Chapter 1

The History of Sepsis from Ancient Egypt to the XIX Century

Johan Sebastián Hernández Botero and María Cristina Florián Pérez

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/51484

1. Introduction

Throughout history, mankind has succumbed to endless infectious diseases which have been responsible of great historical changes; classic examples like "The Black Death" during the late Medieval period, a disease being the cause of profound demographical and social changes that prelude The Renaissance; we can also mention the smallpox epidemic during the New World conquest in the XVI century, a disease which was a direct cause of the pre-Columbian Mesoamerican cultures' holocaust. These are mere examples of well characterized infectious diseases which have had a definite contribution, among other factors, to the development of great scientific and historical changes. As oppose to these notoriously famous infectious diseases, sepsis cannot be categorized as a unique nosological entity studied by medical historians through the history of western medicine. This is the reason why we feel obliged to go beyond a simple description of sepsis throughout history from ancient Egypt to pre-modern times. Therefore, this text also intends to demonstrate how the study and clinical approach of the phenomena in the past, that we've come to know as sepsis, gave way to the development of many important medical revolutions in the XVI and XIX century, especially in the fields of surgery and microbiology respectively.

To make a historical detailed description of sepsis referred to a variety of nosologic entities such as pulmonary, intestinal and/or urinary tract infections is yet a very difficult task, perhaps an impossible one, the latter due to the heterogeneous character of its etiology, also the diverse clinical manifestations, its wide range of complications, these summoned to a whole array of concepts, theories and conjectures applied within many determined cultural contexts in their attempt to describe and understand the meaning of sepsis. Nevertheless, the phenomena we've come to know as sepsis, considered as a potential consequence of any

type of wound, was a clinical phenomena well identify since the Ancient Egypt and can be traced as a defined clinical entity through western civilization history. The time relation between a wound and the appearance of fever was well recognized, as were also the signs of local inflammation and the secondary systemic involvement. This is the reason why we have chosen to approach the history of sepsis through the study of traumatic lesions, and its importance in the development of the germ theory and the rise of modern surgery. Having this approach, we're allow to understand the direct relation between trauma and infection and also the evolution in the concept of sepsis: from the birth of the word itself and its introduction as a medical concept, its etiology and pathophysiology as a disease, to the diverse forms of treatments proposed previous to contemporary medicine; all this in a fascinating journey from the ancient Egypt to the XIX century.

2. Historical evolution of the word sepsis and its introduction as a medical concept

The word sepsis has an unequivocal Greek origin derived mainly from the word [σηψις], which is the original Greek word for "decomposition of animal or vegetable organic matter". We come across the word for the first time in Homer's poems, where Sepsis is a derivative of the verb form sepo [σηπω] which means "I rot" (Geroulanos and Douka 2006). Homer used the word in the 24th song of the Iliad where Priam was led by Hermes, into the Greek camps to beg Achilles for the return of Hector`s body. In vers 414, when Priam is asked for his son`s body, a slave answers: "Neither hounds nor vultures have yet devoured him; he is still just lying at the tents by the ship of Achilles, and though it is now twelve days that he has lain there, his flesh is not wasted nor have the worms eaten him although they feed on warriors." At the end, the Greek hero Achilles is convinced by Priam to return the body and Hector's funerals are carried out (Lattimore 1961). The term is immersed in Greek classic literature and was used by authors like Aristotle among others. Its use and its concept in the ancient Greek world could be the object for a complete revision (Majno 1991). Later on, when we talk about Greece, we will expand this concept along with its antithesis: Pepsis and its importance in the Greek ars medica (see ahead in this chapter: "Ancient Greece: Giving birth to the word Sepsis.") In the context of medical literature we can find the word sepsis in the Hippocratic corpus (Hippocrates 1849; Geroulanos and Douka 2006), cited in the Epidemics book (B. 2,2, Prorret. I.99). Its use was related to an Egyptian concept that will be mentioned later and which explains the origin of some diseases as a consequence of self-intoxication with harmful products derived from the colon. Undoubtedly, the use of this word in Hippocratic literature gave cause to its persistence in some ancient books for more than 2500 years. However, its use as a medical term declined and, on the other hand, a big portion of the classic medical literature was unknown until the Renaissance, because of several philosophical and historical reasons implicit in the Middle Ages, so that the word sepsis, even though persisted in the dusty shelves of ancient collections, undoubtedly was of little use in the Medieval medical context. One of the first bibliographic references in a medical context appears thanks to Matthaeus Silvaticus (circa 1280- circa 1342) a physician from the famous Salerno School who wrote one of the most

famous medical encyclopedias in the late Middle Ages. His Text Pandactae Medicinae was printed in at least eleven editions in various countries between the invention of the printing press and 1500 (López Piñeros 2002). In this text a description of the terms "sepsis" and "virtus" or "septic property" ("Sepsis: Putredo"; "Séptica Virtus: Putredine inducens") is provided, undoubtedly offering a clear reference to the classic Greek concept of sepsis (Silvaticus 1541). This is not surprising. The Salerno Medical School was influenced by Greek classic work translations from Arabic, something very common in the late Middle Ages and the period preceding the Renaissance (Crombie 1987). With this gradual recovery of the most faithful translations of the classic Greek works through the Arab physicians and translators, European physicians could appropriate many concepts that had partially disappeared as it happened with the word sepsis. It is important to remember, however, that Greek medicine gave a lot of importance to the environment and its influence on health, so it is not surprising that the putrefactive phenomena were associated to the disease, reason why we cannot find the first medical uses of the term sepsis in literature related to public health, without a doubt in clear relation to the concept miasma (see ahead in this chapter ""Why then and not before: Germs before the microbiologic era"). Because of this, in 1750 Sir John Pringle, the father of military healthiness, uses for the first time in history the word in his work Experiments upon septic and antiseptic substances (Pringle 1750), a text that made him deserving of the Copley Medal because of his contributions to the birth of Military Healthiness. Pringle was among the first persons to see the importance of these principles in hospitals and camps (Thurston 2000). Some of the first references about the use of the term in several European languages can be found. In English they date from 1858 with the inclusion of the word sepsis in the Oxford English Dictionary. However, we can find the use of the term in previous specialized works. The word sepsis is introduced for the first time in a French medical dictionary in 1834, long before the microbiological revolution, and it is defined simply as putrefaction (Béclard 1834). Similarly, a German medical dictionary from 1845 uses the term in the context of the disease (Busch 1845). By the end of the XIX century the concept sepsis was already well assimilated by the medical community, using it indistinctively with the word septicaemia (Van Arsdale 1886), reason why its use had already been related with the works of microbiology founding fathers (see ahead in this chapter: "Sepsis and the birth of the germ theory"). At the end of the XIX century sepsis and septicaemia were not the only words related; also, words like pyemia (a disease produced by the absorption of pyogenic bacteria and the pressence of pus in the blood) or sapremia (a constitucional disorder due to chemical poisoning by products of bacteria that occurs as a result of putrefactive processes set up by certain forms of bacteria in a wound), (Van Arsdale 1886) had been introduced.

3. Sepsis in the Ancient Egypt

From prehistory, human beings have tried to take care of their wounds in a practice that has evolved from the shamans´ magical approach to the therapies and methods used presently (Broughton 2006). However, some of the practices that remained for centuries and that we would consider modern, have their origins in the ancient Egypt (Mejía Rivera 2002; Broughton 2006).

The oldest report we have about sepsis associated with wounds goes back to Edwin Smith's discovery of a papyrus in 1862 in the Luxor, Egypt outskirts (Breasted 1980). Written arounnd 1600 BC, this papyrus seems to be the copy of another much older manuscript dated in 3000 BC, reason why it is considered the oldest known surgery treatise (Bishoy 2004; Stiefel 2006). Reference to 48 cases of traumatic lesions between wounds, fractures and dislocations in different parts of the body are mentioned in this masuscript explaining their symptoms, signs and their follow up, prognosis and treatment (Breasted 1980). This treatise demonstrates the clinical richness or the Egiptian physician who founded his diagnostic appreciations in a rigorous semiological and systematic method based on the clinical pehnomenon observation through the senses, including the inspection and palpation of the lesions such as a contermporary physician would do it (Mejía Rivera 2002). This empirism allowed the Egyptian general practitioner the construction of the prognosis with a minimum of magic or divinatory elements, supported in the assessment of the primary lesion as well as its subsequent evolution, thus allowing the search for emerging secondary complications, as it would be for us, sepsis evidenced semiologically by a systemic inflammatory response.

In five out of the forty-eight cases there are clear references to fever as a secondary phenomenon in the wound,[1] making special emphasis in its detection during subsequent clinical assessment monitoring the patients' evolution. In some cases fever modifies both treatment and prognosis. Even explanatory notes are made in which concern related with the severity and persistence of the fever profile is shown (Breasted 1980). Nonetheless, fever is not the only sign of infectious complication. In several of the described cases the presence of pus (ryt) as a secondary and late phenomenon is described and associated with a bad prognosis. This is how the Egyptian physicians limited their efforts when performing surgical explorations because of the possibility to promote the lesion suppuration (Blum 2002). Egyptian physicians, without knowing the concept of infection or inflammation, identified some clear signs of what today we know as local suppuration and systemic infection.

In the forty-seventh case, an open wound of shoulder with its flesh turning black is described, and clarifications and therapeutic suggestions in case fever persists are made (Breasted 1980). The identification of a wound with necrotic appearance in the context of a secondary feverish profile demonstrates the capacity of the Egyptian physicians to diagnose what today we know as a gangrenous necrosis phenomenon , accompanied by a systemic inflammatory response. However, the case that surprises the most, because of its semiological accuracy when finding septic and suppurative complications, is the seventh case in whcih the care of a penetrating cranial wound which perforated the sutures is exposed (Breasted 1980; Seara Valero 1995). A clinical case whose diagnostic evaluation is carried out in two moments: a first moment in which the severity of the trauma and

[1] We found fever in the following cases: Case 7: head wound; Case 28: throat wound; Case 23: jaw wound; Case 41: thoracic lesion; Case 47: shoulder with gangrene (Breasted 1980) . All of them are explanations of fever as far as prognosis and treatment.

associated neurological consequences are corroborated, considering it still a treatable wound; it only is considered incurable when, after a second clinical assessment, fever accompanied by flush, perspiration, neck stiffness, convulsions and ram urine odor in the wound are detected (Breasted 1980; Seara Valero 1995). This description evidences the expertise of the ancient Egyptian physicians in the detection of a secondary infecious complication. As we know, presently such profile is compatible with a intracranial suppurative complication accompanied by meningism in the context of a systemic inflamatrory response (Adams 1999). The Egyptian physicians were pioneer in the making of the diagnostic approach of a feverish profile originated in an infected wound, establishing the bases for the Western semiological method to deal with septic patients.

It is well known that before the XIX century a theory about germs did not exist and even less in the ancient Egypt. Nevertheless, even though the Egyptians could not see microorganisms in the intestinal flora, they knew that the intestine contained some type of dangerous material. Egyptians postulated that a dangerous principle spelled WHDW (that tentatively can be pronounced as "ukhedu") could be found there. This dangerous substance could find a way though the blood vessels and intoxicate the complete body (Majno 1991). With the "ryt" and the "ukhedu" concepts it is not surprising that the Egyptians searched for materials that did not decompose and that, consequently, prevented suppuration and bad odors form the lesions. About the therapeutic Egyptian methods one can find disagreements. Some authors propose that Egyptian medicine practiced a therapeutic practice similar to the prehistoric rituals and pharmacopoeia in accordance with pre-technical medicine and, as a consequence, it did not generate greater advances in the wounds infection control (Robinson 1947; Forrest 1982). Nontheless, other authors rehabilitate the therapeutic richness of Egyptian medicine through experiments with different substances used in antiquity (Majno 1975). Other works also support this hypothesis by means of the most rigorous study of the last archeological and historical evidences (Mejía Rivera 2002). Even though some of the first references about wounds cleaning and dressing date from the Sumerians about 2100 BC, we know that the most conservative and apyogenic techniques for wounds care were developed in Egypt. Even though it is difficult to establish whether the Egyptian physician found any association between suppuration and the subsequent development of sepsis, something in their therapeutic practices was oriented to avoid pus formation. In Eber's papyrus (dated in 1400 BC) also found by Smith in the Luxor outskirts in 1862, the use of honey and grease on open wounds as well as pus removal to promote wounds healing are established (Broughton 2006). Some of these principles came to Greek medicine during the IV century BC through physicians trained in Egypt such as Crisipo de Gnido who discovered the use of hemostatic dressing as well as other blodless methods in the management of traumatic lesions. These methods were adopted by some of Crisipo's eminent students like Herófilo (c. 335 BC - 280 BC) and Erasistrato (c. 304 – 250 BC) (Robinson 1947). Diverse ancient texts commonly suggest wound wash with beer, hot water and honey, to cover them subsequently with grease impregnated with herbs and grease dressings (Majno 1975; Forrest 1982). Presently it

has been proved that the ancient Egyptians' ointments based on honey and grease have bactericide action: a mixture with one third of honey and two thirds of butter diminish the S. Aureus y E. Coli count from 105 to 102 in only 24 hours (Broughton 2006). The use of compresses impregnated with wine were also used in former times with an approximate 10% alcohol content as well as the presence of malvoside and enoside pigments (Majno 1975), winw can kill E. Coli colonies in only 60 minutes (Broughton 2006). Botanic studies show that nearly 2,500 plants possess microbiological activities and it is possible that many of them had been used in former times for wounds treatment without having any knowledge about it (Forrest 1982). The reason why these peoples promoted the use of such substances was maybe because of their good aroma and their slow decomposition. Within this framework the Egyptian physician is the pioneer in the observation of nature to try to find tools for apyogen care of wounds (Forrest 1982). As it will be seen in the paragraphs below, through Western history the cleaning of wounds was more the exception to the rule, and it is only natural that all possible means to promote supuration were looked for, an objective which was outstandingly achieved by the Middle Age physicians.

4. Ancient Greece: Giving birth to the word sepsis

In the ancient Greece, medicine suffers deep transformations and the seeds of the care and treatment of wounds paradigm were planted for the centuries to come. Although the Hippocratic body writers were not aware of the concept of microorganism, they identified the suppurative infections clinical manifestations, excelling in their correct description (Siegel 1960). Greeks were perfectly aware of the inherent dangers of the continuous loss of skin, to which respect Hippocratic literature describes: "When a cut becomes inflamed, the neighboring tissues become intumiscent, and the lesion flush and heat spreads through the vessels. If the lesion is located in the leg, the tumors will develop in the groin; if it is in the arm they will prefer the armpit" (Grmek 1991). We can then see how the Hippocratic physicians, without any conceptual knowledge about infection or lymphatic system, accurately describe a skin primary lesion with subsequent local spread, evidenced by lymphangitis and secondary lymphadenitis. Likewise, Greek physicians were well aware of the dangers of a systemic compromise: "A local lesion, heated by humor afflux, makes the whole body become feverish. One can die because of this, especially on odd numbered days" (Joly 1970). This description demonstrates identification of the clinical phenomenon that we know today as sepsis with its deadly consequences, but supporting its pathogenesis through the classic humorism (Forrest 1982). These interactions between humors, tissues, and their implications in the origin of systemic inflammation, explain the therapeutic approach of purulent lesions in ancient Greece but, in order to understand this, first we must review what humorism was and how Greeks conceived disease. In the Hippocratic text Airs, Waters, and Places Hippocrates perfects the theory of elements proposed half a century before by the philosopher and physician Empedocles of Agrigentum (circa. 490–430 BC). In this theory Hippocrates proposed that human beings are composed by four fundamental humors (blood, phlegm, yellow bile, and black bile), representation of the four

elements (air, water, fire, and earth). The health of a particular individual depended then from the adequate equilibrium of such humors (eucrasia), as well as the individual's harmony with the environment. Hippocrates believed that disequilibrium in the humors (dyscracia) was the essential cause for disease to occur (Francis 1985). This would be the support for the Hippocratic-Galen model of physiological-environmental style, a model which would become a dogma until far after the Middle Ages (the implications of this model in the infections approach will be discussed ahead). For the Hippocratic Corpus pus formation in external wounds can appear because of decomposition of mistreated tissues, because of extravasated blood, or because of humor afflux (Grmek 1991). The process was different for internal no traumatic lesions in which purulent collections formed such as abdominal abscesses or empyemas. This process happened because of accumulation and stagnation of blood in the area in addition to the secondary rupture of small vessels or the displacement of phlegm which drained in the area and generated the collection (Grmek 1991). Likewise, Greeks had a different conception about the role of humors in primary systemic infections. They observed the characteristics of these patients' extracted blood and, in the context of feverish-septic clinical manifestations they interpreted the blood physical changes as an increase in the black bile (Majno 1982; Francis 1985; Abbas 2002). These changes consisted of a precipitation of the form component and a darkening of the blood as a consequence of the increase in the globular sedimentation speed and the desaturation of the sample respectively (Shoemaker 1971; Pastrana 2006). As it is known nowadays, these processes are the result of a systemic inflammation which increases the acute phase reactants (Gabay 1999) and diminishes the saturation of venous blood (Shoemaker 1971). This last one is a consequence of the decrease in oxygen transportation, the increase of its tissular extraction or mitochondrial microcirculatory dysfunction (Trzeciak 2005; Cinel 2007). The etiopathogenic conceptions from the humoralism view point made the treatment change if the case was a medical profile originated from an "invisible" inflammation or if the case was a suppurative profile from a traumatic origin with secondary systemic compromise.

Although it seems paradoxical, for the Hippocratic physician suppuration could have a benign or a harmful character. To understand this it is necessary to review two very important Greek concepts: SEPSIS and PEPSIS. These two concepts, which could be understood as some sort of Ying-yang, are fundamental in order to understand suppuration and wounds care. It is difficult to translate accurately and literally the sepsis and pepsis concepts but essentially they represent the decomposition or disintegration processes which could be subject to live matter (Majno 1991). Sepsis is very close to the concept of putrefaction as we understand it nowadays, and it necessarily implies "bad odors" and "putrefaction" processes that occurred in the colon inside the body (maybe this concept was associated with the Egyptian term "ukhedu") and was also associated with the stinking swamps and rotten organic matter (see ahead miasmas). On the other hand, PEPSIS was closer to "firing", "maturation", and "fermentation". The digestive processes in the stomach, as well as tears of milk formation were maturation peptic processes of humors (Majno 1991).

This way we can understand that despite there was not a microorganisms theory, somehow in the ancient world the macroscopic consequences of three phenomena caused by the microbian world could be observed: Putrefaction (SEPSIS) to which all living matter was exposed when it died; fermentation (PEPSIS) which was used to produce wine, vinegar among other ferments and ripe food products; and infection, especially wounds, which somehow was similar to sepsis and that was first explained through the humoral theory, then through miasmas and finally through infection and the germs theory as it will be presented at the end of this chapter.

For the Greeks there existed transformation processes which were subject to humors during the course of the illness either to cause it or to solve it (Grmek 1991). These processes consisted of the body substances maturation and the formation of pus in a lesion did not escape from this principle. Depending on the type of process (benign pepsis, or harmful sepsis) the lesion suppuration essence itself would be explained (Grmek 1991). For this reason, there is a clear distinction from Greek semiology between desirable and undesirable pus. For the Hippocratic physician a darker, abundant, heterogeneous, fetid and bloody secretion was interpreted as part of a bad prognosis inflammatory profile (Grmek 1991), undoubtedly closer to the concept of sepsis. Different from this type of undesirable pus, suppuration could be part of healing only if it had benign semiological characteristics or closer to the humors pepsis. In this context, suppuration helped by means of destruction of already necrotic tissues. For this reason, it is not surprising that the total absence of pus production was interpreted as an ominous sign (Grmek 1991). Nowadays we know that an absence of pyogenic response may indicate an insufficiency of secondary local inflammatory response to the immune system, even more in the context of a malnourished, elderly or weakened patient (McFarlane 1976; Opal 2005). As a result, the Hippocratic physician focused part of his therapeutic efforts in allowing a rather conservative and limited suppuration of the lesions (Grmek 1991). Although there is no clarity about any specific procedure carried out to control excessive suppuration, Greeks are attributed the implementation of abscesses-drainage. In the year 280 BC, a Greek barber invented what we could call nowadays syringe (pyúlkos or pus extractor) which was commonly used to drain purulent foci (Majno 1975). With the disappearance of Greek civilization the surgical drainage practice was buried, to be rescued only a couple of centuries ago when it started to play the fundamental role in the management of sepsis it has today (Dellinger 2008).

It is important to highlight that in the classic Mediterranean world each wound suffered infection to a greater or a lesser extent which made improbable to distinguish between healing on first intention or as a part of the resolution of a secondary infectious process with superimposed suppuration (Majno 1975; Grmek 1991). These physiopathological precisions explain the apparent ambiguity of Greek therapeutics as far as the desire to promote or restrict pus formation. In the first part of the book About Ulcers this therapeutic dilemma is illustrated and referring to the care of a recent ulcer, the Hippocratic Corpus says:

"Recent ulcers, both the ulcers themselves and the surrounding parts, will be least exposed to inflammation if one shall bring them to a suppuration as expeditiously as possible, and if the matter is

not prevented from escaping by the mouth of the sore; or, if one should restrain the suppuration, so that only a small and necessary quantity of pus may be formed, and the sore may be kept dry by a medicine which does not create irritation." [Afterwards on the origin of suppuration] "A sore suppurates when the blood is changed and becomes heated; so that becoming putrid, it constitutes the pus of such ulcers." (Francis 1985)

Erroneously, authors suggest that for the Greek the appearance of pus was not necessary for the positions of defense of wounds healing (Forrest 1982). As it was stated before, for the Hippocratic corpus suppuration was a sign of the transformation process which allowed the wound healing through the maturation of humors (Grmek 1991). Interpreted as a clinical sign, pus could be interpreted as an adequate evolution or a compilation of the wound, a distinction which limited the Greek efforts when promoting pus formation in a conservative approach contrasting with Roman and Medieval medicine.

Hippocratic literature is prolific in the number of substances that can be applied on a wound (Majno 1975; Francis 1985). Postures defending cautery with boiling oil can be found in the texts (Blum 2002), as well as other more conservative postures such as the use of ointments, bandages and baths with wine, water and vinegar (Forrest 1982; Francis 1985; Broughton 2006). Even some references indicated keeping the wounds dry (Francis 1985; Francis 1985). Bandages as a bloodless haemosthasis and healing method were fundamental in the Greek therapeutics. Greeks made of this technique an art reaching great mastery in their production using them for diverse purposes (Majno 1975; Francis 1985; Francis 1985). Its use was accompanied by different substances that impregnated them, favoring the use of wine (Francis 1985), verdigris, green copper ore (Forrest 1982 escences and ointments (Majno 1975). It was also common that venesection was promoted to evacuate blood contanied in the lesion, perhaps with the intention to reduce the blood afflux and the excessive pus formation (Forrest 1982). All these procedures would be adopted by the Medieval Roman medicine, with some qualitative changes as it will be shown below.

5. From Rome to the Medieval Age. *Pus bonum et laudabile*[2] and the downfall of surgery

"Those diseases which medicines do not cure iron cure; those which iron cannot cure, fire cures; and those which fire cannot cure, are to be reckoned wholly incurable." Hippocrates from Cos. V - IV Centuries BC.

The Roman Empire received many of their knowledge from Greek science (Haggard 1947). In general, during the Roman period of Greek medicine the same antiseptic components were used, adding a few ones such as silver nitrate (Broughton 2006). Galen and Dioscorides

[2] "Pus bonum et laudabile" In Spanish: "Pus buena y digna de alabanza". (from Latin: Bonus: Useful and on purpose for something and Laudabilis: praiseworthy). Concept proposed by Galen from Pergamo (129 – 200 d. C.) who made public that wounds healed on second intention and that pus formation was fundamental for healing. This concept stimulated the indiscriminate use of cautery during the Middle Ages, as well as ointment composed by rotten or caustic substances to facilitate suppuration of a lesion.

were authors who standed out in the Medieval Ages as a mandatory reference, being their texts followed as dogmas until the Renaissance. Galen (129 – 200 AD), who would become the undisputed medical authority for the next fifteen centuries, did not contribute too much to the a-pyogen wound care strengthening the previous ideas about the importance of suppurative healing, introducing the concept of Pus bonum et laudabile (Pollak 1970; Forrest 1982; Thurston 2000; Blum 2002). This concept stated that wounds were cured on second intention and that pus formation was fundamental for their healing. This approach stimulated the indiscriminate use of cautery during the Middle Ages period, as well as the use of ointments composed by rotten or caustic substances to facilitate suppuration in the lesion (Blum 2002). Celsus (45 BC- AD 25) was the first Western physician in characterizing the four cardinal signs of inflammation: "Notae vera inflammationis sunt quattuor; rubor et tumor cum calore et dolore". (Forrest 1982; Blum 2002). Regarding wounds, Celsus proposed different treatments from those proposed by Hyppocrates and Galen, applying some of the Alexandrian school[3] developing the first acceptable approximation to haemosthasis (Robinson 1947). However, his work was lost during the Medieval period; his text De Medicina rescued from a church in Milan in 1443 (Paget 2005) was one of the first medicine books printed after Gütemberg's dead (Forrest 1982). In this text Celsus proposed a first line bloodless haemostatic method which consisted in packing the wound with linen moistened with water, vinegar or wine (Celsus 1961). After having the hemorrhage controlled, the edges of skin were moistened with rose oil and butter, and the use of bandages with water continued along with a light diet and rest (Davies 1970). Cautery with caustics was considered the third line and was only used when the vessel ligature had failed in containing the hemorrhage (Forrest 1982). Some of the principles promulgated in his work are the foundation of today's haemosthasis which tried to stop bleeding without destroying tissues or promoting infection (Hontanilla Calatayud 1999). The objective of the classic Greek and Greek-Roman therapeutics in the treatment of wounds qualitatively was the same. Their difference lied on the gradual importance suppuration gained as a fundamental element in wounds' healing. This evolution was evident from the relatively a-pyogenic healing of the Alexandrians (Robinson 1947) to the pus bonum et laudabile concept adopted in the Middle Ages (Forrest 1982; Thurston 2000; Blum 2002).

After the peak of Roman medicine, Arabians became the receivers of medical science by accumulating, translating and commenting many of the classic texts that would serve as a reference for the physicians during the Middle Ages (Haggard 1947). Medical texts survived thanks to the efforts of great translators and commentators such as Hunayn, Avicenna, Rhazes and Averroes who compiled knowledge in important Greek-Arabic summaries allowing discrete advances in clinic (Robinson 1947). Nonetheless, surgery did not share the same luck; as the Middle Ages progressed, the sacred character of nature became preponderant, the human body as a divine creation at God's image and

[3] As mentioned before, it is possible that Celsus had as sources some texts or sources from Alexandrian physicians such as Erasistratus and Herophilus whose master, Crisipo of Gnido was educated in the apyogen surgical techniques in Egypt.

likeness, became an inexplorable taboo which made inacceptable any diagnostic or therapeutic technique that could outrage its sacred character (Mejía Rivera 1990; Mejía Rivera 2005). This giving up of the human being corporal reality exploration added up to the academic and social tendency to see surgery as a "second category" discipline, causing its gradual transformation into an empirical and despicable task separated from the distinguished academic environment of that period. These reasons explain why surgical treatises fell into the ostracism (Haggard 1947). Regarding this, Albucasis, one of the greatest Arabian surgeons, would comment: "The surgical art has disappeared between us almost without leaving any mark. Only in the writings of some ancients we find references: but these, wrongly translated, erroneous and altered have become unintelligible and useless" (Robinson 1947). Undoubtedly Arab literature is influenced mainly by Galen texts whose treatments supported the value of suppuration in the healing of wounds: consequently, during the Middle Ages the use of sutures, wounds exploration and vessels ligature were pushed into the background, making of the painful cautery the appropriate procedure for all kinds of lesions (Robinson 1947; Forrest 1982; Forrest 1982). As it has been discussed so far, the most conservative approaches practiced by Alexandrian and Greek physicians got lost in time and would only be taken up again in the Renaissance thanks to the recovery of lost texts and to the new scientific spirit of that period which allowed the development of an empirical mental attitude that would confront the old preestablished dogmas.

The practice of surgery in Europe remained unaltered during the late Middle Ages because of the use of cautery, a consequence of the unanimous acceptance of pus bonum et laudabile, and it was only in the XIII century that some authors dared to contradict Galen. The first of them was the surgeon from Bologna Teodorico de Borgognoni (1205-1298) who proposed in his work Chirurgia (a compilation of his father's Hugh of Lucca, who was the founder of the Bologna Surgery School teachings) the use of clean dressings to try to keep the wounds dry thus avoiding caustic substances which promoted pus appearance (Forrest 1982). At the same time, in Montpellier, Henri de Mondeville (1260-1320) criticized Galen work, particularly wound healing, and in his work Cyrurgia from 1320 he proposed the use of spring water or boiled water to clean wounds (Blum 2002). In line with this, William of Saliceto (1210-1280) maintained ardently that pus formation was deleterious for both, the patient and the wound, suggesting that healing must be given on first intention (Thurston 2000). However, these works did not have a lot of impact in this period: most of these authors were attacked by their contemporary authors who defended passionately the status quo and the continuity of the Galen paradigm as a dogma. We could summarize the causes of the failure of these new proposals as follows: 1) the lack of a change in the philosophical corpus of each period which epistemologically supported the change of a model; 2) the absence of some anomaly which systematically challenged the paradigm in each period; 3) authors, times, and places cohesion which coincided and supported a growing corpus of evidence that challenged the old paradigm. These obstacles would be surmounted thanks to the Renaissance and the introduction of gunpowder in the war, as well as the great men such as Ambroise Paré, Paracelsus and subsequently the fathers of microbiology.

6. Firearms, the end of the Medieval Ages and the Renaissance. The role of sepsis in the birth modern surgery

As it can be inferred from the previously described, sepsis became a silent partner for barber surgeons in hospices and battle fields taking innumerable lives in olden days. This tragedy was a consequence of the Galen dogma bomun et laudabile, a concept that defined the wounds treatment for many centuries. What made such somnolence of medicine possible? In the first place, many of the surgical procedures in the olden days, particularly the Greek and Alexandrian -less iatrogenic and perhaps more effective- were abandoned or simply lost the medical corpus allowing cautery to become the surgical tool of choice during the last half of the Middle Ages (Hernández Botero 2009). Secondly, within the scientific framework of the period, there existed neither a philosophical nor a scientific corpus which allowed the development of new paradigms in medicine. In this way, the Galen postulates were the guideline, wounds continued to be treated with fire, the injured burned in fever and the pus stench was the norm, and, even though there were isolated and fruitless efforts to fight sepsis, the scientific spirit of that period simply was not ready for a change in paradigm (Kuhn 2004; Hernandez Botero 2009).

In the period of arrows and swords, wounds in the torso or the head ended up being lethal; as a consequence, most of the ancient texts focused on the management of wounds in the limbs which could have a relatively benign prognosis if hemorrhagic shock was not present (Helling 2000). The war surgeon's arsenal in olden days was limited and the efforts were focused in the search for homeostasis through a diversity of techniques from poultice, dressings, and packaging to ligature and cautery (Castiglioni 1941; Singer 1962; Laín Entralgo 1979). Amputation was very-little practiced and the necessary surgical techniques to perform this procedure had not been developed (Majno 1975; Forrest 1982; Helling 2000; Broughton 2006; Hernandez Botero 2009). As we can see, medicine could not offer much for the development of an appropriate surgical management of infected wounds.

Firearms checkmated the Western surgical knowledge because they hastened a dramatic change in the wounds pattern during armed confrontations from their gradual introduction by the second half of the XIV century (Singer 1962; Blum 2002; Chase 2003; Broughton 2006). The primary lesion was now accompanied by the bullet contaminant material, external debris and gunpowder residues (Chase 2003). Serious burns, open fractures, avulsions and extensive lacerations, undoubtedly associated with a significant increase in mortality (Blum 2002; Broughton 2006). This new lesion pattern, as well as an unquestionable increase in mortality produced by non-hemorrhagic shock, started to generate the wrong perception that wounds were being poisoned by harquebus gunpowder. Although the specific author who suggested this hypothesis is unknown, some pioneer surgeons who defended this posture stand out: German surgeon Hieronymus Brunschwig (1450 – 1533), one of the first war surgery text authors, proposed that the increase in mortality was due to a "blood poisoning" caused by gunpowder, and he even proposed in his book Chirurgia in 1497, that the treatment must have been focused in extracting this dangerous substance: *"In case a man has been shot with a gun and the bullet is still in place, he is poisoned by the powder, or part of the*

powder is still in the body, in the arm or leg or wherever the wound may be. Take a seton, push it through the wound, and pull it back and forth to force the powder out... You may then insert a lint plug moistened with bacon or lubricated with ox grease." (Brunschwig 1497). Giovanni de Vigo (1460 – 1520), Italian author introduces the most copied and translated surgical text in his time, Practica in arte chirurgica copiosa (Roma 1514). He makes popular, because of his Galen Midievalist essence, the use of boiling oil on the wounds as an efficient way to counteract the poisoning with gunpowder, and, without any doubt, something equally efficient in producing abundant pus quantity (Robinson 1947). On the other hand, the Italian physician Alfonso Ferri (1515 – 1595) aptly proposed in 1552 that portions of the armor and clothes that remained deep in the wounds were responsible for suppuration and even he encouraged their removal (Thurston 2000). When interpreting these innovative works in war surgery, one can conclude that the increase in mortality was due to an accentuation of sepsis as a secondary phenomenon to the initial wound. This was an awaited situation because of the appearance of more extensive, exposed and contaminated wounds, factors which increased their susceptibility to infection. The so called "blood poisoning" would rather have corresponded to an increase in the sepsis and septic shock cases behind the battle front due, not only to the wounds pattern and contamination, but also to the different treatment promoting their suppuration.

Once the Middle Ages period finished, the Renaissance started and more than two hundred years went by since the harquebus in the European battle fields started to sound in order to have real advances in the war wounds treatment (Singer 1962; Pollak 1970; Forrest 1982; Broughton 2006). The first one happened thanks to the great Swiss physician and surgeon Paracelsus (1493-1541), an angry critic of Hippocratic and Galen medicine who furiously claimed against what was called *"the reprehensible precept that teaches that it is necessary to make wounds suppurate"* (Robinson 1947). His declarations were undoubtedly revolutionary: *"The true physician of wounds is nature. All treatment must be reduced to infection prevention. Complexion, humors, diet and time, and the stars don't have any influence. The results will be determined by a treatment which allows nature to act in peace"* (Robinson 1947). If Paracelsus was the great innovator theorist in the XVI century, it was a French barber who, through empirical evidence, was able throw one more shovelful of soil on the pus bonum et laudabile. This happened in Italy in 1536 when out of serendipity (Mejía Rivera 2004) the French surgeon and father of modern surgery, Ambroise Paré (1509 -1590) decided to put to an end the indiscriminate production of pus. It was during the siege of Turin that the young surgeon found himself in the obligation to use dressings and poultice instead of the standard treatment with boiling oils because of the scarcity of supplies. The anecdote of this finding published in his text *The Method of Curing Wounds Made by Arquebus and Other Firearms* (1545), is well-known:

"The soldiers within the castle, seeing our men come on them with great fury, did all they could to defend themselves, and killed and wounded many of our soldiers with pikes, harquebus, and stones, whereby the surgeons had all their work cut out for them. Now I was at this time a fresh water soldier; I had not yet seen wounds made by gunshot at the first dressing. It is true I had read in Giovanni de Vigo's first book, "Of wounds in general", eighth chapter [Practica in arte chirurgica

copiosa (Roma 1514)], that wounds made by firearms partake venenosity, by reason of the powder; and for their cure he bids you cauterize them with oil of elders scalding hot, mixed with a little treacle. And to make no mistake, before I would use the said oil, knowing this was to bring great pain to the patient, I asked first before I applied it, what other surgeons did for the first dressing; which was to put the said oil, boiling well, into the wounds, with tents and setons; wherefore I took courage to do as they did. At last my oil ran short, and I was forced instead thereof to apply a digestive made of the yolk of eggs, oil of roses and turpentine. In the night I could not sleep in quiet, fearing some default in not cauterizing, that I should find the wounded to whom I had not used the said oils dead from the poison of their wounds; which made my rise very early to visit them, where beyond my expectation I found that those to whom I had applied my digestive medicament had but little pain, and their wounds without inflammation or swelling, having rested fairly well that night; the others, to whom the boiling oil was used, I found feverish, with great pain and swelling about the edges of the wounds. Then I resolved never more to burn thus cruelly poor wounded men. [...] See how I learned to treat gunshot wounds; not by books." (Paget 2005)

These observations have deep epistemological implications. First of all, it is a prototype of what we know today as clinical test with control; in the second place, this discovery through the mixture of the scientific method and out of serendipity actions, in the context of therapeutic difficulties posed by the use of firearms, achieves the beginning of an experimental evidence corpus that would serve to bury Galen dogma that had prevailed for centuries (Kuhn 2004; Mejía Rivera 2004). It is then that young Paré, with only twenty-six years of age, abandons boiling oil, recovering from ostracism, among other things, ligature as a more asceptic hemostasia technique (Robinson 1947), thus reducing significantly the occurrence of infection and setting the bases for new and revoluationary surgical developments (Baskett 2004; Drucker 2008). Even though Paré himself continued being reluctant to surgical exploration of wounds and only performed it when he was going to pull out foreign bodies and fragments of bone (Helling 2000), in few years great advances in exploration of surgical techniques would be achieved. This happened with the publication of his fellow countryman Pierre Joseph Desault (1744-1759) who managed to introduce the modern debridement concept (Broughton 2006). Desault observed that tissue inflammation produces constriction inside the fascias or aponeurosis and attributed to it the cause of gangrene (Broughton 2006). Similarly John Hunter (1728 -1793) identified the deleterious effect devitalized and necrotic tissues have for wounds healing and he proposed their surgical removal (Hunter 1985; Ellis 2001). Subsequently, the Russian military surgeon Carl Reyher (1846 – 1899) combined antiseptic techniques along with the careful mechanical cleaning through surgical techniques, thus giving shape to debridement as we know it today (Helling 2000). Before Desault, Hunter and Reyher, the lesions surgical approach consisted basically in removing the bullet from the wound, inflicting more damage and introducing more contaminants (Ellis 2001). Debridement could generate a preventive approach by allowing the removal of desvitalized tissues thus preventing infection and, similarly, it allowed the surgical approach of the already established sepsis.

In this context, it is necessary to ask: How was the clinical course of the injured person after the introduction of gunpowder in combat? When a soldier receives an extensive damage in a

limb because of a cannonball or an explosion, the wound process suffered a characteristic natural history (Helling 2000):

1. The patient could die during the first hours because of hemorrhagic shock because of extensive vascular damage.
2. If the patient survived the initial hemorrhage, a period of thirty days called "the first inflammation" started, period in which the following might happen in the exact order it appears below:

- Dead produced by non-hemorrhagic posttraumatic shock, this struck within the first 48 hours and was independent from the hemorrhage or gangrene.
- If the patient survived the shock, gangrene started within the five or seven days following the lesion, surely accompanied by fatal septic shock.

3. If the patient still continued alive, he was at the mercy of chronic infections stressed by malnutrition as well as any other preexistent or new disease.

During the primary inflammation period we can differentiate between post-trauma shock and septic shock because of the starting time and their clinical characteristics. Following, Nocholas Senn describes a shock pot-trauma case during the war between The United States and Spain:

"A young soldier has been struck down by a fragment of a bursting shell, which has almost completely severed both legs just below the knee-joint. The patient lies on the ground, motionless. He has lost little blood, but his lips are pale ...the hands are cold, and the pulse at the wrist cannot be felt. The respirations are irregular ...it takes repeated questions to elicit the simplest answer."(Senn 1900)

In those first post-trauma hours many surgeons were aware that the patient's dead might strike from the shock in spite of an adequate control of the bleeding (Helling 2000). This shock of difficult explanation was attributed to neurological causes because of the deceitful characteristics of its appearance and to the patient's inability (Larrey 1812). Nontheless, the specific physiopathology of this shock resides in the molecular response the seriously injured tissues develop; a powerful inflammatory response with systemic consequences which can cause multiple organic dysfunction even if there is not infection (Lenz 2007). The mechanisms responsible of this response have been philogenetically preserved to react energically before diverse inflammatory stimulus (O'Neill 1998; Opal 2000; Beutler 2001). This inflammatory post-traumatic response continues to be a problem nowadays, not only because of the organic damage it generates, but also because it increases the possibilities of systemic superimpossed infection. This association has been called the two impact theory which suggests that the initial inflammatory response is the bridge to develop sepsis through the apoptosis of immune cells or splachnic perfusion with bacterial translocation from the intestinal light (Border 1987; Keel 2005)

Up to this point we have seen the gradual development of some surgical techniques. However we have not tackled amputation, a procedure that, even though bloody and horrible, would be the only hope for seriously injured soldiers during the pre-antibiotic period. Amputation was not a very popular practice through history and there is a variety

of cultural and scientific reasons for that. In the primitive societies this practice was only performed for religious or punishment reasons, never as a medical intervention; primitive human beings were terrified to go to the supernatural world with incomplete bodies (Pollak 1970). Centuries later, Hippocratic physicians did not know how to amputate, but they witnessed how gangrenous limbs of some patients which, without evidence of infection self-mummyfied and fell, process that was called melasmas (Majno 1975). During the rest of the Greek-Roman period amputation continued out of the medical practice and even thouhg some Greek schools improved fundamental techniques to perform this procedure such as the vessel ligature (Robinson 1947), they were never used in the context of such surgery (Helling 2000). Later, during the Middle Ages, these techniques were buried with the rest of the ancient surgical knowledge at the expense of the use of cautery, making it impossible to develop an appropriate amputation technique (Robinson 1947; Helling 2000; Hernandez Botero 2009). Ever since the new and harmful war artefacts were introduced, the need came up to reconsider the approach of a patient with a smashed limb and whose final destination in most cases would be death. Amputation would be the answer to approach these types of patients not only for the bleeding control, but also for the traumatic shock and, of course, the infection. However, it was a hard way.

At the beginning of the XVI century, amputation was seen as a second line therapy and it was reserved as the treatment for established gangrene being treated only when other procedures such as poultice, dressings and cautery had already been used (Helling 2000). Vessels ligature, a fundamental technique when amputating, had not been rescued yet and did not make a part of the surgical knowledge. As a consequence, when amputation was considered, it was performed on the established necrotic tissue in order to avoid hemorraghe, which did not allow to avoid a subsequent systemic infection (Helling 2000). After the advances of surgery in the XVI and XVII centuries, amputation started to earn the place it deserved in the sepsis surgical control.

XIX century: two nations at war, France and England; two conflicting strategists, Napoleon Bonaparte and Field Marshal Arthur Wellesley, Duke of Wellington. Amidst this bloody conflict, their respective surgeons would demonstrate that science goes beyond flags and conflicts. Napoleon's surgeon at that time, Dominic Jean Larrey (1766 - 1842), proposed the use of early amputation as a way to reduce mortality. In his memories he adds: "amputation must be performed instantly. Otherwise, the damaged areas will soon become gangrene" (Larrey 1812). Larrey creates the concept of early amputation, changing an affected limb into a small wound, less contaminated, with more possibilities to control hemorraghe and where infeccion would be inevitable. With great expertise in this procedure, Larrey performed more tha two hundred amputations per day in the Borodino Campaign (Ellis 2001), and could report an approximate of 75% survival rates (Larrey 1812). This concept of early amputation was of paramount importance to avoid both sepsis and the feared post-trauma shock.

On his side, the British surgeon, George James Guthrie (1785-1856), who was Wellington chief surgeon (called "the British Larrey"), describes in his Treatise on Gunshot Wounds the

typical clinical profile of a septic shock which could be observed after the Battle of Waterloo (1815). A clear difference compared with the post-trauma shock description can be seen: *"Pain, heat, redness, tumefaction of neighbouring parts constituting inflammation comes on, which speedily runs into suppuration or gangrene... fever becomes more violent and frequently ends in death in the course of a few day."* (Guthrie 1827). As it can be seen, a temporal distinction between local inflammation and sepsis development in the following days is made, evidenced by the continuous in character feverish profile with a fast physiological decline which ends up in death. In the context of the pre-antibiotic period, early amputation proposed by Larrey was the only option to give hope to a seriously injured soldier because it limited the systemic response to the lesion thus diminishing the damaged tissues to be susceptible of patogen colonization.

However, only a few agreed with Larrey about tissue damaged by itself as the stimulus for "shock and prostration of strength" and about removal using early amputation being an effective way to avoid gangrene. In fact, this point provoked a great debate between the XVII and the XIX centuries; to amputate or not to amputate, that was the question (Helling 2000). Several medical figures added to this controversy, even John Hunter himself, who was inclined towards a more conservative and late use of amputation, arguing that the battle field was the least suitable to perform a surgery of these characteristics (Hunter 1985; Ellis 2001). Even so, history and multiple wars would give Larrey the reason. Guthrie himself collected the Battle of Waterloo data about the total population of 596 soldiers and he found that in the 371 group of patients who were performed amputation in the battle field, mortality was only 22% while in the 225 soldiers group who were performed late amputations (possibly after 30 days), mortality was 37% (Helling 2000). Similar results were observed during the American Civil War (Otis 1883). These data show us that during the pre-intibiotic period the early performance of such procedure had an impact in mortality reducing the incidence of complications such as post-trauma shock and sepsis.

With the disappearance of the pus bonum et laudabile concept it is evident so far how important the advances in the field of surgery were for the sepsis control. However, in spite of the expertise gained with the scalpel, very few has been attained in the identification of the real enemy of the septic patient: microorganisms. Towards the XIX century it was a heroic deed to come out alive from an operating room, and it is no surprise that before the asepsis and antisepsis techniques appeared, surgeries could draw mortality rates higher than 90% (Robinson 1947; Pollak 1970; Ledermann 2008). It was well put by the Scottish physician James Young Simpson in 1847: "*The man laid on the operating table in one of our hospitals, is exposed to more chances of death than the English soldier on the field of Waterloo*."(Pollak 1970).

7. Why then and not before: Germs before the microbiologic period

Let's analyze some approximations to the theory of contagion and infection before the XIX century in which the emphasis will be placed on the reasons why these postulates did not have a greater incidence in the medical corpus in their respective period, and we will stop in

a case that perfectly can summarize the epistemological framework of the rest. Let's begin in Greece again. It was not difficult for the Greek to identify that some of the signs of intoxication such as vomit, diarrhea and, in some cases, fever were similar to the clinical profiles caused by infections. For them, the fact that some diseases, especially feverish ones, affected groups of people closely related or even complete populations did not go unnoticed. What was this poison that could intoxicate, alter humors and also affect a great number of people at the same time and in the same place? Greek physicians did not take long in finding the similarity stinking exhalations had in those sick with the plague and the foul vapors emanating from marshes. These stinking exhalations, called miasmas, were nothing different from the odors rising from putrefaction (in the Greek sense of the word sepsis) of undesirable substances. The putrid swamp areas filled with mosquitoes were clearly related with the appearance of malaria (mal'aria, Roman word for "bad air"),so that Greeks, Romans, and everyone from them on, associated the appearance of feverish diseases with the bad environmental odors that intoxicated the body and caused humorous disorder. This explained for them the appearance of disease like that, in a great number of people in the same place and at the same time (Castiglioni 1941). Another approximation consisted of contagion (from latin 'contigere' meaning 'to touch') which argued that a venous, non volatile material caused the disease while intoxicating the part of the body it contacted permitting humor sepsis to happen. These two theories, both miasmas and contagion, were not something different from a part of the Galen postulates from physiological-environmental essence: according to Galen, disease was the expression of a disorder in proportion to humors or their quality which occurred because of the conjunction of three factors:

- Initial causes: external factors such as heat, cold, miasmas that might produce damaging changes in the humors.
- Precedent Cause: It is the personal predisposition to a disorder which explains why some individuals are more susceptible than others to a determined disease.
- Cohesive Cause: It is the alteration in composition, proportion or quality of humors (dyscrasia) and that could be triggered by the union of precedent and initial causes. The disease was a manifestation of the cohesive cause in which the other factors (initial or precedent) had already acted as a whole or separately.

Which was the fundamental detail here? All therapeutics was directed to this cohesive cause or humorous disorder in order to achieve eucrasia (the adequate humor proportion). In this sense, the initial cause, whichever it was, was an "associated factor" and it was not seen as a neither necessary nor sufficient cause for the maintenance of a disease (Nutton 1983). This indicates that any postulate that intended to pose the existence of invisible living forms able to cause a disease could only be seen as one of the many factors which caused the disease, and different from what is stated in the germs theory in the XIX century, it would hardly be seen as a determinant factor to be attacked with the therapeutics to solve the disease.

Were there in olden days similar approximations to what we know today as germs or different approaches to the humoralism-environmental theory? The truth is that there were.

Years after Hippocrates times, in his book about the generation of animals (Generation of animals. III.xi), Aristotle explains that new animals are born from putrid material4, and he added that sepsis produce small creatures, especially in the putrid mud and in stinking swamps (Majno 1991). These ideas were not forgotten and the Roman writer Marcus Terentius Varro (116 a. C. - 27 a. C.) wrote a text known as Agricultural Topics in three books devoted to his wife Fundania in which he mentions: "In swampy places a multitude of small animals develop which can not be perceived by the eye, but the penetrate the body through the mouth and thenose, and cause terrible diseases."5 These postulates were inside the Humoralism framework because they identified putrefaction in the swamps as the origin of small and dangerous animals, and these would not be something different from an initial cause, another element that would contribute to humorous disorder. Other authors, on the other hand, certainly opposed Hippocratic conceptions. The origins of some of these theories date centuries back reaching Pre-Socratic philosophers from the atomic mechanism such as Leucippus and Democritus (IV and V centuries BC) who suggested the existence of infinite, in varied forms, indivisible and always moving particles which conformed all reality. These atomists postulates would be adopted by Greek physicians such as Caelius Aurelianus, Philo and Asclepiades, representatives of the Methodist medical school from the I and II Centuries AD, who posed an atomic-ontological approach. This approach stated the origin of disease is in the greater or lower particles cohesion which breeds the ground so that, under the concept of atomic entities, diseases can be appropriated to singularities dynamic in character, imperceptible to the eye, and that can affect its environment. The Methodist postulates were treated apathetically because of the medical status quo between the III and the XVI centuries; this is not surprising since they proposed an ontological concept of the disease which was irreconcilable with the Galen doctrines of physiological-environmental type. Later, Arabians who were great receivers of Greco-Roman science increased quantitatively the knowledge about infectious diseases but assumed the physiological-environmental model as a dogma. Authors like Avicenna preferred Galen explanations of air corruption with miasmas, atmospheric changes and astrologic influences instead of any approximation coming from microscopic life as the cause of disease. So, it is not surprising that the seeds of disease, a concept closer to the germs theory stayed asleep in the shelves of the medieval knowledgeable without any practical approximation.

The search for sepsis seeds continues until the mid XVI century. Paré had just published in France his experiences in the Villaine Castle and Paracelsus lied in his grave in Salzburg leaving behind an immense legacy. It was in 1546, in Padua, and emblematic Renaissance city where only three years back Copernicus and Vesalius had published their great works, when a great poet and physician's text saw the light: Girolamo Fracastoro (1478 – 1553). Native form Verona, this author proposed in his text De Contagione et Contagiosis Morbis

[4] This principle, known as the spontaneous generation of life, remained unaltered as a dogma until Luis Pasteur, in the XIX century demonstrated that it was false, thanks to his experiments with microorganisms (see next section).

[5] Rerum Rusticarum – De agricultura Libri Tres: "*…siqua loca palusteria, et quod [arescunt] crescunt animalia quaedam minuta, quae non possunt pculi consequi, et per aera intus in corpus per os ac nares perueniunt atque efficiunt difficilis morbos.*" (Terrencio Varrón 1992)

et Eorum Curatione (Wright 1930) what seemed to be an approximation to the modern concept of contagion6. Because of Fracastoro's presence in the historical framework of great medical revolutions during the Renaissance, a favorable reaction from the different contemporary authors did not take long to come and they considered his text as the first scientific declaration about the true nature of contagion which, suposedly, would anticipate what would become the current germs theory. They also compared the importance of their achievement with that achieved by Puré, Vesalius, and Paracelsus (Singer 1917; Castiglioni 1941; Robinson 1947; Pollak 1970; Howard-Jones 1977). Nevertheless, based in the originality of his conception, the practical application of his context and the scope of his influence, it can be stated that Fracastoro did not have the historical-scientific relevance confered on him. Three reasons can be given for this: 1) Were his postulates original? No. It is well-known that during Fracastoro's times the disease seeds lied, maybe as their bibliographic sources, in three Galen texts; some Plutarch's passages referring to the Methodists; passages from the teologist Isidore making reference to Lucretious7 and some Roman and Medieval agricultural sciences ancient texts (Nutton 1983.; Terrencio Varrón 1992); 2) Did they have some practical application? No. Fracastoro's seeds made part of the multiple initial causes that could have contributed to unchain illness. If the seeds were or were not present was irrelevant because they were not understood as a necessary cause for the disease appearance. In this sense, theorizing about the seeds was a philosophical luxury without immediate medical applications because the therapeutics in that period was focused in correting the humoral disorder as such, and it was not focused on the hypotetical entities that had already acted to unchain it. Within the framework of the old paradigma, it was impossible to accept, until it had not been observed in the microscope and after studies that demonstrated its role in the disease, that a particular entity (semina morbi) was the necessary cause for the appearance of an infection. This ontological approach would only be possible thanks to the disappearance of humoralism and the appearance of the cellular theory and, obviously, the development of microbiology (Howard-Jones 1977; Nutton 1983.; Grissom 2004); 3) Did he have any immediate or subsequent influence? Fracastoro was not an influential professor in a big European university and he was only known locally. His writings, very little disseminated, were hardly rescued the century before last when their first translations appeared in the XIX century which will conclude with the first translation into English in 1930 (Wright 1930). Which was then the real value of Fracastoro? He was a

[6] In 1930 Wilber C. Wright was the first one to translate and publish G. Fracastoro's text in English. A version brilliantly translated into Spanish is available in the collection Clásicos *de la Medicina, Medicina Renacentista III. Gerolamo Fracastoro: De Contagione Et Contagiosis Morbus. Revista MD En Español, Octubre, 1970. p: X1-X8.* In his text, Fracastoro argues that infection is not produced because of unknown causes but because of seeds of the disease: *semina morbi* o *seminaria,* which are imperceptible particles composed by different elements and propagate (*propagare*) and breed (*gignere*) other seeds, and cause corruption at the level of the constituent particles of things. However, at no time Fracastoro specifies that those are living organisms or makes clear precisions about the difference between contagion and infection, or about any of the conceptual meanings.

[7] Lucrecio, great poet in the century I BC, would say in his book *De Rerum Nature*: "I have already shown that there are many seeds useful for our life, but also there are many others that fly around bringing diseases and death" (Nutton 1983). This poet, contemporary author from Asclepiades, probably had access to Methodist texts, or he knew Aristotelian explanations on the animals' formation, or he had access to the hidden but devastating critics that Galen used to do of the Methodists and their texts.

poet and writer who, as a good Renancentist dominated a variety of fields such as geology, physics and geography (Nutton 1983). As a medical author, he took the liberty of leaving behind physiological and environmental-humoralist explanations, and described contagious diseases in purely ontologic terms (Nutton 1983). Even though his vision of disease could not be empirically confirmed and its seeds could not be demonstrated as etiological agents until the introduction of the microscope, Fracastoro is one of the signs of the epistemological rupture with the Galen humoralism which finishes in the XIX century. Fracastoro, in his historical-scientific context, is a clear example of the changes that, as a whole, science, philosophy, and even human beings themselves who practice them, must go through in order to accept a new paradigm. Seen from modern historiography, the reading made of Fracastoro's work is, in essence, a clear example of an anachronistic interpretation of medical historiography because of a clear overvaluation on the side of historian-physicians by the end of the XIX century and beginnings of the XX century that saw in their semina morbi a singular likeness with the microbial pathogen theories which were in their zenith in those years.

During the XVI and XVII centuries there were some theoreticians and scientists who started to question the Galen concept on physiology of the disease and consequently, preestablished conceptions about infection. These men would plant the seeds that later would be harvested during the XIX century. The first of them was the Jesuit Athanasiuus Kircher (1602-1680). This great German scientist whose contributions extend from Biology to Philosophy, transcended Fracastoro and suggested that contagion was due to living organisms (contagia animata), an approach derived from his investigations in the plague patients' blood and pus. Kircher was the first one to infer that the recently discovered animalcules must have been the cause of the disease. However, his microscopic techniques did not allow him to see some free living protozoa without any relation with the disease (Bustíos Romaní 2004).

8. Sepsis and the birth of the germ theory

Until the end of the XVIII century the breaking with Galen humoralism had started consolidating with the anatomopathologic approach inaugurated by Morgagni which allowed locating the disease in a specific place (organ) and with a demonstrable cause, and later, with the works of the German doctor Rudolph Virchow (1821 - 1902) who, after many hours of study with the microscope started to postulate the cellular theory (Omnis cellula e cellula), which invited to find the causes of the disease in the tissular and cellular structures (Pollak 1970). However, and still within this context, humoralists' ideas from the Greco-Roman era about pus were still sounding and the origin of that secretion continued to be a mystery (Grmek 1991; Hernandez Botero 2009). With the development of cellular theory proposed it was already known that cells could only originate from preexistent cells and not from amorphous material which allowed elucidating the cellular character of suppuration. One of his most outstanding students, Julius Cohnheim (1839-1884), published a controversial work in 1873: Neue Untersuchungen ubre die Entzündung (New Studies on Inflammation) in which, based on previous studies about the local origin of white cells

present in pus, could verify diapedesis and the importance of blood vessels in its production through the ingenious studies in frogs mesentery (Malkin 1984). These first advances allowed future advances in the understanding of chemotaxis, diapedesis, and locall inflammation, and they, laid down the foundations for the beginning of immunological and physical chemical studies that opened new ways to understand the phenomenon off inflammation (López Piñeros 1974).

This way we arrive to the XIX century. By this time microbiology was a branch of Botanic, and it will be within some few decades that microbiology not only will change medicine forever, but also the human beings' destiny. Everything begins with a martyr prophet of science: the Hungarian obstetrician Ignaz Semmelweis (1818 – 1865). His story is well known. Semmelweis was able to associate the physicians and medicine students' contaminated hands during autopsies with the increase of puerperal sepsis and theorized that it was cadaverous particles and not "cosmic, hygromatic or telluric" influences the responsible ones for the significant increase in mortality in a maternity ward at the general hospital in Vienna, and through simple hygienic measurements, he could diminish dramatically puerperal sepsis mortality (Charles 1994; Henao 1999; De Costa 2002). Nevertheless, his observations are not accepted by the medical community and after a long struggle for disseminating his theory, he is accused of having lost his mind and he is hospitalized against his will in a psychiatric hospital in Vienna where he dies alone. Through his clinical observations, Semmelweis makes the first attempt to consolidate the ontological character of sepsis, based on the evident etiological specificity of its theory. However, the necessary biological concepts to give a scientific sense to his observations did not exist. It is sad to know that only some years would go by after his dead when Pasteur, without knowing Semmelweis' work (Debré 2000), would isolate streptococcus from purulent lochia of women to whom Semmelweis could have saved (Charles 1994; Henao 1999; Magner 2009).

During the XIX century a good corpus of evidence had already been collected which demonstrated how bacteria appeared to be responsible for sepsis. Vichow's famous helper, the German student Edwin Klebs (1834–1913), reviewed under the microscope multiple samples of autopsies that he collected while serving as military physician during the Franco-Prussian war in 1879. In his revision of more than one-hundred specimens, Klebs found bacteria in almost every case and, even though he supposed erroneously that all of them were all the same type of organism which he called *Microsporon Septicum*, he was one of the first scientist in seeing and relating what no one had seen before: the agents causing sepsis and their role in the clinical phenomena itself (Magner 2009). This revolutionary finding would not have been important if the works of other great researchers who developed the microbiological theory and demonstrated the importance that converting the invisible and theoretical in something practical and visible had not been combined. The concepts about what bacteria are and how they are related to the disease still needed to be matured, answers that would come from both sides of the war in which Klebs had served: France and Germany.

The first lights came from France where a rather mediocre student who desired to be a painting teacher, would revolutionize all the fields of knowledge he dealt with. Louis Pasteur (1822 – 1895), after his prolific career in Chemistry, started to study in depth the world of microorganisms and, after several years of work, he summarized and published in 1865 the results of a fermentation in which he refutes spontaneous generation of life and demonstrated in an irrefutable way the existence of microorganisms.

His works gave cause for important conclusions: He demonstrated that the air is filled with microbes ready to develop and that the putrid liquids can be sterilized by heating. About half way through his career, his studies about fermentation gave him the possibility to state that contagious diseases might be caused by microscopic organisms (Aguirre 1996; Restrepo 1996). After these studies, Pasteur would carry a prolific academic career that would not only allow him great developments in the newborn infectology, but also his works would be the scientific bases , among others, for the practical development that later on would be known as asepsis and antisepsis.

If Pasteur opened the way for bacteriology, a German doctor, Robert Koch (1843 – 1910) consolidated its development as a discipline. After multiple achievements harvested in the study of bacterial etiology of diverse diseases, Koch started to worry since 1887 about the growth of bacteria in wounds and in surgical incisions. From his observations he published that same year the book Untersuchungen über die Aetiologie der Wundinfektionskrankheiten (About Etiology of Traumatic Infective Diseases) in which he exposes his experiments infecting wounded animals with putrid substances. In his work he would explain: "*I conclude that bacteria are not present in the blood or tissues of healthy animals*," however, "bacteria are present in all sick animals [in blood and tissues], and their number and distribution is in such a way that they perfectly explain the symptoms of the disease" (Brock 1999). These observations are a rough draft of what would become Koch's postulates. Without any doubt these postulates could causally relate microbes and sepsis and thus constituted a first look at the disease pathogenesis. Nontheless, Koch's works had a problem: they were completely carried out with animals. But he didi not take too long in establishing a relation in humans thanks to the Scotish physician Alexander Ogston (1844 - 1929),who used the same methods Koch used and could establish in an unequivocal way the relation between bacteria and sepsis and even detailed two different types of coccus: staphylococcus and streptococcus which were present in blood and pus of many septic patients. His publications were pioneer without any doubt and constituted a cornerstone for the study of sepsis in the areas of pathology, surgery and bacteriology (Van Arsdale 1886; Brock 1999; Magner 2009).

The English surgeon Joseph Lister (1827 – 1912) took his observation to the practice even when he did not know his enemy: the microbe. His works were already well advanced when he had access to the first pioneer works in bacteriology and he could start collating his practical results with the experimental and theoretical evidence of the microbiology colossus (Ledermann 2008). In his work what stands out is his particular worry for diminishing infections in open fractures, traumatic lesions and the surgical act in general. Lister observed

that fractures where the skin was intact healed without infection while in the open fractures sepsis and pus drainage were common (Thurston 2000). His observations on amputation wounds and infected wounds took him to conclude that dust of disease was responsible for these complications (Lister 1867; Walker 1956; Ledermann 2008). When Pasterur's work came into his hands, he could finally see the connection between his observations on wounds and the microscopic bacteria responsible for fermentation (Thurston 2000). That is how in 1867 he publishes his work about the antiseptic management of open fractures with carbolic acid (Lister 1867; Lister 1870) which changed forever the treatment of this type of lesions (Schwartz 1932). Lister started to become active in the microbiology studies and he attended the Seventh International Medical Congress in London in the summer of 1881 where he could exchange opinions with Koch and Pasteur. Later he continued updated with these two researchers' work and even he received a copy of the first germs microphotographs in septic rabbits' tissues taken by Koch during his investigations about etiology of infective traumatic diseases (Robinson 1947; Brock 1999).

With the bacterial etiology of sepsis established by the end of the XIX century, many concepts about bacteria already made part of the surgery and pathology texts: Terms like pyaemia, sapremia, purulent infection, putrid infection, septicemia, surgical sepsis and traumatic fever were used indistinctively for the systemic condition that we know today derives from the invasion of bacteria after the colonization of a wound (Van Arsdale 1886). Through their conclusive scientific evidences Koch and Pasteur change animalcules, semina morbi, contagia animata, cadaveric particles, disease powder, in the microbiological revolution, while Lister can take all these concepts into practice saving innumerable lives thus changing medicine practice forever.

9. Conclusions

"...when a man has been wounded who can be saved, there are in the first place two things to be kept in mind: that he should not die from hemorrhage or inflammation" Aurelius Cornelius Celsus. I Siglo d.C.

The identification of the phenomenon we know as sepsis today, secondary to any type of wound, was a constant from olden times to the Middle Ages. The temporal association between lesion and subsequent appearance of fever was well known, as well as the different inflammation signs in the primary lesion and the secondary systemic compromise. The interpretation of these phenomena changed from magical-religious conceptions to the classic humoralism which dominated western medicine for more than a thousand years. The governing paradigm in each period supported the medical and surgical management of wounds, beginning with the relatively a-pyogen healing from the Ancient Egypt and Alexandria, going through the surgical and non surgical management of the classic Greek and Greco- Roman medicine whose therapeutic objective, though qualitatively was the same, varied in the gradual importance suppuration as fundamental healing process gained. Finally, during the Middle Ages, an imminently Galen approach, Arab medicine performed a determined defense of suppuration as a comprehensive part of the treatment and favored

non surgical procedures as cautery in order to facilitate it. This historical evolution was sprinkled by multiple facts of epistemological relevance, In the first place, during the Middle Ages there was a split between the medical knowledge and surgery allowing the gradual loss of surgical knowledge from the classic texts, which explains why during this period the use of sutures, wound exploration and vessels ligatures were pushed into the background turning the painful cautery in the suitable conduct for all types of lesions. Secondly, none of the intents to defeat the Galen dogma "pus bonum et laudabile" succeeded: without a philosophical corpus that supported the paradigm changes, without experimental coincident evidences in time-place which could force such change, and without any anomaly that placed a doubt on the established conceptions, this task would continue to be a chimera. These factors of a strictly epistemological order, explain why the Galen dogma continued taking lives through the Middle Ages until after the Renaissance. Sepsis, understood as an anomaly in Khunian terns, put in crisis the Galen paradigm allowing important developments in medicine; change would finally come with the transformation in the philosophical conception of the disease in which it was accepted that it could be caused by entities and not by simple deviations of normality. This turn from the physiological to the ontological provided the support that would allow the acceptance that those gracious animalcules seen through the microscope lenses, microorganisms, are the real enemies of the injured and infected patient.

Many of the quantitative novelties achieved by medicine during the XX century are nothing but reforms, subtractions and contributions to those models which pioneers from past centuries conceived. As we could observe, these deep ruptures needed a fertile soil in the scientific spirit and in the minds of men of science in order to assume the doctrinal and practical changes which allowed facing up to the scientific challenges. Historiographic misunderstandings like the ones raised by Fracastolo's work, or scientific tragedies such as Semmelweis' life, are irrefutable proof that the development of a discipline is neither an isolated fact from the rest of the sciences and human activities since that discipline nurtures with them, nor an isolated fact from society since it is immersed in it and serves its purposes. To conclude, we might ask a last question: Is sepsis nowadays an overcome challenge? Definitively, no. Sepsis constitutes, today, one of the main challenges in intensive care: it is the main cause of death in non coronary ICUs, up to 35% of patients in these units will suffer the disease. 18 million cases per year with a global mortality of 30% are reported each year. It is responsible for more deaths than AIDS and its incidence will increase in 8% annually. After 40 years of exhaustive research mortality has been reduced in only 10% (Martin 2003; Jaimes 2005). 17 billion dollars per year in costs and attention are spent yearly and, from the medicines researched, several dozen in three decades only two have marginally diminished mortality. It is not surprising then that sepsis has been called with sarcasm "the pharmaceutics cemetery". All these factors show a problem: Is sepsis becoming a systematic challenge for the present medical paradigm? It is very possible since many factors in our world are analogous in medical and social consequences to the challenges that allowed sepsis to take innumerable lives in olden days. Our immune system evolved in a context which demanded the most vigorous answers before the invading

pathogen, a killing or dying fight; however, the game rules have changed. Present and unavoidable conditions in our modern world such as population aging, microbial endurance, immunosuppression, increasing intravenous and other types of invasions are related with an increase in the incidence and seriousness of the disease. These factors not only give advantages to microorganisms but also exert a tremendous evolutionary pressure on us. We have a permanent armed race in which our invaders will always have an advantage over us and we find ourselves unrelentingly urged to innovate from the biomedical sciences. In conclusion, maybe sepsis imposes new challenges of great magnitude in the following years that can allow us, and force us to open new ways to develop new paradigms in this century's medicine… at least that is what the costly lessons of the past teach us.

Author details

Johan Sebastián Hernández Botero
Departamento de Ciencias Básicas para la Salud, Universidad de Caldas, Colombia
Departamento de Ciencias Básicas Biológicas, Universidad Autónoma de Manizales, Colombia

María Cristina Florián Pérez
Departamento Clínico-Quirúrgico, Universidad de Caldas, Colombia
Unidad de Cuidados Intensivos, Hospital Departamental Santa Sofía ESE, Colombia

Acknowledgement

Orlando Mejía Rivera, Julián David Bohórquez Carvajal, Oscar Jaramillo Robledo, Eliana Andrea Castrillon Soto.

10. References

Abbas, A. (2002). Inmunidad Innata - Respuestas fisiológicas y patológicas al lipolisacárido bacteriano. *Inmunología celular y molecular*. A. Abbas, Lichtman, AH., Pober, JS. Madrid, McGraw Hill - Interamericana: 287.

Adams, R., Victor, M., Ropper, AH. (1999). Infecciones del Sistema Nervioso. *Principios de Neurología*. R. Adams, Victor, M., Ropper, AH. Mexico D.F, McGraw Hill - Interamericana: 604-643.

Aguirre, C. (1996). "El Legado de Louis Pasteur." *Iatreia* 9(1): 16-21.

Baskett, T. (2004). "Ambroise Paré and the arrest of haemorrhage." *Resucitation* 62: 133-135.

Béclard, R., Cloquet, H., Cloquet, J., Orfilia, M. (1834). *Nouveau Dictionnaire de Médecine, Chirurgie, Pharmacie, Chimie, Histoire Naturelle.* Paris, Deville Cavellin.

Beutler, B., Poltorak, A. (2001). "Sepsis and evolution of the innate immune response." *Crit Care Med* 29(7): (Suppl):2-6.

Bishoy, M. (2004). "Surgery on Papyrus." *Student BMJ* 12: 338-339.

Blum, Y., Esterhai, J. (2002). "The history of the treatment of musculoskeletal infection." *Oper Tech Orthop* 12(4): 226-231.

Border, J., Hasset, J., LaDuca, J., Seibel, R., Steinberg, S., Mills, B., Losi, P., et al. (1987). "The gut origin of septic states in blunt multiple trauma." *Ann Surg* 206: 427-448.

Breasted, J. H. (1980). *The Edwin Smith Surgical Papyrus*, Chicago University. Chicago Press.

Brock, T. D. (1999). *Robert Koch: a life in medicine and bacteriology*. Washington, American Society for Microbiology Press.

Broughton, G., Janis, JE., Attinger, CE. (2006). "A brief history of wound care." *Plast Reconstr Surg* 117(7): (suppl):6-11.

Brunschwig, H. (1497). *Das Buch Der Cirurgia*. Strassburgo, Johann Grüninger

Busch, D., Dieffenbach, JF., Hecker, JF., Horn, E., Jüngken, JC., Link, HF., Miller, J. (1845). *Encyclopädisches Wörterbuch der medicinischen Wissenschaften*. Berlin, Verlag von Veit - J.W. Boike.

Bustíos Romaní, C. (2004). Higiene y Sanidad en el Mundo occidental. *Cuatrocientos años de Salud Publica en Perú*. C. Bustios Romaní. Lima, UNMSM: 34-35.

Castiglioni, A. (1941). *A History of Medicine*. New York, A.A. Knopf.

Celsus, A. C. (1961). De Medicina. W. T. Spencer. Cambridge, Harvard University Press.

Cinel, I., Dellinger, P. (2007). "Advances in pathogenesis and management of sepsis." *Curr Opin Infect Dis* 20: 345-352.

Crombie, A. (1987). La recepción de la ciencia greco-arabe en el mundo occidental. *Historia de las Ciencias, De San Agustín a Galileo.* A. Crombie. Madrid, Alianza Universidad. 1: 44-67.

Charles, J., Charles, D. (1994). Infeccion posparto. *Infecciones Obstétricas y Perinatales*. D. Charles. Madrid, Mosby / Doyma: 61-67.

Chase, K. (2003). *Firearms: A Global History to 1700*. Cambridge, Cambridge University Press.

Davies, R. (1970). "Some Roman Medicine." *Med Hist* 14(1): 101-106.

De Costa, C. (2002). ""The contagiousness of childbed fever": a short history of puerperal sepsis and its treatment." *Med J Aust* 177(12): 668-671.

Debré, P., Forster, E. (2000). *Louis Pasteur*. Baltimore, Jonhs Hopkins University Press.

Dellinger, P., Levy, MM., Carlet, JM., Bion J., Parker, MM., Jaeschke, R., Reinhart, K, et al. (2008). "Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock." *Crit Care Med* 36(1): 296-327.

Drucker, C. (2008). "Ambroise Paré and the birth of the gentle art of surgery." *Yale J Biol Med* 81(4): 199-202.

Ellis, H. (2001). "John Hunter's teachings on gunshot wounds." *J R Soc Med* 94: 43-45.

Forrest, R. (1982). "Development of wound therapy from the Dark Ages to the present." *J R Soc Med.* 75: 268-273.

Forrest, R. (1982). "Early history of wound treatment." *J R Soc Med.* 75: 198-205.

Francis, A. (1985). *The Genuine Works Of Hippocrates*. New York, Classics of Medicine Library / Gryphon Editions Ltd.

Francis, A. (1985). Hippocrates: On Fractures. *The Genuine Works Of Hippocrates*. A. Francis. New York, Classics of Medicine Library / Gryphon Editions Ltd.: 157-166.

Francis, A. (1985). Hippocrates: On Regimen on Acute Disease. *The Genuine Works Of Hippocrates.* A. Francis. New York, Classics of Medicine Library / Gryphon Editions Ltd.: 59 - 97.

Francis, A. (1985). Hippocrates: On Surgery. *The Genuine Works Of Hippocrates*. A. Francis. New York., Classics of Medicine Library / Gryphon Editions Ltd.: 157-204.

Francis, A. (1985). Hippocrates: On Ulcers. *The Genuine Works Of Hippocrates*. A. Francis. New York, Classics of Medicine Library / Gryphon Editions Ltd: 325-336.

Gabay, C., Kushner, I. (1999). "Acute-phase proteins and other systemic responses to inflammation." *N Engl J Med* 340(6): 448-454.

Geroulanos, S. and E. T. Douka (2006). "Historical perspective of the word "sepsis"." *Intensive Care Med* 32(12): 2077.

Grissom, J. (2004). Explaining Plague in Early Modern Europe: The Role of Contagion in the Theories of Girolamo Fracastoro and Thomas Willis. *History of Science*. Norman, Oklahoma., University of Oklahoma. Master of Arts.: 91.

Grmek, M. (1991). *Diseases in the ancient greek world*. Baltimore and London, The John Hopkins University Press.

Guthrie, G. (1827). *A treatise on Gun-shot Wounds*. London, Burges and Hill.

Haggard, H. W. (1947). *El Médico en la Historia*. Buenos Aires, Editorial Sudamericana.

Helling, T., McNabney, WK. (2000). "The role of amputation in the management of Battlefield Casualities: A History of Two Millenia." *J Trauma* 49: 930-939.

Henao, G. (1999). "La lucha de I. F. Semmelweis en la génesis de un nuevo paradigma." *Iatreia* 12(3): 149-156.

Hernandez Botero, J. (2009). "Recuento histórico y análisis epistemológico de la sepsis secundaria a lesiones y su control quirúrgico: Desde el papiro de Edwin Smith hasta el "pus bonum et laudabile"." *Iatreia* 22(3): 292-300.

Hippocrates (1849). Of Epidemics. *The Genuine Works Of Hippocrates*. A. Francis. London, Sydenham Society: 339-381.

Hontanilla Calatayud, B. (1999). *Cirugía Menor*. Madrid, Marban.

Howard-Jones, N. (1977). "Fracastoro and Henle: A re-appraisal of their contribution to the concept of communicable diseases." *Med Hist* 21: 61-68.

Hunter, J. (1985). *A treatise on the blood, inflammation and Gun-Shot Wounds*. Birmingham, Classics of Surgery Library / Gryphon Editions.

Jaimes, F. (2005). "A literature review of the epidemiology of sepsis in Latin America." *Rev Panam Salud Publica* 18(3): 163-171.

Joly, R., Ed. (1970). *Hippocrates: Des maladies IV*. París, Société d'édition Les Belles Lettres.

Keel, M., Trentz, O. (2005). "Pathophysiology of polytrauma." *Injury* 36(6): 691-709.

Kuhn, T. S. (2004). *La estructura de las revoluciones científicas*. Buenos Aires, Fondo de Cultura Económica.

Laín Entralgo, P. (1979). *Historia Universal de la Medicina*. Barcelona, Salvat.

Larrey, J. (1812). *Memoires de Chirurgie Militaire et Campagnes*. Paris, Tallandier.

Lattimore, R. (1961). *The Iliad of Homer*. Chicago, University of Chicago Press.

Ledermann, W. (2008). "En memoria de Lister." *Rev Chil Infect* 25(5): 351-356.

Lenz, A., Franklin, GA., Cheadle, WG. (2007). "Systemic inflammation after trauma." *Injury* 38(12): 1336-1345.

Lister, J. (1867). "On a new method of treating compund fracture, abscess etc., with observations on the conditions of suppuration." *Lancet*: 326-329, 357-359, 387-389, 507-509.

Lister, J. (1870). "The antiseptic system of treatment in surgery." *Lancet* 2: 287.

López Piñeros, J. (1974). Patología y medicina interna en Alemania. *Historia Universal de la medicina*. P. Lain-Entralgo. Barcelona, Salvat. 6: 123-155. Volumen VI.

López Piñeros, J. (2002). *La Medicina en la Historia*. Madrid, La esfera de los libros.

Magner, L. (2009). *A History of Infectious Diseases and the Microbial World*. New York, Praeger Publishers.

Majno, G. (1975). *The Healing Hand: Man and Wound in the Ancient World*. Cambridge, Harvard University Press.

Majno, G. (1991). "The ancient riddle of sigma eta psi iota sigma (sepsis)." *J Infect Dis* 163(5): 937-945.

Majno, G., Cotran, RS., Kaufman N., Ed. (1982). *Current topics in inflamation and infection.* International Academy of Pathology Monograph. Baltimore., Wlliams & Wilkins.

Malkin, H. (1984). "Julius Cohnheim (1839-1884). His life and contributions to pathology." *Ann Clin Lab Sci* 14(5): 335-342.

Martin, G., Mannino, DM., Eaton, S., Moss, M. (2003). "The epidemiology of sepsis in the United States from 1979 through 2000." *N Engl J Med* 348: 1546-1554.

McFarlane, H. (1976). "Malnutrition and impaired immune response to infection." *Proc Nutr Soc.* 35(3): 263-272.

Mejía Rivera, O. (1990). *Humanismo y Antihumanismo*. Manizales., Fondo Editorial Universidad de Caldas.

Mejía Rivera, O. (2002). *De la prehistoria a la Medicina Egipcia*. Manizales, Centro Editorial Universidad de Caldas.

Mejía Rivera, O. (2004). *Los descubrimientos serendípicos. Aproximaciones epistemológicas al contexto del descubrimiento científico.* Manizales, Universidad de Caldas, Facultad de Ciencias para la Salud

Mejía Rivera, O. (2005). "El nuevo paradigma genético y la naturaleza humana." *Acta Med Colomb* 30: 68-72.

Nutton, V. (1983.). "The seeds of disease: An explanation of contagion and infection from the greeks to the renaissance." *Med Hist* 27: 1-34.

O'Neill, L., Greene, C. (1998). "Signal Transduction pathways activated by the IL-1 receptor family: Ancient Signaling machinery in mammals, insects and plants." *J Leukoc Biol* 63: 650-657.

Opal, S. (2000). "Phylogenetic and functional relationships between coagulation and the innate immune response." *Crit Care Med.* 28(9): suppl: 77-80.

Opal, S., Girard, TD., Ely, EW. (2005). "The immunopathogenesis of sepsis in elderly patients. ." *Clin Infect Dis.* 15(41): Suppl 7:S504-512.

Otis, G. (1883). *The Medical and Surgical History of the War of the Rebellion*. Washington, US Govermment Printing Office.

Paget, S. (2005). *Ambroise Pare and His Times 1510 to 1590*. Whitefish Montana, Kessinger Publishing.

Pastrana, J., García, JP., Civeira, J., Prieto, M. (2006). Bioquímica Hemática: Velocidad de sedimentación globular. *Balcells: La Clínica y el Laboratorio.* J. Valtueña Prieto. Barcelona, Elsevier-Masson: 111-115.

Pollak, K. (1970). *Los discípulos de Hipocrates, Una historia de la Medicina*. Barcelona, Círculo de Lectores.

Pollak, K. (1970). *Los discípulos de Hipocrates, Una historia de la Medicina.* Barcelona, Círculo de Lectores.

Pringle, J. (1750). Experiments upon septic and antiseptic substances. *Philosophical Transactions, of the Royal Society of London*. D. W. A. Millar, T. Durham T. Payne. London, Bulmer, W.

Restrepo, A. (1996). "Louis Pasteur: In memoriam." *Iatreia* 9(1): 22-27.

Robinson, V. (1947). La Medicina Árabe en la Edad Media. *La Medicina en la Historia*. V. Robinson. Buenos Aires, Ediciones del Tridente: 95-96.

Robinson, V. (1947). La Medicina en el Antiguo Egipto. *La Medicina en la Historia*. V. Robinson. Buenos Aires, Ediciones del Tridente: 19-32.

Robinson, V. (1947). La Medicina en la Edad Media. *La Medicina en la Historia*. V. Robinson. Buenos Aires, Ediciones del Tridente: 127-175.

Robinson, V. (1947). *La Medicina en la Historia*. Buenos Aires, Ediciones del Tridente.

Robinson, V. (1947). *La Medicina en la Historia*. Buenos Aires, Ediciones del Tridente.

Robinson, V. (1947). La Medicina Griega en Alejandría. *La Medicina en la Historia*. V. Robinson. Buenos Aires, Ediciones del Tridente: 34-80.

Schwartz, R. (1932). "The historical derivation of the physiological principles underlying the treatment of fractures." *J Bone Joint Surg Am* 14: 17-26.

Seara Valero, M. (1995). *Magia y Medicina*. Madrid, Ediciones Contrastes.

Senn, N. (1900). *Medico-Surgical Aspects of The Spanish American War*. Chicago, American Medical Association.

Shoemaker, W. (1971). "Cardiorespiratory patterns in complicated and uncomplicated septic shock." *Ann Surg.* 174: 119-125.

Siegel, R. (1960). "Epidemic and Infectious Diseases at the Time of Hippocrates: Their Relation to Modern Accounts." *Gesnerus* 17: 77-99.

Silvaticus, M. (1541). Pandectae medicinae. T. Paganum. Salerno: 14.

Singer, C., Singer D. (1917). "The scientific position of Girolamo Fracastoro." *Ann Med Hist*: 1-34.

Singer, C., Underwood, EA. (1962). *A Short History of Medicine*. New York, Clarendon Press.

Stiefel, M., Shaner, A., Schaefer, S. (2006). "The Edwin Smith papyrus: The birth of analytical thinking in medicine and otolaryngology." *The Laryngoscope* 116(2): 182-188.

Terrencio Varrón, M. (1992). *De las cosas del Campo. Traducido por Domingo Tirado Benedí*. México DF, Universidad Autonoma de México.

Thurston, A. (2000). "Of Blood, Inflamation And Gunshot Wounds: The history of the control of Sepsis." *Aust N Z J Surg* 70: 855-861.

Trzeciak, S., Rivers, EP. (2005). "Clinical manifestations of disordered microcirculatory perfusion in severe sepsis. ." *Critical Care* 9(suppl 4): S20-S26.

Van Arsdale, W. (1886). "Sepsis. On the present state of knowledge in bacterial science in its surgical relations." *Ann Surg.* 3(4): 321-333.

Walker, K. (1956). *Joseph Lister*. London, Hutchinson.

Wright, W. (1930). *Gerolamo Fracastoro: De contagione et Contagiosis Morbis Et Eorum Curatione*. New York, GP Putman's Sons - Library of New York Academy of Medicine.