume of blood believed leaked out of the vascular system, which led to shock. This again suggested that blood volume was the crucial determinant of shock.

Crile, Henry Janeway, and Mann all believed that shock occurred as a consequence of blood pooling or sequestration in the abdominal compartment. They each had induced shock (described previously) by manipulating the inferior vena cava or the bowel in a way that may have produced results in the experimental animals that were not reflective of critically ill patients (ie, the abdominal vein blood pooling may have been a phenomenon strictly of the experimental method used and not the true reason for volume loss in shock). During World War I, investigators, such as Wallace,[99] Cannon, and other surgeons, observed that in patients in shock who had abdominal operations, intestinal vein blood pooling and blood extravasation were not found. This observation led Cannon to suggest that fluid must escape from the circulation through the walls of capillaries in a more diffuse manner during shock.[100,101] This theory subsequently led to for a search for a toxic factor as the cause of shock.

Circulating "factors"

The possibility of circulating factors that might adversely affect cardiovascular stability had precedent. The concept of malignant circulating "humors" has existed since the Greek Age[86,102] The concept persisted through the Dark Ages of Europe and into the seventeenth and eighteenth centuries. Benjamin Rush, a signer of the American Declaration of Independence and the foremost North American physician of his day, advocated periodic bleeding to remove these circulating humors for a variety of ailments.[103]

Before World War I, it was known that patients could present in shock after trauma without an obvious loss of blood. At the time, a distinction was made between hemorrhagic shock resulting from obvious loss of blood from a wound and traumatic shock hypotension resulting from injury without obvious loss of blood (wound shock).[99,100] Mapother[104] in 1879 seems to have been the first to suggest that decreased CO in traumatic shock may be caused by intravascular volume loss resulting from extrusion of plasma through the vessel wall from the intravascular space to the interstitium. During the war, Cannon and many other leading physician and physiologists of the

day were deployed to the battlefields during the war to study shock and devise medical and surgical therapies for wounded soldiers. As part of the National Research Council's Subcommittee on the Physiology of Shock, Cannon and colleagues produced the first systematic clinical studies of war trauma culminating in release of the monograph, "Traumatic Shock," in 1923.[101] Their studies revealed a greater degree of hemoconcentration in the capillary circulation than the venous circulation in patients in shock compared with patients not in shock. For example, in wounded patients who were not hypotensive, the capillary and venous red cell counts were equal. In patients who had moderate shock (systolic blood pressure of approximately 90 mm Hg), there was a difference of approximately 1 million per microliter and in patients who had severe shock (blood pressure of approximately 70 mm Hg), the difference between the capillary and venous red cell count was 2 to 3 million per microliter.[101,105] This suggested that after major traumatic injury, increased capillary permeability allowed profound extravasation of fluid from the capillaries leading to hypovolemic shock.

Supporting evidence for a toxic factor causing loss of intravascular volume in shock came from experiments in animals. Sir William Bayliss, the brother-in-law of the famous cardiovascular physiologist, Ernest Starling, gained acclaim for his discovery of the first known hormone, secretin (as part of his studies of the pancreas). Although substantially forgotten today, he was also well known at the time for his shock research. Bayliss and colleagues[105,106] hammered the hind limbs of cats, dogs, and rabbits under anesthesia to cause severe crush injuries. These animals developed signs of shock with hypotension, hypovolemia, and hemoconcentration. Shock did not seem to result from local blood loss caused by bruising as the increase in weight of the traumatized limb was only approximately 11% of the animal's blood volume (a small percentage of the volume known to be lost from the animal) as measured by vital red dilution. If the vessels to the traumatized limbs were ligated, then the animals could be protected from shock; alternatively, if the vessels were left open and the traumatized limb massaged, the blood pressure worsened. Extracts of the muscle in the traumatized area could produce a fall in blood pressure if injected intravenously. These observations suggested that there was a toxic factor causing generalized increase capillary permeability with leak of plasma into the interstitium producing hypovolemia and shock. Realizing that intravenous saline would leak out of the capillaries, Bayliss helped develop a new intravenous compound—6% solution of gum acacia in saline (perhaps the first synthetic colloid)—that was used with apparently good results although less than a liter often was given.[105,106]

The next step was to determine the identity of this putative toxic factor. The agent had to result in capillary stasis with hemoconcentration, increased capillary permeability with general extravascular fluid loss, a decrease in blood volume, and a drop in blood pressure. Several potential "toxins" were studied but histamine was foremost among them as it could reproduce many of the required clinical findings, including tissue edema when injected intravenously, and it normally was found in muscle tissue.[105] Dale, Laidlaw, and Richards produced significant support in favor of the concept of histamine as a mediator of shock in the 1910s to 1920s.[107,108]

The concept of toxin-driven generalized increased capillary permeability as the etiologic basis of shock was challenged by several investigators. Blalock,[105,109] in 1930, and others in later years demonstrated that the local edema caused by trauma extends far beyond the immediate area of injury. Cannon and Bayliss measured the volume lost into the lower limb after crushing an animal's leg. They found that although not all the blood volume lost could be recovered in the immediate area of injury, most was accounted for within the limb. This suggested the possibility that earlier studies

examining posttraumatic fluid redistribution may have underestimated local fluid extravasation and overestimated distant, presumably toxin-mediated, effects.[105] Blalock found in later studies that if a hindquarter amputation was done in animals that had undergone hindquarter trauma, all the loss of blood volume was accounted for in this hindquarter amputation; generalized capillary leak was not required to account for intravascular fluid loss.[105] In addition, Blalock, Dragstedt, Mead, Code, Macdonald, and Woolfe in the late 1930s and early 1940s found that the histamine content of the blood from injured limbs showed no significant increase over control limbs.[105] Using radioactive tracers in the 1940s, Fine and Seligman showed that the rate of I^{131}-labelled albumin loss from the capillaries in the uninjured parts of shocked animals was the same as the rate of loss in normal animals.[105] A toxic factor responsible for causing shock from trauma has never been found even though a variety of hemodynamically active mediators, including tumor necrosis factor and various eicosanoids, are known to be released.

ORIGINS OF THE MODERN ERA OF SHOCK RESEARCH

Many of the advances in our understanding and treatment of traumatic shock physiology have occurred as a consequence of war. Although physicians such as George Crile and Alfred Blalock asked and answered many important questions, the era of modern shock research begins, in many ways, with the progress made during the 2nd World War when human cardiac catheterization was introduced as research tool for the systematic assessment of critical illness. As a consequence, physicians such as Henry Beecher and Andre Cournand were finally able to definitively demonstrate that hemorrhage and fluid loss was major cause of shock in the battlefield.[22,24,110] Along with Dickinson Richards, Cournand (see **Fig. 2**), a French-born naturalized US citizen, led a team of physicians at the Bellevue Hospital in New York City investigating the use of cardiac catheterization on patients suffering from severe circulatory shock resulting from traumatic injury. In 1943, the Bellvue cardiovascular research group reported their classic study of the circulation in clinical shock.[24] In one of the most comprehensive studies of the physiology of shock ever reported, all the major responses of the systemic circulation during traumatic injury were assessed. The investigators measured intravascular pressures through the femoral artery, median basilic vein and right atrium, cardiac output via the direct Fick technique, and multiple metrics of pulmonary ventilation and respiratory gas exchange. This classic study was based upon 36 cases, 16 of which were patient's suffering from skeletal trauma, four from hemorrhage, four from burns, six with abdominal injury and 6 from head injury. Detailed physiologic measurements of all patient's were undertaken on presentation and the presence or absence of the shock state shock state was characterized for each of the preceding categories and further subdivided into gradations of shock severity. Sequential measurements related to cardiac output, minute ventilation, circulating blood volume and multiple other variables similar to a contemporary ICU flow chart were recorded for all patients. These physiologic measurements of the shock state were recorded throughout the course of resuscitation. Obtaining physiological measurements of cardiopulmonary function in these patients definitively demonstrated the cause of traumatic shock- as decreased circulating intravascular volume resulting in a fall in venous return and cardiac output.[24] As a result of these findings, it was determined that the best treatment for traumatic/hemorrhagic shock was a total blood transfusion rather plasma infusion which had previously been used.

During the second half of the twentieth century, physicians became adept at recognizing and providing immediate treatment to patients who had shock, including

aggressive fluid resuscitation, transfusion, operative intervention, antimicrobial therapy, pump failure therapy, and so forth. It has become apparent, however, that patients who have been in shock for a prolonged period of time often develop multisystem organ failure especially when organ support (ie, pressor therapy, mechanical ventilation, or dialysis) is provided to extend life. The concept of multiple organ failure is inextricably linked to that of irreversible shock, as defined by Wiggers.[50] His development of the concept, that shock, if sustained, could lead to irreversible circulatory failure with death as an inevitable outcome, represents the other seminal advance that signaled the start of the modern era of shock research.

The initial studies looking at irreversible shock started in the 1900s and were given increased impetus by the 1st World War.[91] Experiments had been done to determine if there was a relationship between the amount of time an animal was in shock and the severity of the shock on survival. During the 2nd World War, Carl Wiggers,[75,93] one of the foremost physiologists of the past century, performed a series of experiments on dogs varying the blood pressure and the length of time in shock. In a canine model, blood was withdrawn until blood pressure reached a given target (usually mean arterial pressure of 30–65 mm Hg). Animals were left at that blood pressure for a period of time (45 minutes to 5 hours) before shed blood was infused back to the dogs. For a given blood pressure target, prolonged hypotension produced increasingly high mortality. In addition, many dogs recovered from hypotension of 50 mm Hg for 2 to 3.5 hours whereas few dogs survived, even after transfusion of blood back, if the mean arterial pressure had been at 30 to 35 mm Hg for 45 to 60 minutes. At autopsy, Wiggers[92,93] found that the bowel mucosa showed intensive congestion, edema, and hemorrhages with blood or blood-tinged fluid in the lumens of those dogs that failed to survive, whereas the abdominal viscera were pale or pink externally and the mucosa of the intestine appeared normal or only slightly cyanotic and swollen in the dogs that did survive. It was believed that extensive capillary damage occurred only after marked hypotension had existed for a considerable period of time and that the capillary damage was a consequence and not a cause of the hypotension. This was irreversible shock.

At the time, the etiology was believed partly related to bacterial factors.[111,112] In the 1920s, autolysing liver tissue in the abdomen of an experimental animal was believed highly toxic.[105] The basis of this toxicity was hypothesized to be bacteria (such as *Clostridium welchii*), which grew in a state of symbiosis without causing the animal any harm as long as the tissue in which the bacteria were present received an adequate oxygen supply. If the tissue died, the bacteria proliferated and produced toxins, which ultimately killed the animal. The bowel changes seen by Wiggers[92] were believed potentially related to bacteria in the bowel, which released toxins leading to death in the dogs that had irreversible shock. Jacobs and colleagues[113] in 1954 provided some support for the role of bacteria in causing death in irreversible shock by showing that the administration of antibiotics decreased mortality rate (although not totally eliminating it). Other studies suggested a bacterial factor also was associated with irreversibility of endotoxin and bacterial shock.[111] Deriving from his concepts of a toxic factor in irreversible shock, Wiggers[114] initiated the modern search for a myocardial depressant substance in shock, septic or hemorrhagic. This work later was carried forward by others, most notably Lefer and colleagues[115–117] and Parrillo and colleagues.[118]

By the second half of the century, potential irreversibility of shock was well established and formed the theoretic underpinning of concept of the golden hour used for trauma resuscitation, later extended to management of AMI and cardiogenic shock and most recently to therapy of pulmonary embolus or obstructive shock and sepsis or septic shock.[119–123]

Later military conflicts fueled further advances. During the Korean War, the relationship between circulatory shock and risk of acute tubular necrosis and the relationship of survival after trauma with early resuscitation began to be appreciated. During the Vietnam War the dominant shock research concerns became ''shock lung'' (adult respiratory distress syndrome) and postshock infections.

Septic Shock

Septic shock became recognized as a distinct entity in two different conditions—posttrauma wound injury and nontrauma infection. Wounded soldiers were known to frequently develop gangrene resulting almost uniformly in death; however, the connection between wounds and sepsis or septic shock was not made until the Spanish-American War in 1898 when clinicians recognized the disease progression.[3] Nontraumatic causes of septic shock also were discovered in the late 1800s and early 1900s. One of the earliest descriptions of circulatory failure occurring in the setting of infection was by Laennec[54] in 1831. In 1892, the famous William Osler[124] described a ''typhoid state'' occurring in patients who developed fatal pyelonephritis. In 1897, Boise[55] made a clear distinction between shock caused by hemorrhage and shock caused by sepsis.

The association of gram-negative bacteremia with sepsis and septic shock became apparent at the turn of the century. In 1909, Jacob[125] reviewed a case series of 39 patients who had *Escherichia coli* septicemia (ie, bacteremia with sepsis), 41% of whom died. He found that the portals of entry into the blood stream were biliary tract, urinary tract, gastrointestinal tract, and female genital tract. In the 1920s to 1940s, it became recognized that intravenous administration of dead bacilli and antigens (eg, typhoid toxin) could produce hypotension (ie, endotoxic shock).[126,127] In the first half of the of the past century, pyrogen (likely endotoxin) derived from *Pseudomonas aeruginosa* was used therapeutically to treat malignant hypertension.[128] In the 1950s, it became clearer that bacteremias by aerobic gram-negative bacilli were the etiologic agent in many cases of septic shock. In a review at the Minneapolis General Hospital[129] (1950–1951), positive blood cultures for aerobic gram-negative bacilli were found more frequently in patients who died of septic shock.

In Laennec's early description of septic shock, the weak heart sounds of circulatory failure were ascribed to heart failure, one of the earliest written suggestions that circulatory shock was manifested by cardiac failure (although the acceptance of the concept in the medical community predated the clinical description by decades).[81] The concept that severe myocardial failure characterized septic shock persisted through the 1800s and well into the second half of the twentieth century. Theodore Janeway[130] in 1907, Atchely[131] in 1930, and Stead and Ebert[132] in 1940 all referred to the ''the heart [cardiac] failure'' of acute infectious disease and septic conditions.

There were dissenters to the idea that myocardial depression per se dominated circulatory failure associated with infection.[81] Eppinger and Schurmeyer[133] demonstrated that acute infection (sepsis) and traumatic/hemorrhagic shock were associated with decreased plasma volume in 1928. Similarly, Atchely,[131] in 1930, suggested that a ''disproportion between blood volume and vascular bed'' was common to all forms of shock and that the appropriate treatment should be aimed at increasing blood volume. Warfield[134] in 1934 suggested hemodynamic equivalence between untreated septic and traumatic/hemorrhagic shock and suggested, as therapy, saline infusion of ''three to four liters in 24 hours.'' Moon[135] advanced this idea further, suggesting ''a disparity between the volume of blood and the volume-capacity of the vascular system,'' rather than volume loss alone, was the cause of decreased venous return in septic shock. For the most part, however, the idea that volume loss and

venodilatation may have the central role in the hemodynamic collapse of severe infection was not appreciated for decades.

In 1945, Warren and colleagues[136] published one of the earliest studies of ''cold'' septic shock and demonstrated the potential usefulness of ''vigorous anti-shock therapy directed to maintain an adequate circulating blood volume.'' This concept of ''cold'' shock in overwhelming infection was expanded on in Waisbren's[129] study (1951–1952) of gram-negative bacteremia. In that study, two clinical pictures of gram-negative bacteremia emerged—a warm and flushed (toxic) state and a cold, shock-like state. The descriptions by Warren and Waisbren of the clinical characteristics of patients who had overwhelming infection likely represent the basis of later descriptions of warm and cold phases of septic shock that dominated the clinical septic shock literature until the 1980s.[137–139]

Waisbren's early description of warm and cold shock was further explored by other investigators. Clowes and colleagues,[137] in a 1966 dye dilution study, sequentially followed 19 patients who had septic shock that resulted from peritonitis. The 12 patients who recovered promptly maintained a cardiac index of greater than 3 L/min/m^2, throughout their illness. Four patients who succumbed within 24 hours experienced a rapid fall in cardiac index between presentation (approximately 4 L/min/m^2) and just before death (approximately 2 L/min/m^2). Three other patients who responded initially but deteriorated and died between 5 and 7 days after presentation had initial low cardiac indices (approximately 2 L/min/m^2) that rose to normal (3–4 L/min/m^2) within days and then fell again preterminally (to approximately 2 L/min/m^2). This view of septic mortality as a biphasic hemodynamic phenomenon was supported by several other early clinical reports that suggested that most cases of septic shock were associated with low CO and increased SVR (for review[139]).[140–142] In 1973, Nishijima and colleagues[138] provided a simple meta-analysis of seven studies performed up to that time correlating survival with cardiac index. A strong association was shown to exist between elevated cardiac index and survival in patients who had sepsis and septic shock. These human studies were supported by animal models using intravenous bolus injections of endotoxin or live organisms.[139,143–147] Almost all of these models produced shock characterized by reduced CO and elevated SVR.

Unfortunately, just as the animal studies were seriously flawed by the assumption that endotoxin or live organism infusion mimics human sepsis, the human studies were undermined by the use of central venous pressure as the best available estimate of left ventricular end diastolic volume (ie, left ventricular preload). Despite this, several studies from that era hinted at the possibility that volume status might be a crucial determinant of cardiac index (and outcome) in sepsis and septic shock. MacLean and colleagues,[148] in 1967, demonstrated that patients who had septic shock could be separated into two groups based on low or normal central venous pressure and CO. The investigators suggested that volume replacement would be the most appropriate therapy for hypovolemic septic patients who had low central venous pressure and decreased CO. In 1970, Blain and colleagues[149] proposed that depletion of circulating volume accounted for decreased CO during human septic shock. Weil and Nifhijima[142] similarly noted a relationship between total blood volume, cardiac index, and survival in patients who had septic shock.

In marked contrast to previous studies, Wilson and colleagues[150] were able, in 1965, to demonstrate that normal or elevated CO usually characterized septic shock in humans. Wilson was among the first to comment specifically on the divergent hemodynamic profile of human septic shock (increased CO and decreased SVR) compared with cardiogenic or hemorrhagic shock. He also noted that this profile

was distinct from that of lethal canine endotoxic shock (low CO and high SVR) but that inadvertent administration of small, sublethal amount of endotoxin to humans resulted in an elevated CO and peripheral vasodilatation.[150,151] The work by MacLean, Weil, Blain, and Wilson helped to set the stage for the shock classification systems of shock that followed in a few years. Wilson's view of the hyperdynamic nature of septic shock did not become broadly accepted, however, until the widespread introduction of pulmonary artery catheters with thermodilution CO capacity to critical care units.

Cardiogenic Shock

The history of cardiogenic shock must necessarily focus on the history of coronary artery disease, as AMI is the most common cause of cardiogenic shock. The first recorded description of angina pectoris was by William Heberden,[152] who presented "a disorder of the breast" before the Royal College of Physicians of London in 1768. Most physicians believed that myocardial infarction ("angina pectoris") was a uniformly sudden fatal event; thus, for 125 years, no further progress was made. In 1880, Carl Weigert[153] reported on the pathology of these patients. He noted that many seemed to have coronary thrombosis and atherosclerosis. In 1881, Samuelson[154] first described the clinical manifestations of AMI evolving into cardiac collapse (cardiogenic shock). At the end of the nineteenth century and the beginning of the twentieth century, physicians noted that some patients were surviving this supposedly sudden and fatal event. In 1896, George Dock[155] presented his case series of four patients at the Alumni Association of the Medical Department of the University of Buffalo; one patient survived 1 week after the onset of the attack. In 1910, Obrastzow and Straschesko,[156] from Russia presented two cases of AMI that were diagnosed before death. In 1910, James B. Herrick,[157] who had earlier the same year first described sickle cell disease, suggested that the concept of universal sudden death after AMI was wrong. Efforts were undertaken to determine how to treat these patients and to determine the cause of AMI and cardiogenic shock. The initial treatment of AMI in patients surviving to hospitalization was simple sedation and bedrest.[158] Wearn[159] at the Peter Bent Brigham Hospital in Boston recommended that "every effort [be made] to spare the patient any bodily exertion" to prevent sudden cardiac rupture and death. Early mortality of patients surviving to hospitalization with known AMI was more than 30% in the first decades of the twentieth century.[158]

The care of patients who had AMI improved with advancements in technology. In 1903, Willem Einthoven, a physiology professor in Holland, devised a string galvanometer, which was able to record human electrocardiograms.[160] With this information, physicians learned to recognize patterns suggestive of AMI and learned that the most common reason for sudden death was ventricular arrhythmia. In 1947, Beck and colleagues[161] reported successful open chest cardiac defibrillation on a child who had undergone surgery to correct a defect in the sternum. In 1956, the same group[162] reported open defibrillation in a 65-year-old physician who had fibrillated post AMI. For a time, open thoracotomy, direct cardiac massage, and internal electrical defibrillation became standard management of cardiac arrest.[163] In 1956, Zoll and colleagues[164] developed an external cardiac defibrillator and demonstrated the efficacy of externally applied countershock for therapy of ventricular fibrillation. In 1960, Kouwenhoven and colleagues[165] from John Hopkins Hospital demonstrated the efficacy of sternal compression, external electrical defibrillation, and mouth-to-mouth resuscitation in restoring cardiac function to patients who had suffered a ventricular fibrillation arrest. Also, in the 1960s, Peter J. Safar established public education of cardiopulmonary resuscitation. This, combined with the establishment of coronary

care units in 1962 by Meltzer in Philadelphia, Brown in Toronto, and Day in Kansas,[166] led to the identification of more and more patients who developed cardiogenic shock.

In the first half of the past century, significant advances in understanding clinical aspects of AMI and cardiogenic shock were made. The first description of the hemodynamics of cardiogenic shock is credited to Fishberg and colleagues[56] in 1934 when they contrasted the clinical findings of cardiogenic shock from AMI to cardiac dysfunction from mitral stenosis. In 1939, Harrison[167] established cardiogenic shock as a clinical entity distinguished from other forms of shock. Later, Wiggers[168] stated, ''myocardial failure is the crux of the circulatory [shock] which follows acute myocardial infarction.'' In 1952, Agress[169] suggested a definition of cardiogenic shock as ''a reduction of approximately 30% in mean systemic arterial pressure, maintenance of this reduction with no upward trend for at least 30 minutes, electrographic evidence of severe ischemia; and the absence of arrhythmias that could account for the arterial pressure reduction.'' Clinical research in patients initially consisted of descriptive autopsy studies. These studies showed that the location (anterior or posterior) of myocardial necrosis had little relationship to the occurrence of cardiogenic shock but that the size of infarct was crucial.[170–173] Rosenberg and Malach,[174] Walston and colleagues,[171] and Harnarayan and colleagues[175] all found shock more common in patients who had large acute infarcts. Page and colleagues[172] looked at 20 patients who had fatal AMI and shock, 14 patients who had fatal AMI without shock, and 20 patients who had fatal shock but no AMI. Of the 20 patients who had AMI and shock, 19 had lost over 40% of left ventricular myocardium (old and new infarct) and one had lost 35%. Of the 14 patients who had AMI and no shock, 12 had lost less than 30% of left ventricular myocardium, one had lost 35%, and one had lost 40%. Of the 20 patients who had fatal shock but no AMI, all had widespread, microscopic-sized foci of necrosis but no large areas of necrosis. These findings helped provide fairly strong evidence that the amount of myocardium infarcted was important in determining whether or not a patient developed cardiogenic shock.

Initially, the underlying mechanism of cardiogenic shock was not well understood. It was known that the myocardium was nourished from blood that it received via the coronary arteries as opposed to the blood in the ventricular cavities. The favored hypothesis for cardiogenic shock was AMI resulting from coronary occlusion. The many investigators reporting the incidence of coronary thrombosis, however, in patients dying of AMI demonstrated that incidence varied significantly, from 21% to 95%.[176] With such a large range, it was not clear whether or not coronary thrombosis was the cause or a consequence of cardiogenic shock. Some believed that coronary thrombosis was the result of slower blood flow in the coronary circulation associated with cardiogenic shock.[176] Investigators performed experiments on animals, including ligation of different coronary arteries alone or serially; injuring the myocardium by direct trauma, heat, or electricity; and injecting microbeads into the coronaries.[177,178] In general, it was difficult to produce cardiogenic shock as the animals fibrillated with immediate death or recovered quickly without shock. With time, investigators determined that injection of microbeads into the aortic root occluded many small coronary vessels leading to progressive sublethal myocardial injury. By adjusting volume status and peripheral vascular tone, cardiogenic shock could be achieved in animal models. The introduction of selective coronary angiography in 1962 by Mason Sones from the Cleveland Clinic in Ohio[179] eventually allowed investigators to appreciate the importance of coronary occlusion as the primary etiologic agent inciting AMI and cardiogenic shock.

To study the hemodynamic effects of myocardial infarction and cardiogenic shock and to develop methods of treatment, the National Heart, Lung, and Blood Institute

funded a group of myocardial infarction research units in the United States in the late 1960s and early 1970s.[166] The relative roles of CO, ventricular filling pressure, and peripheral vascular resistance in producing cardiogenic shock required clarification.

The introduction of the balloon-tipped, thermodilution-capable pulmonary artery catheter in the mid-1970s signaled the ability to systematically assess CO in clinical shock states. With the advent of this device, studies measuring CO and filling pressures with calculation of peripheral vascular resistance could be routinely performed. Kuhn, Gunnar, Loeb, and Rahimtoola performed several clinical hemodynamic studies.[180–182] They noted that increased peripheral vascular tone and supplementation of intravascular volume status could prevent hypotension despite having a low CO. They also were able to make recommendations on the use of vasoactive agents, volume, and other therapies based on hemodynamic parameters leading to modern approach in use today.

Given the understanding that the primary problem leading to cardiogenic shock is AMI resulting from coronary thrombosis, efforts were undertaken to improve coronary perfusion and to support the circulation during the period of shock. Fluids, diuretics, and inotropic agents, including norepinephrine, digitalis, glucagons, and vasodilators, were used to support the circulation during pulmonary edema and cardiogenic shock in the early years. Because the amount of myocardium infracted correlated to the likelihood of cardiogenic shock and cardiogenic shock often is a harbinger of death, efforts were undertaken to limit the infarct size by improving myocardial perfusion. Fletcher and colleagues[183] and Verstraete[184] started the use of thrombolytic therapy into the coronary arteries to dissolve thrombus in the late 1950s and 1960s. The use of intravenous thrombolytic therapy became common in the 1980s after the results of the GISSI[185] and the ISIS-2[186] were published. The intra-aortic balloon pump was first developed for use in humans in 1968 by Kantrowitz and colleagues[187] to improve coronary perfusion and decrease left ventricular afterload. Cardiac surgery began to flourish after the development of the heart-lung machine by John Gibbons in Philadelphia in 1953 but emergency coronary artery bypass surgery to revascularize jeopardized myocardium did not develop until approximately 20 years later.[188]

SUMMARY

This narrative reviews the development of some of the major early ideas regarding the etiology and pathogenesis of shock. Most of the early history of shock has been related primarily to traumatic shock. The more recent history of the shock syndromes centers on differentiation of the clinical syndromes and their individual clinical and pathologic characteristics. Over time, the definitions, classification systems, pathogenic theories, and treatments have evolved. This evolution has been driven by the dedicated physicians and physiologists of the past on whose shoulders current intensivists and shock investigators now stand. The progress made also has been aided by a constant development of improved assessment technologies from the mercury sphygmomanometer, through the balloon-tipped, thermodilution-capable pulmonary artery catheter to current cutting-edge ICU technology that includes 3-D echocardiography and MRI. Today, shock is not a single syndrome and the definition of shock no longer is descriptive in nature. The most accepted current definition involves oxygen supply and demand at the cellular level. This oxygen supply/demand imbalance causing shock also can have various causes—hypovolemia, cardiac dysfunction, vascular failure, or obstructive processes that impair cardiac filling. Today's challenges of adult respiratory distress syndrome, multiple organ failure, and multiresistant infection are different but no less important than those faced by our predecessors who

worked to determine the etiology and basic pathogenesis of shock. Hopefully, in the future, our successors will look back on these efforts with the same respect that physicians and investigators of this era hold for the pioneering work of Crile, Blalock, Cannon, Wiggers, and their colleagues in the past.

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