Sepsis and Septic Shock: A History

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KEYWORDS

• Sepsis • Septic shock • History • Endotoxin • Cytokines
• Coagulaiton • Nitric oxide • Sepsis hemodynamics

Infectious disease has been a leading cause of death in humans since the first recorded tabulations. For example, available evidenced suggests that one third to one half of the entire population of Europe and Asia were wiped out in the Black Death Plague of the early fifteenth century. Evidence for the presence of sepsis in humans stretches into antiquity. Emperor Shen Nung's 2375 BC treatise on the treatment of fever using the herb, ch'ang shan, is one of earliest known written references to pharmacological therapeutics. From Hippocrates and Galen, to Lister, Fleming and Semmelweiss, this article reviews the notable historical figures of sepsis research. The early descriptions and theories about the etiology (microbial pathogens), pathogenesis (toxins and mediators), and treatment of sepsis-associated disease are also discussed.

SEPSIS AND THE ANCIENT GREEKS AND ROMANS

The word "sepsis" derives from the Greek "σηψιζ" which refers to the "decomposition of animal, or vegetable or organic matter in the presence of bacteria."[1] The first use of "sepsis" in the medical context occurred over 2700 years ago in the poems of Homer. In this use, the term "sepsis" derives directly from the word "sepo" (σηπω), which means "I rot." The term is also found in the writings of the great physician and philosopher Hippocrates (circa 400 BC) in his Corpus Hippocraticum. Hippocrates is well known for the introduction of the concept of dysregulated body humors (the bodily fluids of blood, yellow bile, black bile, and phlegm) as a cause of disease. Hippocrates viewed sepsis as the dangerous, odiferous, biological decay that could

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occur in the body. It was further believed that this biological decay occurred in the colon and released ''dangerous principles'' that could cause ''auto-intoxication.'' Hippocrates was one of the first to examine antisepsis properties of potential medicinal compounds including alcohol in wine and vinegar.

Galen (129–199 AD) was a prominent Roman physician and philosopher of Greek origin. Galen was also a well-revered historical figure in the study of the theories of sepsis. Based of his keen powers of observation, he was considered an authority on medicine. His initial writings and theories on medicine remained largely unchallenged until some 1500 years later.

Galen's practice was devoted to blood letting and the drainage of abscesses, but it was the use of medications to treat disease that was his passion. His collection of medicinals (''apotheca'') was the forerunner of today's apothecary (pharmacy). One of his most popular medicinal creations was theriac, a mixture of over 70 substances.[2] It was used for everything including the treatment of venomous bites, inflammation and to ward off the Black Death. No doubt theriac's popularity stemmed from one of its main ingredients: opium.

It was Galen who first described that wounds healed by secondary intention. He also theorized that the formation of pus (he described it as ''laudable pus'') was critical to the healing of injured tissues. This theory remained unchallenged until Leonardo DaVinci and Andreas Vesalius in the fifteenth century questioned the purported benefit of wound suppuration.

Further building on the putrefaction theories of the Greeks, the early Romans were convinced that within swamps, sepsis resulted from the production of invisible creatures that emitted putrid fumes called ''miasma'' or ''miasmata.'' The theory that these harmful organisms spontaneously generated formed the basis of the public health initiatives of the Romans. To the Romans, health and hygiene were paramount. Thus, early health initiatives were directed at eliminating these swamps and the creation of safe and elaborate water delivery systems and communal baths. Unfortunately, early Roman physicians did not develop the theory of infectious disease transmission by contact and preventive measures to reduce transmission were never implemented.

EARLY WORK ON THE TRANSMISSION OF INFECTIOUS DISEASE AND THE DISCOVERY OF "ANIMACULES"

Marcus Terentius Varro, in ''De re rustica libri III'' (three books on agriculture circa 100 BC), was the first to articulate the notion of contagion. He suggested, ''small creatures invisible to the eye, fill the atmosphere, and breathed through the nose cause dangerous diseases.'' In the millennia since his insightful analysis, major pandemics of bubonic and pneumonic plague, cholera, smallpox, measles, tuberculosis, syphilis, gonorrhea and influenza have devastated the human population.

In ''De contagione et contagiosis morbis'' (1546), Hieronymus Fracastorius wrote of ''contagium virum,'' the first clear suggestion of what has become to be know as the ''germ theory.''[2] In his treatise, three forms of contagion were described. He theorized that that the transmission of infections was either by direct contact, indirectly through infected articles (foments), or by transmission from a distance (airborne). He further proposed that the transmission of infection was due to tiny bodies that had the power to self-replicate and multiply. His theories bore a superficial but notable resemblance to Koch's postulates that came some 300 years later.

It wasn't until 1684 that the theory of spontaneous generation of infection began to be refuted. Francisco Redi (1626–1697) conducted experiments on the putrefaction of meat.[3] In an ingenious yet simple experiment, he placed meat in pots and covered it

with either mesh gauze or an airtight seal. For a ''control group'' he left one container of meat open to air.

He discovered that when the meat was left open to air, flies landed on the meat and it was soon covered with maggots. In the meat that was in the gauze covered pot, maggots were only present on the gauze but not on the meat itself. Meat that was in the pot covered with the airtight material had no maggots on it whatsoever. This led Redi to conclude that rather than the meat generating the ''spontaneous'' organisms, it seemed that the flies were attracted to the meat and laid eggs on it, thus creating the maggots.

This compelling experiment challenged the spontaneous generation dogma expounded by Galen. Ironically, the contemporaneous development of the microscope was used to refute Redi's experimental results. The microscope allowed visualization of ''tiny animals'' and was used as proof that putrefaction could spontaneously generate these organisms.

Galileo was the first to develop a compound microscope that was essentially a modification of his telescope. Because of technical problems, however, the images created by his microscope were blurry and had poor resolution. Therefore, despite Fracastorius' theorizing about the transmission of infectious agents, little work was initially carried out to discover or describe potential pathogenic agents.

It wasn't until several hundred years later that the resolution of the microscopes improved and allowed scientists to study life at a cellular level. Anthony van Leeuwenhoek (1632–1723) had no scientific background or medical training, yet he was able to build his own compound microscope and made a number of significant discoveries to advance the study of infectious disease.[4] Leeuwenhoek's first description and drawings of ''animacules'' in 1674, including spheres, rods and spirals (ie, cocci, bacilli and spirochetes), paved the way for other scientists to further develop germ theory (**Fig. 1**).

THE GOLDEN AGE OF GERM THEORY: SEMMELWEISS, LISTER, KOCH AND PASTEUR

The nineteenth century ushered in an era of exponential growth in the knowledge of the origin and transmission of infectious disease. Joseph Lister, Ignaz Semmelweiss Louis Pasteur, and Robert Koch were all physicians in the nineteenth century who contributed seminal advancements in the origin of sepsis.

The earliest of these men, Ignaz Semmelweiss (1818–1865) was a physician in Vienna, Austria. In 1841, he worked on a maternity ward in a hospital and noticed that there was a high rate of death from childbed fever, also called puerperal sepsis.[5] Semmelweiss further observed that women whose deliveries were assisted by midwives had a significantly lower rate of infections than those who were assisted by medical students (2% versus 16%). At the time, medical student's practice was to perform autopsies on the women that had died the previous day, and then without hand washing, proceed to perform deliveries later in the day.

It wasn't until one of his colleagues died of an infection (acquired after cutting himself accidentally during an autopsy) that Semmelweiss made the connection between the medical student deliveries, autopsies, and puerperal sepsis. Semmelweiss commented: ''The fingers and hands of students and doctors, soiled by recent dissections, carry those death-dealing cadaver's poisons into the genital organs of women in childbirth.''[6]

Semmelweiss then instituted a hand washing policy in his maternity ward before patient contact and he saw the rates of puerperal sepsis drop to less than 3%. Despite these impressive results, the concept of hand washing was not met with great enthusiasm by the medical establishment of the day. Semmelweiss was told that ''Doctors

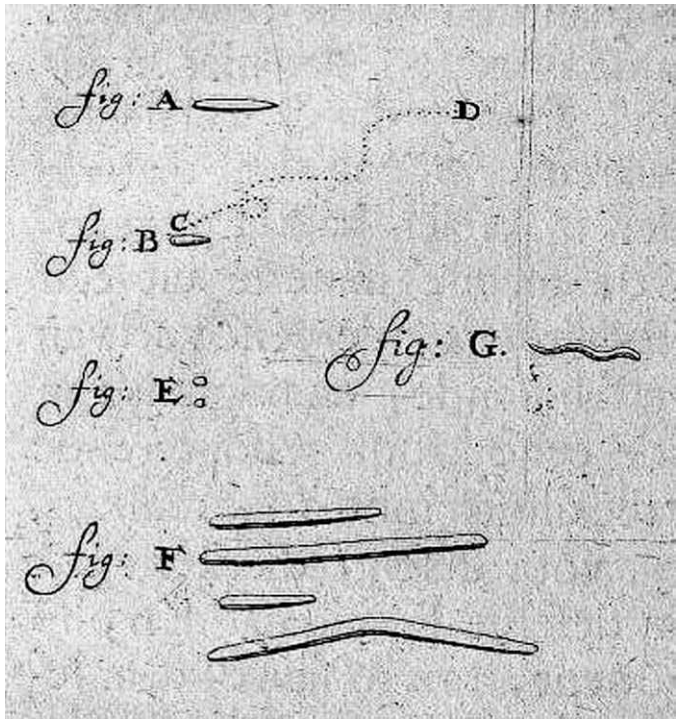

Fig. 1. Leeuwenhoek's first drawings of "animacules" including spheres, rods and spirals (ie, cocci, bacilli and spirochetes).

are gentlemen, and gentlemen's hands are clean." He was fired from his position in the hospital and later died in an insane asylum of an infection he acquired after a finger laceration. Ironically the infection was probably due to either *Staphylococcus* or *Streptococcus*, and thus bore a striking resemblance to puerperal sepsis. It is also somewhat ironic that 160 years after his discovery of hand hygiene as an important tool in infection control, many medical professionals still fail to utilize this key preventative measure on a routine basis.

The mid-nineteenth century also saw the exponential growth of surgical procedures. The development of anesthetics reduced the fear and pain associated with surgery. However, the incidence of infection and resultant death from postoperative sepsis paralleled the rise in the number of surgical procedures performed.

Joseph Lister (1827–1912) (**Fig. 2**) was born in England shortly before Semmelweiss' observations on the cause of puerperal sepsis were published. He was born to parents with scientific interest; his father was a member of the Royal Society of Fellows. At the age of 17, Lister entered University College of London and subsequently graduated from medical school in 1852. He accepted a surgical internship at the Edinburgh Royal infirmary, and it was here that he challenged the perceived etiology of wound suppuration that was widely held at that time.[7] Despite the findings of Redi and Leeuwenhoek and the early bacterial classification system developed by Christian Ehrenberg (circa 1838), it was still widely believed that wound sepsis was due to contagions in the air. Lister astutely observed that wound sepsis occurred in patients who had open wounds and theorized that the infectious agents gained access to the body through breaks in the skin. Lister eventually accepted a position

Fig. 2. Portrait of Joseph Lister (1827–1912).

as Professor of Surgery in Glasgow. He was placed in charge of a new facility whose mandate was to reduce the deaths from postoperative sepsis. His early efforts in this regard were disastrous as 45%–50% of patients died of infections.[8]

Around the same time, Louis Pasteur (1822–1895) was conducting his experiments on the germ theory of disease. Pasteur boiled broth (to sterilize it) in flasks that had swan shaped, curved necks. He allowed the flasks to remain open to air. Microbes invariably were present in the neck of the flask but were not in contact with the broth. In the flasks where the broth did not contact the microbes that accumulated on the neck of the flask, no growth occurred and the broth remained clear. Pasteur tipped some of the flasks so that the broth was in contact with the neck of the flask, and the microbes from the air. Those flasks that were tipped consistently demonstrated a change in the broth from transparent to opaque, indicating bacterial growth. Pasteur thus clearly demonstrated that putrefaction required living organisms and finally disproved the spontaneous generation theory of disease transmission.[3,6]

Eventually, Pasteur formally proposed "Germ Theory" to the French Academy of Medicine in 1878. Later he presented data demonstrating streptococci as the cause of puerperal sepsis.

News of Pasteur's experiments found its way to Lister in England. This news led to the formalization of Lister's own thoughts regarding germ theory as it related to wound sepsis. Lister hypothesized that the fermentation that Pasteur demonstrated was the same process that Lister observed in his patients with infected wounds. Lister then emulated the approach of an acquaintance, an engineer who was able to eliminate the odor from sewage with the use of carbolic acid. By the addition of carbolic acid to wound dressings, Lister was able to significantly reduce the rate of wound sepsis and death in his hospital.

In 1867, Lister presented his research to the British Medical Association demonstrating his wards at the Royal Glasgow infirmary were free of infections for 9 months. The same year, *The Lancet* published his seminal paper "On a New Method of treating

Compound Fracture, Abscess, etc., with Observations on the Conditions of Suppuration," Lister's first paper on antisepsis.

Despite the impressiveness of his results, the medical community at large was slow to accept his findings, and this frustrated Lister. He wrote: "but the carrying out of this rule implies a conviction of the truth of the germ theory of putrefaction, which, unfortunately, is in this country the subject of doubts such as I confess surprise me, considering the character of the evidence which has been adduced in support of it."[6]

In 1877, as Chair of Clinical Surgery in King's College, Lister introduced his theory of antisepsis to the department. He all but eliminated the smell of wound sepsis on the wards. That same year, under aseptic technique, he performed an open patellar repair that was successful and did not result in postoperative sepsis. This was remarkable at the time, as this operation was associated with a high rate of death. News of his success was widely publicized and resulted in a paradigm shift in the surgical community and resulted in the reduction of postoperative infectious complications.

Lister further revolutionized the field of antisepsis by discovering that sutures soaked in carbolic acid and cut short further reduced wound infections. Interestingly, in the 15th and sixteenth century, gunshot wounds were thought to be poisoned. For that reason, a suture (or seton) was intentionally placed in the wound and left to suppurate to facilitate healing.

Like many scientists of his day, Lister conducted experiments using himself as a subject. He worked on trying to find the right concentration of carbolic acid in dressings that provided an adequate amount of antisepsis, without being caustic to skin, a problem that affected both wounds and surgeons' hands.

During the same era as Lister and Pasteur, Robert Koch (1843–1910), who would eventually be recognized as one of the fathers of modern microbiology, was also working on the germ theory of disease. Koch was able to demonstrate that sheep infected with anthrax had tiny rod shaped organisms growing in their blood. He was able to culture and grow this agent with nutrient gelatin that he created. Inoculating healthy sheep with the cultured material also led to the development of anthrax. Koch then formulated his famous postulates on the identification of infectious agents. Koch said that in order to establish an agent as the cause of disease: (1) the agent must be isolated from the diseased animal; (2) the agent must be grown in culture; (3) infection of a healthy host with the culture must produce the disease; and finally, (4) the same organism must be recovered from the newly infected animal. Koch, along with his partner Julius Petri (who created the eponymous plate), were instrumental in developing modern microbiological techniques that allowed the furthering of the germ theory of disease.[3,6] Koch is also credited with the demonstration that steam could sterilize instruments with greater efficacy than the chemical disinfectants of the day. This led to the first surgical autoclaves by Ernst von Bergmann and Curt Schimmelbusch in 1885, a seminal event in the development of modern aseptic surgery.

MAGIC BULLETS AND EARLY ANTIBIOTICS

The use of agents to treat infection and sepsis goes back at least to the time of Hippocrates who used myrrh, wine, and inorganic salts to treat wounds. The Chinese utilized moldy soybean curd to treat carbuncles, boils and other infections some 2500 years ago. Up until the germ theory became accepted, therapy for infections remained strictly empiric. With the germ theory fully entrenched in the medical community, attention then turned to the targeted eradication of these newly discovered infectious organisms.

The development of modern antibiotics is often credited to Alexander Fleming's discovery of penicillin. However, it was Paul Erlich (1845–1915) who first theorized about the existence of compounds that might kill these newly discovered causative agents of infection and sepsis. Erlich's early work focused on the identification and staining of bacteria. Erlich theorized that if bacteria were able to selectively take up dye, then perhaps this property would allow the creation of a ''magic bullet,'' as he called it, to kill the bacteria. The discovery of *Treponema pallidum* as the causative agent of syphilis in 1905 set Erlich out to discover a compound that killed the bacterium but didn't harm the host. After many unsuccessful attempts, Erlich finally discovered his magic bullet after more than 600 other compounds failed. The compound he created was called ''salvarsan'' and contained arsenic. It soon became the standard treatment of syphilis.[2]

Thirty years later, the discovery of sulfa drugs as viable antimicrobial agents was directly attributable to Erlich's work. Gerhard Domagk (1895–1964) in 1935 showed that when prontosil red (a dye commonly used to stain bacteria) was injected into mice, they seemed to be protected from developing sepsis when infected with streptococci. It was later realized that the dye was converted in the body to sulfanilamide. Several compounds were then created that had increased effectiveness against bacteria. For his work, Domagk was awarded the Nobel Prize in 1939.[9]

Sir Alexander Fleming (1881–1955) was born in England and, at the suggestion of his brother, became a doctor. His initial posting was at the St. Mary's hospital where he was an assistant bacteriologist. He served during World War I and saw many soldiers die from overwhelming infection and sepsis. This observation fueled his interest in discovering a cure for infections.[10]

Fleming's discovery of penicillin, like other great scientific discoveries, was serendipitous. While working on the properties of staphylococci, Fleming discovered that some of his culture plates had been contaminated with a spore of the blue mold *Penicillum notatum* from a neighboring mycology lab. Fleming noticed that there was an area around the mold where bacteria didn't grow, and he was able to identify the substance that caused the bacterial inhibition. He called the substance ''penicillin'' and published his work in 1929 (**Fig. 3**). Fleming had difficulty purifying the substance,

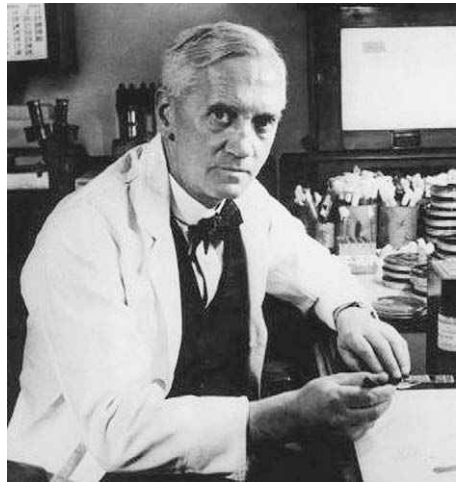

Fig. 3. Sir Alexander Fleming.

and didn't think, at the time, that it would be an important contribution to the treatment of infections.

Ernest Chain, a chemist, and Howard Florey, a pathologist, studied Fleming's work while they were both at Oxford. They were able to deduce the structure of penicillin and then developed the process to purify and mass-produce it. Fortuitously, their discovery came in time for the Second World War, a development that doubt saved tens of thousands of soldiers from a septic death.

Despite Fleming's initial skepticism about the utility of penicillin, he made several important observations about bacterial resistance. He noted that bacteria became resistant to the effects of penicillin if they were exposed to too little concentration of the drug or for too short a duration. Fleming also was an accomplished painter and used bacterial culture as his paint. He used *Serratia* for red, different species of *Micrococcus* for yellow, red and pink, and *Bacillus* for purple.[8]

The work of Fleming, Florey and Chain opened the floodgates of antimicrobial development and ushered in the golden era of antibiotics. For their combined work, they were awarded the Nobel Prize in 1945. Streptomycin, the first aminoglycoside antibiotic, was developed the same year they were awarded the prize.

THE DISCOVERY OF THE ROLE OF ENDOTOXIN

Very early in the descriptions of infectious diseases, there was controversy as to the mechanistic cause of death. The debate as to whether contagion or 'miasmata' ultimately resulted in death dates back to the time of Galen and Hippocrates.

Early physicians recognized that the malodorous smell emanating from patients with the plague bore a similarity to that found in swamps and marshes. This observation led the early physicians to conclude that there was some decay or putrefaction process that was going on in the patients that was similar to what was occurring in the swamps. The reasoning was then extended, and the thought of the miasma or miasmata (from the Greek meaning to ''pollute'') as the cause of the disease was postulated. The rapid spread of diseases, such as the plague through the air, was used as proof of this theory. However, the common practice at the time was to isolate patients for 40 days to quarantine them. The reason that this seemed to decrease the spread of the disease could not be adequately explained by these early physicians. The remnants of this historical concept of miasma as cause of disease persist today in the term ''malaria'', literally bad air, used to name the parasitic disease.

The alternative belief was that a poisonous material that was created by the putrefaction process caused disease. In distinction to the miasma hypothesis, those that subscribed to the contagion (from the Latin contigere, to touch) view of infectious disease thought that direct contact between an infected and susceptible individual was necessary to transmit infectious disease.

One flaw in the contagionist's reasoning was that a single contact with a sick person could transmit so much poison that it would be fatal for the affected person and potentially thousands of others. It was the hypothesis of Jacob Henle (1809–1885) that the contagion could reproduce in the body of the susceptible host and lead to further infection.[11] The implication of this conjecture was that the contagion had to be a living organism in order to reproduce. Henle later went on to become one of Robert Koch's teachers and his early postulates on the transmission of infectious disease clearly influenced Koch later work.

With these theories in mind, the search began for the mechanism of action of these poisons. It seemed unusual that infective material could have such serious consequences for a host organism. It appeared that a remarkably small amount of infectious

particles caused serious toxicity and even death, which seemed out of proportion to the apparent inoculum size.

The heat sensitive toxins isolated by Ludwig Brieger (1849–1919) in the culture supernatant of diphtheria were the first true exotoxins to be discovered.[11] These toxins were noted to be produced during the life of the parent microorganisms. Other organisms studied also seemed to have these heat labile toxins that acted as mediators of disease.

Richard Pfeiffer (1858–1955) (**Fig. 4**) was researching the mechanism of cholera pathogenesis using *Vibrio cholerae* but could not find the typical exotoxin that had been described in other organisms. Pfeiffer inoculated guinea pigs with *V cholerae* that had either been actively or passively immunized. Much to his surprise, the animals still died, but no organism was found in their abdominal cavity. It appeared that the bacteria had undergone lysis and a toxic intracellular factor had been released. Pfeiffer then showed that the toxic factor was not destroyed by heat like the typical exotoxin. It was, thus, not a classic heat sensitive exotoxin protein generated during bacterial growth that caused the guinea pigs to die. His experiments led him to conclude that there was a heat stable substance in the bacterial cell wall released with cell death that was responsible for the toxic effects of *V cholerae.* He named this substance ''endotoxin'' (because it came from inside the cell) and went on to discover this substance in several other bacterial species.[11]

Later, Italian pathologist Eugenio Centanni discovered the relationship between Pfeiffer's endotoxin and the ability of bacteria to cause fever. He found that these substances were chemically inseparable from the bacterial cell wall and he named the material pyrotoxin, from the Greek meaning fire.

Further work in the twentieth century by Osborn and Nikaido has demonstrated the numerous bacterial species that use endotoxin as a pathogenic mediator. They are also largely responsible for determining the chemical composition of the substance including the O antigen, core region and lipid A components of endotoxin.

Fig. 4. Richard Pfeiffer (1858–1955), discoverer of endotoxin.

THE COAGULATION SYSTEM

The coagulation cascade is well preserved throughout phylogeny. Even primitive organisms without an organized circulatory system have a rudimentary coagulation system.[12] It is thought that this system was developed to isolate invasive microbes and prevent them from gaining access to the whole organism.[13] In retrospect, the involvement of the coagulation system in overwhelming infection is reflected in history in the purpura associated with plague and other overwhelming ''pestilent fevers'' of antiquity. Hornung recognized a form of febrile purpura as early as 1734.[14] Manasse provided one of the earliest experimental demonstrations of disseminated intravascular coagulation as a consequence of microbial pathogens in 1892.[15] Disseminated microthrombi were found in experimental animals subjected to endotoxic shock through injection of heat-killed Salmonella. Two years later, Sanarelli noted a generalized, preterminal purpura in monkeys subjected to a similar insult, a phenomena he labeled ''epithalaxis''.[16] In 1926, Zdrodowsky and Bren provided the first detailed pathological description of disseminated microthrombi in association with a bleeding diathesis in endotoxic shock.[17] Early in this century, the role of infection as a source of coagulopathy was well recognized in recommendations that source control could lead to resolution of ''thrombocytopenic purpura hemorrhagica.''[14] Many other overlapping terms were used to describe what is now recognized as disseminated intravascular coagulation. The first use of this term in the published literature is found in 1951, although it use did not become routine until the 1960's.[18–20]

Because patients with purpura fulminans had evidence of micro-and macrovascular clotting at the time of autopsy, and activation of the coagulation system secondary to the infection was postulated as the cause of this, treatment with anticoagulants during infection was proposed to potentially have therapeutic benefit. In one of the earliest efforts to treat infection with anticoagulant therapy, Friedman and colleagues treated a patient with aortic valve endocarditis with an infusion of heparin for 10 days in 1938.[21] The infusion had to be stopped ''early'' as the patient deteriorated and suffered a fatal intracranial hemorrhage (likely from pre-existing cerebral embolus). Antibiotic therapy was not given to this patient. Ironically, the next article in the journal was on the antibacterial activity of sulfanilamide. Several other reports over the ensuing years described the combination therapy of heparin and antibiotics with mixed results.

Based on this early work, other clinicians began to use anticoagulant therapy on patients with infections. In a report from 1959, Little reported the successful treatment of infection-associated purpura fulminans with heparin and antibiotic therapy.[22] The patient recovered from her infection and did not require amputation of her limbs, presumably because of the improved blood flow to her limbs because of the heparin. Little and other investigators of the period also showed that coagulation was altered and fibrinogen decreased in some patients with sepsis and septic shock.

The extreme example of the coagulation defects in sepsis is in fulminant meningococcemia. This disease results in a widespread activation of the coagulation cascade with a simultaneous suppression of fibrinolytic pathways. Although this phenomenon was reported as early as the late 1950s, there was no mechanistic explanation as to how infection could activate the coagulation cascade. It wasn't until the discovery of cytokines (see below) that the complex interactions between the coagulation system and the inflammatory system began to be appreciated.

During the 1960s and 1970s, significant and parallel discoveries regarding the coagulation and inflammatory cascades were being made. In one of the earliest reports linking pro-inflammatory mediators to a pro-coagulant state, Nawrooth and colleagues demonstrated that interleukin-1 (IL-1) induced an endothelial procoagulant that

eventually became known as tissue factor.[23] Other investigators then showed that other substances related to the inflammatory cascade, namely endotoxin, complement and viruses were able to activate the coagulation cascade.

Even before the mechanistic explanations of the interaction between these two systems was elucidated, clinicians were using newly discovered and purified natural anticoagulants in severe disseminated intravascular coagulation (DIC) to attempt to prevent organ system dysfunction. In one of the earliest reports, Schipper and colleagues infused antithrombin III ([ATIII], a serine protease that affects the intrinsic, extrinsic and common coagulation pathways) into patients with DIC to try and reduce the organ damage from a dysfunctional coagulation system.[24] This approach seemed to have some beneficial effects. It wasn't until 20 years later that it was discovered that low levels of this natural anticoagulant portended a higher rate of death in human septic shock.

Eventually, several novel anticoagulant therapies were tested in humans in several large randomized controlled trials.[25–27] These included antithrombin III, tissue factor pathway inhibitor, and activated protein C. Unfortunately, only the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study examining activated protein C yielded positive results with a 6.1% reduction in absolute mortality.[26] Despite this positive trial, there were some controversies with the results of the trial, due to changes in the study protocol during the study.[28,29] A subsequent trial in patients at a low risk of death of sepsis did not show a benefit of the drug.[30] As a result, the study is being repeated in patients with a high risk of death from sepsis.

CYTOKINES

It could be argued that the earliest work on cytokines dates back to the time when fever, swelling and pain were noted to be associated with wounds containing pus. The origin of modern cytokine research probably is found in the observations of Rich and Lewis in 1932; they observed antigen-mediated inhibition of neutrophil and macrophage migration in tuberculin-sensitized tissue.[31] By the 1940s, ''soluble factors'' derived from the white blood cells from the pus of patients with infection were found to have effects on the body.[32]

Menkin, in 1944, was the first to attempt to purify the factors possessing the ability to induce a febrile response in animals from inflammatory exudates.[33] Menkin called these factors ''pyrogens'' from the Greek word ''pyros'' meaning ''fire.'' These factors were subsequently shown to be contaminated by endotoxin (see above). The difficulty in studying these factors prior to the 1970s was that the technology to elucidate the structure of these novel molecules was in its infancy. For the most part, scientists were left with only phenomenological observations of their purified factors.

Subsequently, a series of studies suggested the possibility of biologically active soluble factors released from a variety of cell types. One of the earliest descriptions of the effect of a purified cytokine was by Isaacs and Lindenmann who described and named ''interferon'' as a factor; it was produced by virus-infected fibroblasts in 1957. The substance was so named because it interfered with the production of new viruses and made uninfected cells resistant to infection.[34,35] David and colleagues, as well as Bloom and Bennett, independently described the first lymphokine, a macrophage migration inhibitory factor that inhibited migration of macrophages in response to microbial antigens in 1966.[36,37] In the 1970s and 1980s, the field of cytokine biology went through rapid expansion and several new factors were discovered. As it became apparent that a wide variety of cell types could generate soluble factors with a wide variety of biological activities related to immune function, Cohen proposed the inclusive term ''cytokine'' for these factors.[38,39]

In 1971, Gery and colleagues described a monocyte/macrophage-derived thymocyte mitogenic factor derived from human peripheral blood, which they termed "lymphocyte activation factor."[40] This factor, the first known monokine, is now known as interleukin-1(IL-1). The earliest studies of what would later be recognized as IL-1 probably occurred in the work of Menkin and Beeson (circa 1943–1948) when they demonstrated the pyrogenic activity of the protein component produced by cells in rabbit peritoneal exudate.[33] Despite potential contamination with endotoxin, it is likely that a significant portion of the pyrogenic activity of the exudate was related to IL-1. Interleukin-1 is now widely recognized as having a central role in the pathogenesis of sepsis, based on a large body of research spearheaded by Dinarello, Wolff, and colleagues.[41,42]

Along with IL-1, tumor necrosis factor was among the earliest monokines found to have a central role in sepsis and septic shock. The term "tumor necrosis factor" derives from its earliest known biological activity as described by Carswell in 1975.[43] His research described it as a cytotoxic protein found in the blood of endotoxic-shocked animals that could mediate hemorrhagic necrosis of mouse sarcoma tumors. Initially, this compound was also referred to as "cachectin" in recognition of its ability to modulate adipocyte function by suppressing lipoprotein lipase (producing hyptertriglyceridemia), which resulted in rapid weight loss in experimental animals.[44] Eventually, Beutler and colleagues were able to demonstrate that cachectin and tumor necrosis factor were the same compound. A group of investigators including Tracey, Beutler, Lowry, Cerami and others elucidated a central role for tumor necrosis factor in septic shock and other systemic inflammatory states.[45,46]

The discovery of the role that cytokines played in the activation of the immune system led clinicians to investigate these substances as therapeutic targets for the treatment of sepsis and septic shock. Both cytokines and anti-cytokines have been studied as potential therapies to modulate the immune response to sepsis. The pleiotropic effects of these molecules account, in part, for the failures of cytokine and anti-cytokine clinical trials in human sepsis. There has been more success in utilizing these molecules anti-inflammatory effects for conditions such as rheumatoid arthritis.

NITRIC OXIDE

Shortly after the discovery of the role of pro-inflammatory cytokines in sepsis, a central mediator of their effects on the vascular system was found. This factor dilates blood vessels and so plays a key role in the pathogenesis of sepsis. This factor was initially called endothelial-derived relaxing factor (EDRF) and eventually discovered to be nitric oxide (NO). A discussion of the history of sepsis research would not be complete without a discussion of this unique substance.

The history of the discovery of NO dates back to 1948 when Folkow and colleagues described the vasodilatory effects of cholinergic stimulation of arterial vessels in the hind limb of a cat.[47] This vasodilation was abolished by atropine and the inference was made that acetylcholine released from sympathetic nerve endings resulted in the dilation of smooth muscle. When the vessels were studied in vitro, however, acetylcholine consistently caused the vessels to contract.[48]

The discrepancy between the behavior of arteries in vivo and in vitro was explained in a serendipitous discovery by Furchgott in 1980. Arteries that were studied in vitro typically had their adventitia and endothelium removed to obtain a pure smooth muscle preparation. Furchgott's technician had inadvertently neglected to remove the endothelium for one of the experiments and the vasodilating properties of acetylcholine were again realized. This led Furchgott to hypothesize that there was an endothelial-derived factor that caused the smooth muscle to relax. He thus named it "EDRF."[49]

It was not until the 1980s that the nature of EDRF was elucidated. At the time, the vasodilatory effects of nitroglycerine (NTG) and sodium nitroprusside (SNP) were known to be mediated through the sequential generation of nitric oxide and cyclic guanosine monophosphate (cGMP).[50] In addition, acetylcholine was known to depress the contractile function of isolated cardiac myocytes through a cGMP-dependent mechanism. Nonetheless, for many years the potential link between acetylcholine mediated vascular relaxation and NO/cGMP was unrecognized. Eventually, it was shown that EDRF exerted its vasodilatory effects by working through the cGMP system.[51] The similarities between EDRF and NO were well described by 1986; in 1987, two independent laboratories published conclusive proof that NO was EDRF.[52,53] Furchgott, Ignarro and Murad were awarded the Nobel Prize in Medicine in 1998 for their part in the discovery of NO and its impact on the vasculature.

NO is now recognized to play a pivotal role in the pathophysiology of cardiovascular collapse in sepsis. In the normal state, endothelially produced NO regulates microvascular tone and is responsible for local leukocyte adhesion and platelet aggregation. When sepsis develops, NO is produced in substantial excess by endothelium and adjacent vascular smooth muscle.[54] This excess NO production results in the intense venodilation and vascular collapse of septic shock. In addition, nitric oxide also appears to be substantially responsible for sepsis-associated myocardial depression.[55]

Other investigators have found that NO also binds to cytochromes in the respiratory chain of mitochondria resulting in the termination of cellular respiration and the onset on anaerobic metabolism.[56] Thus, one of the theories about the mechanism of organ dysfunction in sepsis is that of NO-mediated mitochondrial dysfunction. Like so many other targeted therapies for sepsis, the inhibition of NO synthase in clinical trials showed no benefit, and had to be stopped early because of an increase in mortality in the treatment arm.[57]

CLASSIFICATION AND CLINICAL THEORIES OF SEPTIC SHOCK

Although work originating from the battlefields of World War I clearly linked traumatic shock associated with substantial, obvious bleeding to a loss of circulating blood volume, the origin of traumatic shock in the absence of defined hemorrhage was unclear.[58] The accepted explanation for this phenomenon remained a variation of the vasomotor paralysis theory of shock. It was postulated that nonhemorrhagic, post-traumatic shock (''wound shock'') was caused by the liberation of ''wound toxins'' (histamine and/or other substances) that resulted in ''neurogenic'' vasodilation and peripheral blood pooling. However, after the war, Blalock and others demonstrated in animal models that nonhemorrhagic traumatic shock was caused by the loss of blood and fluids into injured tissue rather than circulating toxins resulting in stasis of blood within the circulation.[59] Nonetheless, this concept was one of earlier enunciations of the currently accepted pathophysiologic paradigm of sepsis and septic shock.

Although hypovolemic shock associated with trauma was the first form of shock to be recognized and studied, by the early 1900s it was broadly recognized that other clinical conditions could result in a similar constellation of signs and symptoms. Sepsis as a distinct cause of shock was initially proposed by Laennec (1831) and subsequently supported by Boise (1897).[60,61]

In 1934, Blalock developed the precursor of the most commonly used shock classification systems of the present. He subdivided shock into four etiologic categories: hematogenic or oligemic (hypovolemic), cardiogenic, neurogenic (eg, shock after

spinal injury), and vasogenic (primarily septic shock). Shubin and Weil, in 1967, proposed the additional etiologic categories of hypersensitivity (ie, anaphylactic), bacteremic (ie, septic), obstructive, and endocrinologic shock.[62] However, as the hemodynamic profiles of the different forms of shock were uncovered, a classification based on cardiovascular characteristics (initially proposed in 1972 by Hinshaw and Cox) came to be accepted by most clinicians.[63] In this categorization, septic shock was considered a form of distributive shock caused by loss of vasomotor control resulting in arteriolar and venular dilation and—after resuscitation with fluids—characterized by increased cardiac output with decreased systemic vascular resistance.

HEMODYNAMICS

Since the 1960s, the understanding of the cardiovascular manifestations of septic shock has progressed through three phases. This progression in the understanding of the hemodynamic characteristics of the syndrome has been related to the application of increasingly sophisticated monitoring and investigative techniques to critically ill patients.[64,65]

The first phase, which predated the development of the flow directed pulmonary catheter by Swan and Ganz, described two progressive forms of septic shock: warm and cold. Warm skin and bounding pulses despite hypotension characterized warm shock. The other form of septic shock was characterized by cold clammy skin, a thready pulse, and hypotension. This was called cold shock. A few patients who were monitored invasively demonstrated that warm shock was associated with a high cardiac output (CO) and cold shock was associated with low CO. Based on these measurements, it was concluded that septic shock survivors went through an initial hyperdynamic phase of septic shock and then improved. Those patients who eventually succumbed to their disease went into a shock state that resulted in myocardial depression and low CO. Several clinical human studies and some experimental (endotoxin model) animal experiments seemed to confirm this observational finding.[66,67]

Further work showed that survival correlated with an increase in CO. Part of the initial confusion as to the now well-accepted hyperdynamic (high cardiac output/low systemic vascular resistance) profile of septic shock related to the lack of a simple method of measuring CO and true preload at the bedside. Initial clinicians were utilizing the central venous pressure as a surrogate of left ventricular end diastolic volume (LVEDV). Subsequently, many studies demonstrated that central venous pressure poorly correlated with measures of LVEDV in critically ill patients, especially those with sepsis.

Wilson challenged this widespread belief of the nature of the hemodynamic profile of septic shock as being a low CO state in 1965.[68] He and his colleagues were the first to describe the high CO low systemic vascular resistance (SVR) state of sepsis and distinguish it from the low CO/high SVR state of cardiogenic or hemorrhagic shock. Despite his findings, the hyperdynamic hemodynamic profile of septic shock that he noted did not become entrenched in medicine until the development of the flow directed pulmonary artery catheter.

Werner Forssmann, a German physician, was the first person to place a catheter into the heart. He performed the procedure on himself in the operating room and then climbed a stairwell to a radiographic machine to confirm the position of the catheter with a radiograph. For his efforts, he was summarily dismissed from his position and went into training in urology. Further advances in right heart catheterization were not made until 1964 when R.D. Bradley described the use of a pulmonary artery catheter (PAC) in critically ill patients.[69]

Harold Swan, a cardiologist from the University of California at Los Angeles, working with William Ganz developed the idea of a flotation-directed pulmonary artery device with a balloon on the end of the catheter. Although likely apocryphal in nature, some written accounts suggest that Swan came up with the idea of the balloon tipped catheter while watching boats in the Santa Monica Harbor. Swan and Ganz were performing studies in canines evaluating methods to place catheters into the pulmonary circulation. One afternoon they received a catheter with a balloon on its tip, and they placed the catheter in the right atrium of a dog, blew up the balloon, and the catheter ''disappeared.'' This occurred repeatedly, until the investigators realized that the catheter was being rapidly transported to the pulmonary artery where (because of the narrow scope of the fluoroscopy machine), it was off the screen. That afternoon, Swan and Ganz immediately used the same catheter (following sterilization) in a myocardial infarction patient in the coronary care unit recording bedside pulmonary artery pressures and allowing evaluation of cardiac performance using these hemodynamic values. A description of their landmark invention was published in 1970, and the catheter is more commonly and eponymously referred to as the Swan-Ganz catheter.[8,70]

The use of the PAC resulted in the second phase in the understanding of the hemodynamics of septic shock. The widespread use of the PAC resulted in the broad acceptance of the current hyperdynamic, high cardiac output nature of resuscitated septic shock. It became clear that many patients with septic shock had low initial filling pressures, as measured by the pulmonary artery wedge (occlusion) pressure. This indicated that septic patients were often hypovolemic upon presentation, and with adequate fluid resuscitation, patients consistently demonstrated a hyperdynamic state with high CO and low SVR.

Despite the mounting evidence of a hyperdynamic state of sepsis, the belief that septic shock was associated with myocardial depression and a low cardiac output persisted. The application of portable radionuclide cineangiography led to the third phase in the understanding of the hemodynamic nature of septic shock.[64] This technique was used to prove the hypothesis that the myocardium was depressed in sepsis, despite the hyperdynamic state demonstrated with PACs. In the first described study, Calvin and colleagues in 1981 demonstrated a subgroup of septic patients with an increase in left ventricular end diastolic volume and a decrease in ejection fraction.[71] In a subsequent study of serial hemodynamics and nuclear scans by Parker and Parrillo, 15 of 20 patients with septic shock demonstrated a reduced ejection fraction during the first 2 days after septic shock onset.[72] This decrease in ejection fraction and increase in LVEDV improved within the time course of the resolution of sepsis (7–10 days) (ie, the myocardial dysfunction was reversible). Interestingly, nonsurvivors of septic shock did not demonstrate the dilated, hypokinetic ventricle that survivors developed.

It is now known that many patients with septic shock develop a reversible depression in their ejection fraction that lasts for 7–10 days. Despite this reduction in ejection fraction, CO is maintained at higher than normal levels, secondary to an increase in LVEDV that causes a higher CO. Further research has demonstrated that sepsis also causes a reversible decrease in the lusiotropic function of the heart (ie, diastolic dysfunction).[73]

Early work by Parrillo and colleagues showed that circulating myocardial depressant substances were present during sepsis. Parrillo showed that serum from patients with early sepsis decreased both the amplitude and velocity of cardiomyocyte contraction in healthy rats.[74] The substances in the serum were identified to be TNF-α and IL-1. Further work indicated that TNF-α and IL-1 cause myocardial depression through the production of intracellular mediators, particularly NO and cyclic GMP.

Other possible mediators include: sphingosine, eicosanoids, platelet activating factor, and leukocyte lysozyme.

The description of the hemodynamics of septic shock is a burgeoning field of research. The ongoing research in this area includes using the hemodynamics of sepsis to potentially predict outcome.[75]

SUMMARY

The early descriptions of sepsis date back to antiquity. The initial theories of infectious disease espoused by Hippocrates and Galen remained largely unchallenged until Lister, Koch and Pasteur rapidly advanced the field and resulted in a paradigm shift in the way we view sepsis. Building on their work, twentieth century scientists have begun to unravel the molecular mysteries of sepsis, which has allowed for an improved understanding of the pathophysiology of the disease. With the sequencing of the human genome, single nucleotide polymorphisms have started to become a new tool in the armamentarium that allows scientists to predict who will suffer adverse consequences of infectious disease. The continued research into sepsis has already resulted in a decrease in mortality when compared to historical controls, and results will no doubt continue to improve.

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