5-1-1940

Gas gangrene : with special reference to treatment

Richard C. Cullen

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Gas Gangrene

with

Special Reference

To Treatment

by

Richard C. Cullen

Senior Thesis
Presented
to the
College of Medicine
University of Nebraska
Omaha
1940
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INTRODUCTION

To one acquainted with the literature on this formidable disease, the subject has a bewildering effect. Its astounding complicity of the literature is staggering, and from its birth, in its steady climb up the hill of time, it has been developing into one of civilization's most horrible afflictions. It is a disease which appears to be little understood by the average physician, and for that reason infrequently recognized except in later stages. The disease is so destructive in its steady progress and so grasping upon the claims of life that it is viewed with dread by the surgeon and as a dire calamity by the patient.

The increased speed of our civilized world and its numerous mechanical monsters with their ability to produce the most horrible types of wounds in the human body, have indirectly raised the disease of gas gangrene from almost obscurity to a pedestal alongside of our commoner diseases. In a recent Insurance Company Report they estimated that almost a half million people had been killed on highways of the United States in the past fifteen years. Industrial accidents and the ever increasing use of farm machinery add to the company of the maimed. Because of the ever increasing
The infection gas gangrene has been known as a definite disease entity since 1853, when maisonneuve at the meeting of the Academy of Sciences, reported two cases of gas gangrene and declared that there existed a certain variety of traumatic gangrene to which he gave the name "gangrene foudroyante". (85) Prior to this there were numerous cases of "gangrene with emphysema" reported, but no differentiation was made of this type from other forms of gangrene.

Gangrene, as a clinical entity, has been known as long as medicine has been practiced. Hippocrates makes mention of gangrene in his writings, and used the word "ramollissement" meaning "to soften" in describing the condition. (86) In describing a case which might well have been gas gangrene, he said, "Criton of Thaso commenced to experience pain in his foot; in his great toe -- he went to bed the same day. He had a slight chill, some nausea and then a little fever; he became delirious during the night. On the second day there was swelling of the entire foot over the whole ankle, which was a little red and tender; there were present tiny black blebs and he had a great fever. The sick one was completely out of his head. He died the second
day after the onset of the illness." (40)

Celsus, during the first century, undoubtedly had a stillbirth as a result of gas gangrene, for on extraction of a dead fetus he wrote, "It may so happen that the child may be distended with a humor from which there flows a fluid with a fetid odor." (40) He used the word "canorum" to describe gangrene. (85)

Liston, Heister and Pearson knew of the putrefaction of tissues and used the word "sphacelus" to indicate the condition. Richard Wiseman, personal surgeon to Charles II in the seventeenth century, thus describes a case of gangrene, "The lips sink and are flaccid, a gleet followeth, and the flesh within withers, also the pulse and the sense in the part do both languish." (85)

There is a wide gap in literature from the report of Celsus during which time no mention is made of any cases which might be classified as gas gangrene.

Quesnay, in 1745, in his writing "Gangrene of Putrid Dissolution of the Numerical Mass" spoke of, "the subcutaneous emphysema, the erysipelatous color of the skin, and the rapidity of death." He gives credit to Peyronnie for being the first to fully describe and furnish exact observations on this gangrene with emphysema. (40)

In 1771 De La Motte published reports on two cases which were no doubt cases of gas gangrene. Thomas Kirkland in 1786 may have recognized gas gangrene as
a distinct disease entity, as he describes a case as "gangrene of the emphysematous type." (40)

In Fabricus de Hildenh's works in 1746 the infection is mentioned and the first attempt to explain its etiology is found. "It is my belief," he says, "that the principle cause of this terrible ill is some venomous humor which nature has driven into these people." (40)

The infection was seen during the Napoleonic Wars early in the nineteenth century resulting from wounds, and, although the incidence is not available, it was undoubtedly rather high, and brought the disease to the fore in the minds of the medical world as evidenced by the increase in the literature on the subject during the early parts of the nineteenth century.

Valpeau reported on several cases during the Napoleonic Wars and was the first to recognize the disease as a complication of fractures. He also considered the emphysema as being of importance in the process of the gangrene. Larrey, during the Wars, knew and described the infection. In his articles he spoke of the rapid spread of the infection which in a few hours spread from the injured limb, and was often fatal in less than ten hours. Trifaud about the same time gave credit to Rendut and Charvean as the first to experiment with the disease and says that they were able to reproduce the
disease experimentally in animals. (40) Dupuytren wrote several lectures under the name of "spontaneous emphysema," and described a rapid decomposition of tissues occurring in trauma. (85) This was followed in 1836 by Martin de Bazas, who gives a case history of gangrene with emphysema in a patient with a crushed foot and in whom death occurred in twelve hours. Bazas became interested in the gas present in the tissues and was the first to analyze it. He noted its inflammability and demonstrated the presence of hydrogen sulphide as the most prominent component. (10) About the same time Malgaigne attempted to explain the cause of the gangrene with emphysema. "I think," he declared, "that there occurs under the influence of shock and stupor a special change which attacks life just as an excessive cold will kill the sperm in an egg and which will destroy the vitality of a blood clot without any appreciable changes in the appearance." (85)

At the meeting of the Academy of Sciences in 1849, Chassaignac described four cases which showed what he called "empoissoynement traumatique." He believed the condition due to some poison which was present far in excess of the mechanical injury preceding the disease. (85) At the meeting of the Academy in 1853, Maisoneuve made his report on gas gangrene, and considered it a
distinct disease entity. "In this disease of gangrene foudroyante," he says, "there is first a putrifying gas developed in the interior of the veins during life; and second, that this gas circulated in the blood and caused a fatal poison."(85)

During the Crimean war we have evidence that gas gangrene was a prominent complication of wounds. Calleron with the allied forces, reviewed sixty-five case histories in 1854, collecting material from study of casualties in the war. Pirogoff, with the Russian forces, described the disease, and evidently not having heard of Maisonnéeve's "gangrene foudroyante," called it "primary nephritic gangrene."(19)

May, in 1857, reported a case probably of gas gangrene, and was the first to discover air in the veins at autopsy. "This case," he says, "resembles one reported by Maisonnéeve in 1853, and called by him gangrene foudroyante."(82) In 1859 Erickson describes a case of a man who was dragged by a horse through dirt, receiving numerous lacerations of the thigh in which gangrene developed. He describes the limb as follows, "Limb is cold, being often greatly swollen and readily pitting, afterwards by much tension and edema of subcutaneous tissues, causing the part to assume a brawny hardness; there is sometimes crackling from the
generation of gas."(35)

Cadge in 1863, reported in detail on traumatic gangrene and divided gangrene resulting from trauma into two types, local and spreading. In distinguishing between the two he states that in simple or local gangrene the mortification is arrested at the point of injury, but in spreading gangrene the loss of vitality oversteps this boundary, extends rapidly up the limb and is invariably fatal. In local gangrene the injury itself is the principle cause for the death of tissue. In the spreading type he considers that the constitution of the patient is at fault and that the blood or blood vessels are probably so discorded and unhealthy that they predispose to the spread of the gangrene. He states that nineteen out of twenty cases of traumatic gangrene will remain localized. He also believed the gas present in the tissues was the product of decomposition in the dead parts.(16)

Greene, in 1864, described the finding of gas or air in the veins, and believed that this was the cause of death. (48) Bottini, in 1871, declared that the condition was of an infective nature, but no causative organisms were ever reported by him. (19) In 1873, Ashhurst reported on a case of spreading gangrene resulting from lacerations received by a lion. He agreed with Cadge's
theory and states, "The injured thigh was enormously swollen, emphysematous and crackling from the gaseous products of decomposition." (1)

It was a peculiar fact that all during the American Civil War there was not one case of gas gangrene reported in the literature. It was observed however, in the Franco-Prussian War, but had rather a small incidence.

At this stage in the history of gas gangrene the nomenclature for the condition consisted of numerous synonyms among which were, emphysematous gangrene, spreading gangrene, traumatic gangrene, gangrene foudroyante, primary nephritic gangrene, malignant edema, gangrene gazeuse and many others. Because of this complicity of names, the literature from this period on is very confusing, and it is difficult to determine whether many of the cases reported under these numerous names were actually cases of gas gangrene as we know it today. In 1882 Molier and Ponget, for the first time, used the present day term gaseous gangrene. (12)

Up to 1894 there were no cases on record where a patient had ever survived a proven case of gas gangrene. Mann, in this year, reported on a patient definitely diagnosed as emphysematous gangrene of the hand and arm who recovered, and without amputation. (81) It is questionable however, whether this was a case of gas
gangrene or malignant edema, because of the similarity between the two conditions. Halstead, in 1896, said, "The disease that is known as emphysematous gangrene or gangrene gazeuse resembles closely, and, as a matter of fact, cannot be clinically distinguished from malignant edema." (51) Nekins became interested in differentiating between the two infections and made a careful study of all cases resembling either disease reported between the years 1860 and 1892, fifty-two in all, and found that thirteen of the total were without doubt cases of malignant edema and not gas gangrene, and others of the series may not have been gas gangrene. (51)

The next two decades added little and only a few scattered cases were reported among which Fraenkel, in 1897, reported four unusual cases of the disease developing as a result of hypodermic injections. (44)

Camp, just prior to the World War in 1912, wrote an excellent treatise on gas gangrene infection in which he put forth the theory that malignant edema and gas gangrene were one and the same disease. He says, "No doubt time will prove that both conditions (malignant edema and gas gangrene) are the same, since many of the authentic examples of each are characterized by three cardinal features, namely, gangrene, emphysema or gas in the tissues, and a wild type of infection." (19) Thus
it appears that even up to 1912 the infection of gas gangrene was far from being a clear picture in the minds of medical men.

Then came the World War with its devastating toll of human life and gas gangrene made its appearance in its most horrible forms. The disease appeared early in the conflict and was a very unpleasant surprise to the surgeons. Prior to this time it had not been described as a usual complication of gunshot wounds so that case upon case appeared throughout the hospitals on all fronts. The huge mortality in soldiers from this disease in the early part of the War stimulated a great deal of research on the subject so that in the latter years of the struggle, the literature on the subject was voluminous. Between the years 1914-1919, more research was done on gas gangrene than was done during all the years previous or after the war, and it was during this period that the complete etiology and pathology was worked out. Drastic changes in treatment also evolved from the work, as will be discussed later in this paper.

With the finish of the war, interest in gas gangrene began to wane once again because of the scarcity of cases occurring in civil life. This is evidenced by the decline of literature written on the subject during the period
1920-1927. However, with the advent of our present day mechanized age, with its increased speed of automobiles, airplanes, motorcycles, etc., the increase of gas gangrene as complication of injuries received in accidents, again aroused interest and started further research on the subject. During the past decade, the incidence of the infection has gradually been on the increase, until at the present time the practitioner, who years ago probably would not have seen one case of the disease during his lifetime, may expect to be confronted with it at anytime today. The present day status of gas gangrene is well summarized in Malone's words, "From the great number of cases of gas gangrene which are being reported with increasing frequency, we must conclude that the possibility of its occurrence is always present, and there is little that we can do to lessen this possibility." (79)
ETIOLOGY

Long before Pasteur made his discovery of bacteria as the cause of infection, numerous men had attempted to explain the etiology of gas gangrene. In 1746, Hilden's theory that some venomous humor was driven into the body by nature, was the first attempt. Rendut and Charvean in the early part of the nineteenth century were able to produce gas gangrene in animals by inoculation from an active case, but no attempt to establish any definite cause of the disease was mentioned. (40) Malgaigne a little later, thought that with the shock of an injury some special change occurred in the body which attacks life, and he likens it to a freezing process. (85) Chassaignac, in 1849, thought that the infection was due to some poison in the body, and little did he probably realize at that time that his theory would be similar to the present day theory of the cause. (85) Maisonneuve thought that the gas first developed inside the circulatory system and eventually gave rise to a fatal poisoning. The finding of a large number of cases which at autopsy showed air in the veins correlated well with the theory of Maisonneuve, and such men as Greene and may agreed that the gas in the veins was the principle
factor in the disease.(82) (48)

With the advent of Pasteur's historic discovery of bacteria, the possibility of gas gangrene being caused by some organism was held forth. The first to consider this possibility was Bottini in 1871, who described the disease as being on an infectious basis.(19) Pasteur, in 1876, in his bacteriological studies of suspected cases of gas gangrene, isolated a small spore forming bacillus to which he gave the name Vibrion septique, and thus concluded that this bacillus was the etiological agent in gas gangrene. Five years later, in 1881, Koch and Gaffky studied the same organism in greater detail and gave it the name, bacillus edematis maligni.(125) Billroth, in 1882, still held to the theory that bacteria were not the causative factor, but considered the cause to be decomposition of the mortified elements occurring in the disease. These products apparently were able to diffuse so rapidly that he thought that they might be caused by the action of some ferment.(85)

Up to the last decade of the nineteenth century the general consensus was that Pasteur's Vibrion septique was probably the chief etiological agent in gas gangrene.

Welch and Nuttall, in 1892, reported a case of a
patient with a large sacculated aneurism of the arch of
the aorta which had eroded through the chest wall and
ruptured with resulting death. At autopsy the heart and
blood vessels everywhere were found to contain gas
bubbles in large amounts, and a generalized subcutaneous
emphysema was also present. From the blood of the
patient they cultured organisms which were non-motile,
encapsulated baccilli, and were present wherever gas was
found. To this organism they gave the name Bacillus
aerogenes capsulatus. This bacillus was studied in
detail with different media and animal experimentation,
and described by Welch as, "large, straight or slightly
curved, encapsulated, non-motile, obligatory anaerobic,
gram positive bacillus with square cut or slightly
rounded ends, which occurs singly, in pairs, clumps or
short chains." He was unable to demonstrate spore
formation. The question of whether the organisms were
present in the blood stream during life was studied by
means of animal experimentation. These experiments
showed that the bacillus is incapable of development
in the circulating blood during life, as might have
been predicted from the anaerobic character of the
organism. "However," Welch says, "if the bacilli
should find access to dead tissue, old fibrinous clots,
cavities such as the uterus or intestine, under these
conditions where the amount of free oxygen is reduced to a minimum, there they might grow; and if the places where they develop communicate with the circulatory channels, then the gas produced and with it the bacilli might enter the circulation." He also attributed death in these cases to the presence of gas in the vessels, but makes no mention of associating the Bacillus aerogenes capsulatus with the disease of gas gangrene. (126)

One year later, 1893, Fraenkel isolated the same organism and evidently not yet having heard of Welch's report, called the organism Bacillus phlegmonis emphysematose. In his later monograph, he reports results of examination of four cases of gaseous phlegmon in which the above organism was present in all cases. Fraenkel is considered to be the first to infer that this bacillus was the cause of gas gangrene, and Welch himself, in an article in 1896, gives him full credit for this association. (127)

In 1894, Professor Novy, a German, described a bacillus somewhat similar to Pasteur's Vibrion septique, and called it Bacillus edematis maligni No. 2 to differentiate it from the Bacillus edematis maligni No. 1 of Koch. He found this organism would produce a rapidly fatal form of septic emphysema. Its chief
difference from Koch's bacillus was its lack of spores. Undoubtedly, however, Novy was describing the same bacillus that Welch had reported previously.\(^\text{51}\)

Mann, in 1894, reported a case of emphysematous gangrene of the hand which had spread to the arm, and bacteriological studies from the gangrenous portions revealed the presence of two types of organisms. One was definitely identified as streptococcus pyogenes, while the other was a bacillus which was anaerobic. The colonies of the latter were round with irregular contours, with little projections from all around their edges giving them a bristly appearance. Microscopic examination revealed it to be identical with the \textit{welch bacillus}. By injecting rabbits with this bacillus, Mann showed that large doses could be given into the circulation without any severe symptoms following; but if the animals were killed shortly after inoculation, rapid and extensive emphysema would develop throughout the tissue. In no instance did the growth take place before the death of the rabbits, thus proving that the bacillus may be present in the blood stream and yet no emphysematous gangrene would develop unless there was destruction of tissue previously. The case of Mann proved that \textit{Bacillus aerogenes capsulatus} could grow in the living body and cause
great destruction locally and constitutionally. Mann was also the first to differentiate Vibrion septique as the cause of malignant edema, and states that the only way to distinguish between malignant edema and gas gangrene is by bacteriological study.\(^{(81)}\)

About this time several cases were reported by Ernst and Graham, and Steward and Baldwin, in which Bacillus aerogenes capsulatus was found in cases of abortion with a rapid post-mortem development of gas in the blood vessels.\(^{(81)}\)

Halstead, in 1896, did numerous bacteriological studies on a case of gas gangrene, and from the deep tissues of the gangrenous wound was able to culture an aerobic and facultative coccus, and an obligate anaerobic bacillus. This latter bacillus was not the same as the Welch bacillus, and was described as a bacillus about the thickness of anthracis, but shorter. It was non-motile with no spores, gram positive and did not form strings. It was different from the Bacillus aerogenes capsulatus in having no capsule, absence of peculiar odor from culture, and not increasing in number when introduced into blood vessels of animals. It was different from the Bacillus edematis maligni in that it was non-motile and gram positive and did not form spores. Inoculation of rabbits with this new
bacillus had no effects either subcutaneously or intravenously. However, after producing an injury to the tissues by thrusting a needle deep into the muscles of the thigh and then inoculating, a marked swelling and emphysema appeared on the following day. Halstead concluded that, "The disease recognized clinically as emphysematous gangrene may be due to infection with: 1. Bacillus edema mali, 2. Bacillus aerogenes capsulatus, 3. Bacillus coli commune, or 4. to two or more other forms of bacilli that as yet have not been isolated." (51)

In 1897 Veilon and Zuber described the Bacillus aerogenes capsulatus and called it Bacillus perfringens, and Migula, in 1900, suggested the bacillus welchii in honor of its discoverer. (30)

Weicklein, about this time, described the findings in three cases of gas phlegmon, and isolated a bacillus which he regarded as the bacillus of malignant edema, but which was subsequently shown to differ from that bacillus in several important particulars. (35)

Thus at the beginning of the twentieth century, such a large number of different organisms had been isolated and so many names had been given to identical organisms that the etiology was even more confusing than before any organisms had been discovered.
In 1900 Welch collected forty-six cases of proven gas gangrene in which the Welch bacillus was found in every case, and in thirty cases was found associated with other organisms, usually streptococcus or staphylococcus. He stated, "While it has been demonstrated that various bacteria may be concerned in producing gaseous affections, it is now evident that the bacillus which I discovered in 1891, and to which I gave the name bacillus aerogenes capsulatus, is the one whose causative agent is best established and most frequently in action." (128)

Up to the time of the World War the general attitude was that both Vibrion septique and the Welch bacillus were the chief etiological factors in gas gangrene, and although other organisms may be present, they played very little or no role in the pathologic process. The War brought forth a flood of bacteriological studies in an attempt to prove the definite causative agent, and thus possibly do something to reduce the heavy mortality accompanying the infection.

In the early part of the War many bacteria were found in wounds, but the blame could not be definitely fixed on any one organism, and in many cases there was mixed infection. Bacillus aerogenes capsulatus was found present in the greater number of cases. An interesting
and important observation made at this time was that the number of gas producing organisms gradually decreased as time went on, and as these decreased, there was a corresponding increase in the pus producing organisms in the wound. (106)

Weinberg and Sequin isolated a new anaerobic bacillus in 1915 and gave it the name Bacillus oedematiens, and in the latter part of the War discovered another anaerobe which they named Bacillus histolyticus. Numerous other anaerobic bacteria were reported during the War, among which were; Bacillus fallax, Bacillus haemolyticus, Bacillus egens, the Reading bacillus, and Bacillus bellonensis. In addition several aerobic bacteria were associated with the disease. In 1922, Sordelli added another anaerobe and called it Bacillus Sordelli. (43)

At the present time the recognized gas-forming group of organisms consists of about twenty-five anaerobic and from ten to fifteen aerobes. Of these, four are now considered to be the most usual organisms associated with gas gangrene; these are, Bacillus welchii, Vibrion septique, Bacillus oedematiens, and Bacillus histolyticus.

Dean, in bacteriological studies of eighteen cases during the War, found Bacillus edematis maligni present in fifteen and Bacillus welchii in only thirteen. (26)
Vincent found Bacillus welchii present in 82 percent of the gas gangrene cases in the wounded of the World War. Vibrio septique was present in about 10 per-cent and Bacillus cedematians in about 4-5 per-cent. He also found Bacillus histolyticus and Bacillus fallax rarely. (116) Joseph reported 121 cases of gas gangrene in which Bacillus perfringens was present in 82 per-cent, typical Vibrio septique in 28 per-cent, non-typical vibrio septique in 11 per-cent, and Bacillus bellonensis in 35 per-cent of the cases. (58) Millar, in 1932, collected 607 cases of gas gangrene from the literature, and in this large series the following organisms were found as shown: (85)

<table>
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<th>Organism</th>
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<tbody>
<tr>
<td>Bacillus welchii</td>
<td>231</td>
</tr>
<tr>
<td>Organism described as anaerobic</td>
<td>32</td>
</tr>
<tr>
<td>Bacillus welchii plus streptococcus</td>
<td>25</td>
</tr>
<tr>
<td>Bacillus malignant edema</td>
<td>13</td>
</tr>
<tr>
<td>B. welchii plus streptococcus and staphylococcus</td>
<td>6</td>
</tr>
<tr>
<td>Bacillus welchii plus cocci</td>
<td>3</td>
</tr>
<tr>
<td>Vibrio septique</td>
<td>1</td>
</tr>
<tr>
<td>Bacillus welchii plus miscellaneous bacteria</td>
<td>19</td>
</tr>
</tbody>
</table>

Meyer, in a recent discussion, says that practically all cases show evidence of Vibrio septique in the wounds, and that it is the chief causative organism. He believes that Bacillus welchii is often present.
in a minor role somewhat similar to the presence of the colon bacillus in typhoid fever. He was able to take cultures in which only Bacillus welchii were found in other laboratories, and demonstrate the presence of Vibrion septique in most of them. (83)

The question of whether any one of the four most frequently found organisms is capable of initiating the disease in pure culture was answered by Vincent who found if he injected separately into two guinea pigs, pure cultures of Bacillus welchii and Vibrion septique, he was not able to produce gas gangrene. However, if he injected a mixture of these organisms with Bacillus sporogenes (a non-pathogenic anaerobe) a typical gas gangrene developed. It is therefore evident that Bacillus welchii or vibrion septique may multiply alone in the muscles, but the association of them gives them an activity and toxicity of still greater magnitude. Vincent concluded that the maximum activity of the microbes of gas gangrene results from their combined activity. (116) Milch verifies Vincent's beliefs and defines gas gangrene as, "a clinical picture resulting from the symbiotic effects of anaerobic and aerobic organisms introduced into wounds." (84) Other men, including Parke and Williams, are of the opinion that in some cases of
gas gangrene, Bacillus welchii is met with in pure culture, and may be the sole etiological agent.

Bwolby, in 1914, inoculated a guinea pig with water, in which dirt from the trenches had been dissolved, and within eighteen hours it was dead of a gangrenous cellulitis. (11) Distaso, two years later, showed that anaerobic bacteria were present in large numbers in the intestinal tract, and concluded that most of the gas gangrene cases in wartime were due to the infection of human feces on the ground. (29) Simonds examined the uniforms of soldiers and found that all the uniforms worn by soldiers in the trenches contained spores of anaerobic bacteria, and more than 80 per-cent contained spores of Bacillus welchii. (104) Gage has proven that gas bacilli can and do occur in finished products made from wool and hair from animals. He demonstrated that wads of cotton in shot gun shells were capable of producing gas gangrene. (45) Zessler and Rassfeld found Bacillus welchii in 100 per-cent of two hundred soil samples examined. (18)

Since these early discoveries of the distribution of gas forming bacilli, further studies have revealed that Bacillus welchii can be cultured from normal samples of milk, water, shellfish, cheese, flour, wheat, barley, rice, oatmeal, air, canned sausages, lettuce, potatoes,
etc. It has also been cultured from the mouths of newborn infants, normal salivary glands, pancreas, normal urine, and the vagina, and one man even has isolated the organism from a surgical scalpel immediately before making an incision. In fact, it is difficult to find anything from which anaerobic bacteria cannot be cultured, and hence its spores are likely to persist indefinitely on anything that can be contaminated by dust or dirt and this means practically everything.\(^{(31)}\)

Dean, in 1914, theorized that the Bacillus welchii and Vibrion septique organisms apparently possessed powerful enzymes, one which was able to attack carbohydrates, and the other acting on the proteins. He found that when the bacteria were grown on a media containing a carbohydrate, so that the bacilli could form an acid, the growth was very rapid and vigorous. He said that these bacteria were essentially saprophytic and had little power to multiply in living tissues, but in dead tissue they were able to grow rapidly and produce poisonous substances which acted on the adjacent healthy tissue and destroyed it, thus producing more culture for the bacteria to multiply in.\(^{(26)}\)

Bull and Pritchett, in 1917, were of the opinion that it was not the bacteria themselves that caused the pathology of gas gangrene, but rather some poison
entering the circulation and which might arise from, 1, bacilli, 2, from the disorganizing tissue, or 3, it may be some acid which disturbs the mechanism of hydrogen ion concentration of the body fluids. By numerous animal experiments they found that Bacillus welchii yielded certain toxic products under certain conditions. This toxin, when injected intravenously, was found to have a hemolyzing effect on the blood, but when injected subcutaneously, a resulting local inflammation and necrosis occurred. They concluded that the cause of death in gas gangrene was due to the production of this toxin which may produce death by its local destructive process of tissue, or by its blood stream invasion and general intoxication. Henry, a few years later, demonstrated that a portion of the Bacillus welchii toxin contained properties which makes it capable of destroying the vitality of living muscle, and to which portion he designated as a myotoxin. In the last few years, Gleney and his associates in their detailed observation of Bacillus welchii toxin, discovered four distinct toxins produced by this organism, and to which they gave the names, alpha, beta, gamma, and delta toxins. Thus the gravidy of gas gangrene is dominated by the peculiar feature that the anaerobes which cause it are not pathogenic in themselves, and unless they are
in combination with their toxic metabolic products, or are allowed to form them, they are absolutely harmless.

Lately, the entire anaerobic group of bacteria have been grouped under the name Clostridium, which more than ever adds to the confusion of the nomenclature of organisms giving rise to gas gangrene. In order to attempt to enlighten the reader, the following grouping is put forth with corresponding synonyms for each organism, and a few present day characteristics of each group.

1. *Clostridium welchii*
   a. Bacillus welchii
   b. *Bacillus aerogenes* capsulatus
   c. *Bacillus* perfringens
   d. *Bacillus phlegmonis* emphysematosae

   This organism is the greatest producer of gas and is most often found isolated in gas gangrene. It may be found alone, but is usually associated with other organisms.

2. *Clostridium edematis maligni*
   a. *Vibrion septique*
   b. *Bacillus edematis maligni*
   c. *Bacillus* of Ghons and Sachs

   This is a rather rare, slender, motile, spore organism, which also produces a classic form of gas gangrene. It produces less gas, but causes more edema, and therefore predominates in edematous lesions. It
produces the disease malignant edema, and is often present in gas gangrene.

3. Clostridium Novyi
   a. Bacillus oedematiens
   b. Bacillus bellanosis
   c. Bacillus edematis maligni No. 2

This bacillus is polymorphic and may resemble other anaerobes. Its toxin produces a special white edema which more or less completely masks the gas infiltration.

4. Clostridium histolyticum
   a. Bacillus histolyticus

This organism is a common associate in gas gangrene and greatly resembles Vibrio septique. It is generally considered non-pathogenic and is of the proteolytic variety of organisms, being responsible for the odor so characteristic of gas gangrene. It appears to thrive only on destroyed muscle tissue. (52)
INCIDENCE

Before the world War and our present day mechanized civilization, gas gangrene was considered more as a medical curiosity, and the majority of men knew little or nothing about the infection. Because of the lack of knowledge before the twentieth century, it is a question whether all cases reported up to that time were actually cases of gas gangrene. Such Wars as the Napoleonic and Crimean Wars in the nineteenth century had cases reported, Balleron reporting sixty-five during the Crimean War. With each succeeding European War, the incidence has increased, due undoubtedly to the more powerful weapons developed and the resulting increase in wounds of the type prone to develop gas infection. Simonds attributes the higher incidence of gas infection in war to the penetrating nature of the injuries, as spores capable of causing the disease are probably no more abundant in the soil of battlefields than in the dust from the cities. (104)

Trifaud, in 1883, reported 123 cases of gas gangrene, but Welch, in 1900, was able to collect only forty-six proven cases of gas gangrene from the literature. (128) Five years later, Steward had collected a total of sixty-five cases, and Camp in 1912 had a total of 123 cases,
making a total of 187 proven cases of gas gangrene reported up to the beginning of the World War.(19)

The War brought many estimates as to the incidence of gas gangrene in wounds, varying from 1.5 to 3 per-cent of all wounds. In Evacuation Hospital No. 8, A.E.F., between September 10 and November 13, 1918, 4,741 wounded were admitted to the hospital. Of these, 206 required amputation, 96 or 46.6 per-cent being for gas gangrene.(106) Hanson calculated that out of 128,265 wounds of the soft parts received by U.S. soldiers during the conflict, 1,389 or 1.08 per-cent were complicated by gas gangrene, and of 25,272 wounds complicated by fractures, 1,329 or 6.26 per-cent developed gas gangrene.(52) Vincent in his statistics, states that from March, 1916 to the end of the War, there were 1751 cases of gas gangrene.(116) In the English troops the incidence of gas gangrene occurring in wounds was about 11 per-cent in the early part of the war, but with earlier and better care this was reduced to 1 per-cent in 1918.(125)

During civil life the disease has gradually increased in incidence since 1920. Weintrob reported eighty-five cases out of 618,105 patients entering Bellevue hospital from 1911 to 1926.(128) Millar collected 607 cases from literature, not including those reported subsequent to
lister's era and trifaud's 123 cases. His report likewise included only gas gangrene of the extremities.(33) In 1931, Hanson collected 5,449 cases from literature including all cases of gas gangrene ever reported, both during civil and military life.(32) The rapid increase in the incidence of the disease is shown by Nelson, who had 349 personal cases in the six year period 1930-1936, only about one-fourth the total number reported in U. S. soldiers for the entire World War.(31) Some idea of the prevalence of the disease during the last decade may be gathered by the number of personal cases of the following men: Kenning, 75 cases; Rhinehart, 30 cases; Stone, 67 cases in eleven years; Chormley, 35 cases in five years; Barthen, 34 cases in four years; Bates, 32 cases in six years; Caldwell, 19 cases in two years; Veal, 54 cases in seven years;oller, 36 cases in eight years. The impression that gas gangrene is infrequent in general civil practice is far from being a fact today, as shown by the above evidence.

The incidence of gas gangrene in regard to the type of the original wound, was studied by Simonds. In 175 cases collected from literature, he found the original wound to be, compound fractures in 61 cases, lacerated wounds in 20, operation wounds in 11, gunshot wounds in 10, and hypodermic needle punctures in 9. The disease
and very little gas gangrene is reported in the South. Physicians have reported a number of cases of gas gangrene following hypodermics given when patients were lying between woolen blankets. The fact that all uniforms worn during wartime are of woolen material, may be a factor in its high incidence in wars. (30)

The age incidence of gas gangrene seems to reach a peak during the most active period of life, generally from twenty to thirty years of age. Millar, in his 607 cases, showed a gradual increase in incidence from birth up to twenty to thirty years, and then a gradual decline up to eighty years. No cases were found in this series over eighty years of age. (85)

Vincent states that the frequency of gas gangrene cases during the War was greater during the summer season, while Dixon above, has observed a marked drop in cases in the South during the summer months. The statistics of Millar show very little variations during the seasons of the year, his largest number of cases occurring in the month of March and the smallest number during August. The difference in number however, was not large enough to classify gas gangrene as a seasonal disease.

The sex incidence of this disease shows a marked predominance of males over females. Though the cases during Wars have been a large factor in this predominance,
Millar had 395 male cases and only 69 females in his cases occurring only during civil life. Undoubtedly the activity of the male as compared to the female is the factor involved in the higher incidence.

Veal has made an interesting observation as to racial incidence. Although negro patients furnished less than one-half of the admissions to Charity hospital in New Orleans, sixty per-cent of the cases of gas gangrene during the past seven years occurred in the negro race. Since there are no other records of the racial incidence of gas gangrene in the literature, any special susceptibility of certain races to the disease has not yet been proven.

The curve of the incidence of gas gangrene has made rather a sharp upturn the past few years, and with the whirl of modern life getting faster and faster, the incidence will undoubtedly continue increasing even more in the future.
SYMPTOMATOLOGY

and

DIAGNOSIS

The symptoms of gas gangrene, while not always reflecting a definite classical descriptive picture, are enough alike in all cases that a diagnosis is not a difficult problem, provided one is on the alert. History, symptoms, and laboratory findings are the chief factors in making a diagnosis.

Emrys-Roberts, after studying a large number of cases, recognized three main clinical types of gas gangrene according to symptoms and the course of the infection. These they named, common type, fulminating type, and the delayed type. (33)

The common type is most seen, and is that type where the wounded has been lying out 12-24 hours before being seen. This is the type that usually develops a few hours after the first debridement of a wound has been done. These patients when first seen look ill even though they may have only a trivial wound. They are flushed, with a raised temperature and rapid pulse. The wound itself looks dirty and exhibits a curious characteristic unpleasant pungent smell. A few hours later, as the absorption of the toxins increase, the flushed skin is replaced by a pallor. Finally a pale
lemon color of the skin appears, and the sclera become icteric. The patient now looks profoundly ill. His tongue is dry and foul, the pulse running and soon imperceptible, and the respirations are rapid and shallow. Vomiting is usually a distressing feature -- in the last stages becoming black from gastric petechial hemorrhages. Mentally, these patients are perfectly clear although mild delirium may occur. If such cases are untreated, the infection runs its course and death occurs in 12-24 hours after the time of wounding.

The fulminating type is characterized by a rapid sequence of events. In these cases the gas gangrene infection may be well developed only a few hours after being wounded. Before the patient has recovered from the initial shock and the effects of the primary hemorrhage, the infection of gas gangrene becomes well established. It is this symptom complex of shock, hemorrhage, and exhaustion, associated with anaerobic infection, that combines to produce these fulminating cases. These patients appear cold, pale, restless and are generally vomiting. The extremities are cyanosed, pulse is imperceptible, and the systolic blood pressure is around 50. Locally, the wound presents the characteristic smell and signs of dead muscle. In these cases extensive gas formation may occur after a
very short space of time. Death occurs in from 12-24 hours or less after the wound.

In the delayed type of gas gangrene, the resisting powers of the patient, both local and general, have overcome the infection up to a point, and the latent infection is at first limited to the surface of the wound. About two or three days after cleaning up the wound, constitutional symptoms develop, showing that the latent period has come to an end, and the process of infection has begun to spread inwards. A typical picture of the common type then develops. This process may come on even several weeks after the original wound. (33)

Wallace, for the purpose of clinical description, also divides gas gangrene into three groups, and bases his division on the amount of tissue involved by the infection. He names the groups, group gangrene, massive or segmental gangrene, and fulminating gangrene. Group gangrene is the condition when only one group of muscles is involved, while the massive or segmental type results from the shutting off of the blood supply from a segment of a limb, so that a whole segment or even a whole extremity may be involved. Fulminating type is practically identical with the fulminating type described above by Emrys-Roberts. In this latter type, amputation will not stop the process, even though it is made above the apparent infection and through healthy
The early appearance of the wound may be simply that of bruised and torn muscle. Very often, however, the appearance is peculiar and the extruded muscle shows a dry, deep purple, or blackened surface, which at first sight suggests dry fecal material. Later on the wound becomes moister and there is a thin foul discharge mixed with bubbles of gas and droplets of fat. Still later the discharge becomes copious and bright yellow. The amount of odor present varies, but is described as putrid or mousy, and sometimes is extremely penetrating and overpowering.

There are three zones of the infection characteristically present according to Kenning. The first zone, or primary focus, consists of a tearing wound with ragged necrotic edges and having a foul exudate which contains gas, bacilli and spores. Foreign bodies may or may not be present in the wound. The second zone is adjacent and presents an area of hemolytic edema in the subcutaneous tissues and contains gas bacilli. The third zone is formed by the remote areas having a toxic yellow edematous fluid with small bubbles of gas and showing discolored areas over the skin surface. Characteristic crepitation can be elicited from this zone.
Color changes in the skin of a limb containing a gas infection are rather typical and may be of some benefit in making a diagnosis. The first essential change in color is that due to the swelling of the part. The skin looks tense and is paler than normal due to the blood being squeezed out of the capillaries by the pressure. This simple pallor is next replaced by a dirty cream tint which is definite evidence that gas gangrene is present. The subsequent changes in the skin are quicker and more dramatic. Areas of purple staining appear which enlarge and coalesce. The margins of these discolorations are irregular but fairly distinct, and the skin between them is a grayish white appearance. Soon there appear blebs filled with fluid which is stained by altered blood. In the final stage the purple is succeeded by a dark yellow-green tint which is due to bacterial action. (118)

In order to be able to establish beneficial treatment in cases of gas gangrene, a diagnosis must be made within the first 24 hours, so it behooves every physician to be alert for the earlier signs of infection and not wait until the disease is so far advanced that a lay person could make the diagnosis.

Tenopyr call attention to two suggestive symptoms that appear early -- first, pain which is disproportion-
was twice as frequent in lacerated wounds as gunshot wounds, and six times more frequent in compound fractures than gunshot wounds. This refutes any impressions gained from war reports that gas gangrene was peculiarly incidental to gunshot wounds.\(^{(2)}\)

Guthrie is of the opinion that the infection is endemic to certain soils, especially those richly fertilized. The correctness of this belief is well born out by the prevalence of gas bacillus infection on certain war fronts, and its rarity or absence on others. Army reports show that the infection was not common on the Russian front where mobile warfare in the lake and forest countries was fought; it was comparatively rare on the Italian front where mountain warfare was fought, but it was exceedingly common in the trench warfare in France and Belgium where soil was rich from years of extensive fertilization.\(^{(49)}\) The absence of any gas gangrene in the American Civil War may be explained by the fact that there was little fertilization in the comparatively new country.\(^{(123)}\)

Dixon has pointed out that gas bacillus infection does not occur in the South during the summer, and furthermore, that injuries followed by gas gangrene always occurred through woolen clothing. In summer, woolen materials are not used for clothing or bed clothes,
ate to the amount of injury, and second, the acuteness of intellect displayed by the patient. (112)

Earlier diagnosis may be facilitated by the use of the laboratory, including blood counts, bacterial culture of the wound, and x-ray of the soft tissues. Because of the hemolysis produced by the bacterial toxins, anemia is a prominent and characteristic feature of gas gangrene, and red blood cell counts of from one to three million may occur. Eliot states that anemia is by far the most common associated symptom of this disease. (32)

Cultures taken from the wound and proving positive for the presence of anaerobic bacteria are almost a diagnostic finding and practically clinches a diagnosis. An easy cultural method for Bacillus welchii was established during the War by Wallace; the so-called "stormy fermentation". In this procedure, tubes of litmus milk, recently boiled to drive off the residual oxygen, are inoculated with swabs from the wound and excised tissue, and incubated at 37 degrees centigrade. Within seventeen hours, a reaction occurs in the litmus milk typical of Bacillus welchii -- an acid clot, torn by gas. Smears from this contain Bacillus welchii. (120) Boland offers the following method for getting a fast culture of anaerobic bacteria. Swabs from the wound
are placed in 10 cc. of fresh meat extract bouillon made faintly alkaline and containing 1 per-cent dextrose. A layer of sterile liquid petroleum is poured on top, one cc. in thickness, thus insuring anaerobic conditions. This is incubated at 37.5 degrees centigrade and noticed at 6, 8, 12, 16, and 24 hour intervals. The appearance of gas bubbles after six hours indicates a specific gas former. Gas sufficient to penetrate the oil layer is almost positive indication of gas bacillus. It seems to the author, however, that a great deal of valuable time may be lost in waiting for a culture to become positive, and although it may clinch a diagnosis, I do not think should ever be the sole criteria in diagnosing a case of gas gangrene. 

During the war Davis introduced X-ray as a reliable aid in the diagnosis of gas gangrene. Plates of the involved limbs reveal the presence of even minute quantities of gas in the soft tissues, and with the development of better roentgen procedures since that time, it has become a valuable diagnostic aid. Rhinehart has run a series of gas gangrene cases, half
of which were diagnosed clinically and the rest by X-ray examination. Of 30 cases, 19 were diagnosed clinically, the shortest time of diagnosis being 12 hours after injury and the longest time 75 hours, or an average of 50½ hours after injury that diagnosis was made clinically. 11 of the 30 cases were diagnosed by X-ray, the shortest time being 2½ hours and the longest, 72 hours after injury, or an average of 18.2 hours after injury. It is evident from the above results that X-ray is valuable in making an earlier and accurate diagnosis of gas gangrene. Most men at the present time recommend X-ray of all suspected cases of gas gangrene. Gas shadows are usually present in six to twelve hours after the original injury. Examination should be repeated every few hours to determine whether these shadows have increased or decreased. An increase in gas shadows indicates the presence of gas infection while a decrease in shadows indicate that they were due to the presence of air introduced at the time of injury.

Lastly, the history is of profound importance in making a diagnosis of gas gangrene. Open, crushing wounds, lacerations, injuries resulting from explosive violence and compound fractures occurring in such a manner that earth and materials, especially woolen cloth, have contaminated them, must inspire a fear of anaerobic
infection. Especially is this true if there are signs of injury to the blood supply of the wounded area. With any such history, and symptoms which have been related, plus the finding of gas in the soft tissues by X-ray, a diagnosis of gas gangrene should be a comparatively simple problem.
Pathogenesis

The pathogenesis of gas gangrene consists largely of numerous theories put forth by different men, and as to which ones are most correct there is still somewhat of a question, although some have been fairly well substantiated.

Fraenkel believed that symptoms were due to absorption of decomposition products from the affected tissues. Metchnikoff, Korentschewsky, and others thought the bacteria had an endotoxin, and it was the absorption of this that caused gas gangrene. (125) Dean believed the pathological process due to the action of enzymes which were produced by the bacteria. (26)

Taylor, from his extensive studies on the pathology of gas gangrene, held forth a mechanical theory. He believed the pathological process results from the pressure of the gas produced by the action of Bacillus welchii on the carbohydrates of the muscle. This gas becomes confined to the muscle sheaths, and with its increase in pressure brings about an ischemia by the compression of blood vessels, and a resulting necrosis. He classifies the pathology of the disease into five phases:
Phase 1 -- Dormant stage. In this stage the infection is localized in the wound. Gas bubbles may be present, and smears and cultures show the presence of the Bacillus welchii.

Phase 2 -- Stage of Acute Gaseous Distension. This stage is the result of obstruction to the escape of the gas which has been generated in the wound. This obstruction appears to be the factor determining the development of a malignant from a comparatively innocent form. Death of the affected muscle occurs in this stage from anemia produced by the pressure of gas and from the exotoxin of the bacillus. Taylor has been able to demonstrate by means of a manometer attached directly to a muscle, that a pressure as high as 23 pounds or 1.5 atmospheres is built up in the muscles by the gas. Permanent thrombosis of vessels may occur in this stage and are the result of vascular obstruction.

Phase 3 -- Explosive stage. This phase is characterized by the rapid extension of the swelling associated with subcutaneous crepitus, and probably the result of rupture of the muscle sheath and the escape of gas contained within it into the surrounding loose and usually edematous subcutaneous tissue.

Phase 4 -- Stage of Systemic Intoxication. This is probably due to the absorption of the toxic by products
of the disintegrating muscle tissue which was killed during phases 2 and 3. Taylor demonstrated by experiments that the exotoxin produced by the Bacillus welchii did not have the power of splitting sugars and producing gas, and concluded that a toxin from the dead muscle, which he called tissue toxin, was responsible for the systemic intoxication.(109) The gas produced has little or no importance as a toxic.(110)

Phase 5 -- Stage of Septicemia. The terminal invasion of the blood by the bacilli, when it happens, is probably a very late phenomenon occurring approximately at the time of death.(107) Thus Taylor concludes that the mechanical action of the pressure of the gas produced is usually the most important part of the infection, and any toxin produced by the bacillus plays only a minor role.(119)

Conradi and Bealing divide the process into two stages. The first is the formation of lactic, butyric, propionic and succinic acids from the muscle carbohydrates and these bring about the edema and necrosis. The second stage is the saprophytic stage during which the spore forming organisms gain a foothold and bring about putrefaction.(125) Later work has proven that Bacillus welchii and Bacillus fallax metabolize the sugar and fat of the muscle into butyric acid and give to the process
the sour odor and the brick red color of muscle. The proteolytic bacteria are mainly Bacillus sporogenes and Bacillus histolyticus. The latter is only able to grow in muscle which has been previously destroyed by the saccharolytic bacteria, and its chief function is the breaking down of proteins for the subsequent action of Bacillus sporogenes. This latter group of organisms acting on the mass of destroyed tissue is responsible for the characteristic odor of gas gangrene.\(^{(12)}\) The odor results from the production of sulphide gas by the organism. Fieldman is of the belief that Bacillus welchii, Vibrion septique, Bacillus oedematiens, and Bacillus sporogenes all are capable of breaking down either carbohydrates or proteins with the production of hydrogen and carbon dioxide.\(^{(42)}\)

d'Este Emery thinks that the toxin produced has a specific affinity for the leukocytes, thus destroying the natural protection of the body. To have a sufficient supply of these it is necessary that the circulation be intact. The toxin when present in large amounts inhibits immigration and kills the leukocytes. If there is no free escape of the toxin it accumulates to such an extent that it soaks through into the healthy tissue beyond and kills the defense leukocytes present at the edges, thus allowing the gangrene to
spread. (119) This observation seems to explain better the failure of nature to arrest the disease, but offers no explanation of how the living tissues are killed.

Sir Almroth Wright believed that the essential factor is an acidosis, both local and general, the former being more pronounced. Two chemical factors are present, he states. First the blood is made less alkaline by the action of the microbes. Secondly, the antitryptic power of the blood is minimized by the disorganization of the white corpuscles. Since the organisms of gas gangrene grow best in acid media and are destroyed by the leukocytes, these two factors, namely — the process of blood digestion producing an acidosis, and the voiding of trypsin by the decomposition of the white corpuscles, form a vicious cycle whereby the bacillus is enormously assisted in growth. (131) Wright's theory has been borne out by the finding of an acid imbalance in a great many cases of gas gangrene.

Mull and Pritchett say that bacillus welchii infection is not an acid intoxication, but an intoxication with definite and very potent toxins produced by the growth of the bacilli in the tissues of the body. With their animal experiments they definitely proved the presence of a hemolysin causing blood destruction, and another portion which acted locally and which they said
was the initial factor in producing edema and necrosis. (14) This theory has been discussed previously under etiology. The theory that the portion of Bacillus welchii toxin other than the hemotoxin was a specific myotoxin was advanced by Henry. He did experiments to show that when a piece of fresh viable muscle was subjected to the action of this toxin, it swells up and becomes opaque after several hours. Microscopic appearance of these swollen bits of muscle resembled very closely the histologic picture described in studies of human gas gangrene. The experiment showed that the toxicity of Bacillus welchii, under certain conditions, is reduced by muscle tissue while the hemolytic portion is unaffected either in amount or toxicity. Certain cases of gas gangrene which seem to be progressing favorably, and then suddenly die from heart failure may be explained as due to this myotoxin coming in direct contact with the heart muscle. (54)

Recent experiments by Callender indicate that Bacillus welchii toxin is capable of lowering the oxidation concentration of the tissues which in turn favors anaerobic growth, and he is of the opinion that this lowered oxidation in the tissues is the principle factor in the producing of the disease.

Bashford thought that the toxin produced in gas gangrene acts upon the endothelium of vessels, giving
rise to thrombi with the resulting decrease in circulation. He is of the opinion that this is the initial process, and that the destruction of capillaries, veins, and lymphatics by this toxin is the outstanding feature of the rapid spread of infection. (3)

In the past few years, Glenny and his associates have been able to isolate four toxins produced by Clostridium welchii. Alpha toxin is probably the portion described as a myotoxin by Henry. Beta toxin is a necrotic, non-hemolytic toxin causing purple reactions in guinea pigs after intracutaneous injections and probably identical with the necrotic producing toxin of Mull and Pritchett. Gamma toxin, whose action has yet not been determined. Delta toxin is the hemolysin, and the same as the one found by Mull and Pritchett. (47)

Recent experiments have shown that the presence of calcium salts is an important factor in enabling the bacilli to gain a footing. Particles of wood, cloth, paper and other foreign materials, after being soaked in a suspension of Bacillus welchii, were injected beneath the skin of mice with no results. However, when the same materials under the same conditions were injected with $2\frac{3}{4}$ mg. doses of calcium chloride, a typical gas gangrene developed in every animal. Calcium nitrate and calcium acetate when used had the same
effect. Bullock and Cramer, who did this work, thought there was evidently some local change produced by the calcium which lessened the defense mechanism of the tissues and allowed the bacteria to act. This may explain the fact that gas gangrene develops in so many fracture cases with their loss of calcium around the fracture site. Calcium is also present in soil with which wounds are frequently contaminated. (15)

Clinical observation has clearly shown that a defective blood supply is the principal cause of the organisms gaining a footing in the body when they have once been introduced into wounds. Such causes of defective blood supply to a part in this infection are: 1) death of tissues from violence or injury, 2) inefficient splinting leading to injury of vessels or tissue, 3) constriction of limb by tourniquets, bandages, etc., 4) damming back of discharge by packing introduced into the wound or by dressings in which discharges have been allowed to dry and cake, 5) hemorrhage, cold and shock which produce low blood pressure are also potent factors. (57) Grens feels that the circumferential swelling in the extremities acts as a tourniquet to produce defective circulation. (95)

The role played by aerobic bacteria in the pathogenesis of gas gangrene has been somewhat of a
disputed question. In the Base Hospital No. 15, A.E.F., it was found that the activity of the gas bacillus was self-limited and practically confined to the first week of the disease, with a drop in anaerobes from 38 to 7 per cent during the first seven days, and an accumulation at the same time of the common pyogenes in the wound. Fatal cases were prone to show a high incidence of aerobic bacteria. Anaerobic infections showed a high death rate, but a short period of danger to life. It was found that most of the cases dying after the first week, were due to a streptococcus septicemia and should not have been attributed to anaerobic bacteria. There has been very little evidence in the literature that aerobic organisms play any role in the pathogenesis of gas gangrene other than that of secondary invaders, although Finesilver thinks that they directly aid the process of infection by utilizing the available oxygen in the tissues and also by diminishing the patient's resistance. Manheims also thinks that the virulent hemolytic pyogenes are capable of enough proteolytic action and tissue destruction to simulate the clinical picture of gas gangrene.

Taylor has reported two interesting cases of so-called metastatic gas gangrene, in which secondary
infection occurred in another portion of the body other than the original site. The secondary sites were both in gluteal muscles upon which the patients had been sitting. At death cultures from the blood were sterile. He is of the opinion that there is a temporary invasion of the blood stream by the bacilli, and that the vitality of a muscle mass may be lowered enough by continuous subjection to pressure and interfere with its circulation enough, that it may become a site for activity of these bacilli during their temporary blood invasion. (108)

Milch, in rather an unusual theory, says that anaerobic bacteria are always present in human tissue. He killed 216 hogs and 77 per-cent showed bacteria latent in their muscles, 37 per-cent being anaerobic. Human tissues also, he thinks, have their normal bacterial content and under special circumstances, such as impaired circulation, presumably sterile tissues may become the "locus minoris resistentiae" in which organisms normally present in the body may localize. (84) Thus, cases of gas gangrene occurring in amputation stumps where the amputation was done high above the line of demarcation and through healthy muscle tissue, may be explained on this "latent bacteria" basis. (84)

Rather numerous cases of gas gangrene developing following therapeutic injections have been reported,
Junghans reporting 60 and Marney collecting a total of 86 cases from literature. (91) (53) The cause here is undoubtedly due to the introduction of anaerobic bacteria either from the skin or the needle. Since there is very little tissue destruction, Tenopyr thinks that the local pressure caused by the injected solution produces a local ischemia and thus favoring the growth and action of the bacteria. (113) Mullaby in his case of gas gangrene resulting at sites of injection, was able to get a positive blood culture and concluded that the organisms were in the blood stream and the slight trauma of the injections offered suitable foci for these circulating organisms to come to rest and develop. (89)

Gross Pathology

Gas gangrene is definitely a muscle disease and McNee states that he has never seen the infection start where there was no injury of muscle present, and no examples of gas gangrene beginning and remaining in the subcutaneous tissues has yet been met with. (90) Accordingly, the study of the gross and microscopical pathology of the infection involves mainly the pathology of the muscle tissue.

Depending upon whether the blood supply to the part involved is intact or not, the pathology is somewhat
to the touch and next to it lies the normal contractile muscle. (59)

In massive gangrene, the gross pathological changes are essentially the same as already described for group gangrene with circulatory injury, except that more muscle tissue is involved, and even an entire limb may show the pathological changes.

Microscopic Pathology

The microscopic detail of this infection was studied by McNee and Dunn in 1917, and their work is still used as the classical picture of the microscopic pathology. They took sections of muscle beyond the spreading margin of the infection, through the margin itself, and finally through the gangrenous muscle itself. A transverse section of the muscle taken beyond the spreading margin of the gangrene showed essentially normal muscle tissue with no histological changes. On transverse section through the involved portion of the muscle, the fibers were found not to be shrunken as one would think, but often were found to be swollen. In spite of this the fibers are all separated off completely from the interstitial tissue, leaving a clear space between, while the interstitial tissue forms a regular network between them. The staining reaction of the fibrils are quite
different. When the blood supply is interrupted, segmental or massive type of gangrene results and all muscles of a segment in the limb distal to the arterial occlusion die and become infected. If the blood supply remains intact or an artery to a single group of muscles is occluded, group gangrene results, and the infection is limited to a single muscle group.

Grossly, group gangrene shows the presence of a dead single or group of muscles, while next to these dead muscles lie normal muscles. The disease, so to speak, is a longitudinal one tending to spread in the longitudinal axis of muscles, so that single muscles are involved from end to end while neighboring ones are untouched. The first change noticed in the muscle is its change from a normal red purple to an opaque, brick red color and a loss of contractability. This stage of the process is given the name "red death" by Wallace.(118) About this time, the gas being generated in the muscle becomes obvious to the eye as bubbles, which can be pressed up and down between the fibers. The substance of the muscle now becomes more friable and the color changes from the brick red to a yellow color, and in the end becomes a greenish brown and finally black. The connective tissue lying in immediate contact with the diseased muscles may be little altered. At other times it may
be filled with white, yellow, or blood-stained edema. Gas may or may not be present in the areolar tissue, and when it is present tends to follow along the perforating arteries, and it is this gas in the subcutaneous tissue that gives rise to the crepitation so distinctive in this disease. It is also this gas passing along the spaces occupied by the cellular tissues inclosing the vessels and nerves that gives rise to the sensation of painful tension which is one of the first subjective symptoms.\(^{(116)}\)

At the spreading margins of the infected muscle a rather definite change is seen. The margin is sometimes fairly sharp, but in other instances is irregular, due to the fact that the process has spread further in some of the individual fibers than others. The muscle fibers at the margin are paler and duller and have somewhat the appearance of a bloodless muscle. At the advancing edge, the muscle is firmer to touch and this firmness is continued back into the gangrenous portion of the muscle.\(^{(90)}\)

In muscle which still has an intact blood supply, the infection is limited to the portion of the muscle involved by the wound. The surface of the wound is dry or dirty looking, or in some cases black. Next to this is a red area, which is limited toward the sound tissue by a yellow sinuous line. This line is raised and hard
different, being an almost uniform eosin tint, while the dots which represent individual fibers are not present. This uniform pink appearance of the fibers is due to disintegration and coagulation with a resulting gelatinous mass staining uniformly throughout. The sarcolemmal nuclei of the separated fibers stain brightly throughout, but finally in the last stages disappear. McNee found that the spaces between the muscle fibers and the interstitial tissue were actually filled with fluid. He concluded that this fluid was a toxic material and spread along between the interstitial tissue and the fibers, killing the latter as it spread, and paving the way for the entrance of bacteria and their subsequent production of gas by their action on the dead muscle fiber. (90)

Early, the bacteria are seen only in the interstitial tissue, but as the muscle fibers disintegrate they are seen in the fiber itself. Transverse sections also revealed that bacteria were present in the interstitial tissue of the normal muscles beyond the spreading margin of the gangrene.

Longitudinal sections of muscle fibers through the area revealed little more than the transverse section. The normal fiber is seen to change very suddenly at a definite point from its normal stain to the uniform
staining. This point is the margin of the gangrenous area. A definite loss of the striations typical of normal muscles is also evident in the longitudinal sections. (90)

Emrys-Roberts traces the lytic changes in individual muscles through the following stages during the process of the disease: -- Blurring and eventual loss of cross striations; exaggeration of longitudinal striae; swelling of the fiber, changes in staining properties, and the formation of fluid-containing perifibrillar spaces in which are suspended the toxins and bacteria; fragmentation of the fiber with marked lysis; and finally phagocytosis by the leukocytes at and near the wound surface. (33)
TREATMENT

The evolution of the treatment of gas gangrene has been a gradual trend from radical procedures to more conservative measures at the present time. One fact remains true to the present day however, and that is, all untreated cases of proven gas gangrene are invariably fatal. It is evident from this that the loss of life from this disease is dependent wholly upon treatment, and since proper treatment instituted early in the process will properly control it, every physician should have a clear knowledge of the latest therapeutic measures, even though his knowledge of the pathology and etiology may be somewhat lacking.

Up to the latter part of the nineteenth century there was only one form of treatment for gas gangrene, and that was, amputate the moment morbid appearances present themselves. Wadse in 1863 recommended waiting for the cessation of the gangrene and supporting the patient until a line of demarcation formed, and then amputating either close above this line or through the granulations.(16)

Up to 1894 there was no case of gas gangrene that had survived the disease. Kraenkel in this year, knowing that the bacillus causing the disease could not live in
the presence of oxygen, suggested that the parts be freely incised so as to admit access of air to the diseased tissue and at the same time put some oxidizing agent such as hydrogen peroxide in the wound.(44) Mann, using this more conservative method, reported the first case of proven gas gangrene to live. He treated an infection of the arm and hand by wide long incisions and kept the hand in hot corrosive sublimate 1-1000 every twenty minutes.(81)

In 1912 Camp collected a series of 187 cases of which the gross mortality was 48 per-cent. In this group, 50 cases were treated by amputations with 18 deaths or a mortality of 30 per-cent. Thirty of the cases were treated conservatively with only 3 deaths resulting, and these all from complications other than the gas gangrene. He advocated conservative treatment be tried first, and if unsuccessful, then amputate.(19)

Debridement

Experience during the war has established beyond question that all grossly infected contused wounds should have an early and thorough debridement, with care to remove all foreign material and devitalized tissue. This prophylactic procedure will prevent many dirty wounds from becoming the seat of a gas infection. If
the wound is seen early, debridement consists of resection of the entire area of devitalized tissue to insure a healthful base and a good blood supply. Dead muscle should be removed to a point where healthy muscle is present as evidenced by bleeding, contractility, and color. Tenopyr gives the following method for cleaning up a dirty contaminated wound and with which he has had good results. "Place sterile olive oil into the wound and sterile compresses saturated with olive oil over the wound; then the skin is thoroughly cleansed with tincture of green soap followed by alcohol, ether and benzene; and then the skin is painted with tincture of iodine. The wound is then cleaned thoroughly with benzene, washing out all the olive oil. Debridement is then done."(112) Rhodes recommends scrubbing all dirty wounds with soap for fifteen to twenty minutes until every pocket of the wound and especially the torn, loose, reflected periosteum and medullary cavities of the bones are thoroughly cleansed. He then flushes the entire wound with ether followed by debridement and another ether flush.(99) In the history of the treatment of gas gangrene numerous antiseptics have been used in the cleansing of the wounds. Iodine, iodoform, Labarraque's solution, silver nitrate, hypochloride of soda, soap, flavine, rivanol, dichloramine, ether, alcohol, and
formol are only a few. (84) It is a question just how much good these antiseptics accomplish, because those strong enough to destroy the bacteria also cause death of tissue thus predisposing to spread of infection, while those that are non-injurious to tissue are not bacteriacidal.

Most men recommend leaving the wound wide open after debridement. Pieces of gauze may be laid in the wound, but no packing or bandages should be applied because of hindrance of the blood supply. Menopyr thinks that if all the infected tissue is thought removed, the wound can be closed, watching the next few days for signs of gas infection, and if it does appear, all sutures should be removed and the wound laid wide open again. (112) Guthrie emphasizes delayed closure for all dirty wounds of at least one week, and if the wound is already badly infected, wait eighteen days before closure, being guided by bacterial counts and cultures for streptococcus, and by the condition of the patient. (49)

Irrigation

Irrigation is the next important consideration. The accepted policy during the War and up to the present day has been to insert Carrol Dakin tubes into the debrided area beneath the skin and between muscle planes,
and instill with some germicidal or oxidizing solution. The most universally used solution has been Dakin's solution. The mechanical cleansing as well as the proteolytic character of this disinfectant seems to sterilize the entire wound without any deleterious effect on the tissues. Pilcher, during the War, had very poor success with Dakin's solution in that it had no effect on deeply infiltrated tissues nor did it decrease the amount of edema and gas in the tissues. Accordingly, he looked for a solution that would relieve the tension in the tissues and also act as a bactericidal agent, and finally developed quino-formol solution which contained quinine, hydrochloric acid, glacial acetic acid, sodium chloride, formol, thymol and alcohol. The solution was hypertonic to relieve the edema, and the acetic acid and quinine gave it analgesic properties. It was also highly bactericidal and quite unirritating to the tissues. Pilcher took 100 cases of gas gangrene which had been receiving Dakin's solution for ten days with no effect, and used quino-formol. The edema and gas disappeared remarkably soon and not one case needed amputation. Since this solution had no proteolytic properties, he recommends the use of Dakin's solution to remove the debris after the quino-formol has checked the infection. Although Pilcher had excellent results
with his solution, for some reason it has not been taken up generally so that other reports as to its efficiency are not available.

Knight is very much opposed to the use of Dakin's solution and says that he knows of no better culture medium for anaerobes than Dakin's solution. He recommends the use of 1 per-cent solution of acetic acid as it is not irritating to the skin and is far superior to Dakin's solution. (69)

Fraenkel, in 1894, first suggested the use of oxidizing agents to oxygenate the tissues and render them unsuitable for growth of anaerobic bacteria. Since that time many have been tried, hydrogen peroxide being the most widely used. The results with these agents have been somewhat disappointing, and their value in acting to check the infection is questionable. Delbert showed experimentally that the gas bacillus grew better on muscle tissue previously treated with hydrogen peroxide than on muscle not treated. (84) Maes says the use of oxidizing agents is absurd because oxygen stays in the tissues only a few minutes, while spores live for years. Patients, he says, get well in spite of the use of oxidizing agents, not because of the use. He advises the use of permanganate of potash, not because of its oxidizing power, but for its antiseptic value. (30)
In spite of the above men's opinions, most textbooks recommend the use of some oxidizing agent, and some men are of the opinion that they are beneficial. Warnshuis has had good results by using a continuous drip of permanganate solution 1:1000 into the wound and also infiltration of the crepitant portions of the leg with the solution, thus encircling the extremity with a block of permanganate.(122) Other solutions recommended for irrigation include, formalin 1-2 per-cent(97), hexylresorcinol(95), hypertonic saline solution(131), magnesium chloride 1-2 per-cent(84), and quinine hydrochloride 1 per-cent.(110)

In order to determine the relative merits between Dakin's solution and hydrogen peroxide, Millar ran a series of cases using hydrogen peroxide in 47 cases and Dakin's solution in 37 cases. The mortality in the cases receiving hydrogen peroxide was 29.3 per-cent and in the cases receiving Dakin's solution, 33.3 per-cent. Thus the difference in their values is evidently not enough to recommend one over the other.(85)

Despite the arguments over which is the better solution for irrigation, the fact remains that irrigation is an important part of the treatment of gas gangrene, and should always be instituted regardless of what solution is used.
Serotherapy

Serotherapy, which before the World War was unknown, has now developed into such importance that we consider it to be one of the most important factors in the control and treatment of gas gangrene.

Bull and Pritchett in their experiments on Bacillus welchii toxin, found that these toxic products exhibited antigenic activities and readily gave rise to the formation of active antitoxic substances. They prepared the first antitoxin against Bacillus welchii which, when injected into guinea pigs conferred a definite passive immunity which persisted for two weeks. When used therapeutically in guinea pigs already inoculated with Bacillus welchii, the infection was regularly arrested. In 1918 Bull first tested the use of his antitoxin in the British troops with rather disappointing results. In some cases a marked improvement was noticed, but the results were far from uniform and the experiment was not considered as a success. From the time of the above experiment to the end of the War, other sera were introduced. Weinberg developed sera against the three main organisms of gas gangrene, namely, Bacillus welchii, Vibrion septique, and Bacillus oedematians. He recommended that the three sera should be injected immediately in the wound and the neighboring tissues, and then, after
a bacteriological examination, continue giving the sera of the most prominent organism found in the wound.

Leclainche and Vallee, of the French Army, developed a polyvalent serum against the same three organisms that Weinberg had made his individual sera against. Sacquepee treated 190 cases of proven gas gangrene with this polyvalent serum and recorded a mortality of 13 per-cent as compared to a mortality of 75 per-cent in a control series of non-treated cases.(28)

Ivens tested the preventive use of both Weinberg's and Leclainche's serum in a large series of cases during the war. 222 cases were given 10 cc. each of anti-perfringens, anti-Vibrion septique, and anti oedematiens serum of Weinberg. Where the antitoxin was given at or before the first operation, there was no deaths from gas gangrene. In 14 of the cases the serum was given at the same time that amputation was done and of these, 12 recovered.

154 cases were each given 30 cc. of the polyvalent serum. Out of the 154, 19 cases were fatal, but only 6 were due directly to the gas gangrene. In 57 cases, both Weinberg's and the polyvalent serum were given prophylactically together, and only one case of gas gangrene developed in the 57 cases. Ivens concluded that Weinberg's serum was of real value in preventing gas gangrene, and when used in curative measures it was a disintoxicating agent.
of great value if used in sufficient quantities. He stated that the polyvalent serum seemed to have a marked influence on the after-history of the cases with coincident streptococcus infection, but did not appear to be of value in the preventive or curative treatment of gas gangrene. (56)

Vincent, knowing that the maximum activity of the microbes of gas gangrene results from their combined action, theorized that in order to get a serum with the maximum preventive and curative effect, it was necessary to immunize the horses which produce the serum with a mixture of the causative organisms. A serum obtained by mixing together serum of horses immunized separately against the organism will not give a maximum action, but when a mixture of the organisms are injected into one horse, their association gives them considerable increase in virulence, and it turn the serum would be more active. Following this theory, Vincent developed a polyvalent serum in which he used twenty strains of organisms. The serum was put into use in 1918 both as a prophylactic and a therapeutic measure. 20 cc. doses were given as a preventive to a large number of wounded soldiers with the amazing results that not one case of gas gangrene developed among the wounded who had received the serum. When used as a therapeutic measure
in cases with gas gangrene already developed, Vincent reported a mortality of only 14.81 per-cent and many of these died from other causes. (116)

Thus at the end of the War the place of serum in the treatment of gas gangrene was very indefinite. Reports of different men conflicted so much as to its value, and so many statistics were obtained without controls, that one could not definitely recommend serum in the usual treatment of gas gangrene.

Because of the small number of cases occurring in civil life after the War, the interest in this form of therapy waned. In fact the only serum manufactured for several years was Weinberg's anti-perfringens serum, and this was only available in a few of the larger cities.

Millar has reported favorable results from the use of perfringens antitoxin by using 10 cc. as a prophylactic dose and 200 cc. as a curative dose. (87) Tenopyr reports 24 cases treated with perfringens antitoxin with a 29 per-cent mortality and only 7 cases needed amputation. He recommends giving the patient 200 cc. of the antitoxin immediately upon diagnosis and repeat this dose in 6-24 hours. "Usually after 400 cc., he says, "there is a drop in temperature, decreased pulse and the gangrenous process stops and the patient feels much better." (112) Clifton reports a case of gas
gangrene spreading from the arm to the shoulder where large amounts of perfringens antitoxin were given. Amputation was necessary, but Clifton gives credit to the serum for saving the patient's life. (22) Kenning advised use of perfringen antitoxin to be given every four hours in 100 unit doses and giving six to ten doses depending on the severity of the infection. He recommended giving it intravenously instead of intra muscular. (66) Coller has had rather disappointing results with the perfringens antitoxin. In his series of 36 cases treated with the serum, he had the astounding mortality of 58.3 per-cent. (23)

The unit of perfringens antitoxin, according to the requirements of the National Institute of Health, represents that amount of antitoxin which protects a 350 gram pigeon against one test dose of toxin for a period of 24 hours. (67)

Kling, in an unusual experiment, used normal horse serum in treating four cases of gas gangrene with a noticeable improvement, especially in the toxic symptoms. On experimenting with pigeons he found that Bacillus welchii toxin was not neutralized by normal horse serum, but it did have the ability to detoxicate, probably through some unspecific action on the toxin. He recommended the use of normal horse serum only when
antitoxin was not available. (68)

It was not until 1932 that a polyvalent serum similar to Vincent's appeared on the market. The prophylactic serum, as we now have it, is in combination with tetanus antitoxin. This contains 1500 units of tetanus antitoxin, 1000 units of perfringens antitoxin and 10 units of Vibrion septique antitoxin. Lederle's polyvalent serum is the therapeutic serum and contains 10,000 units of perfringens antitoxin, 10,000 units of Vibrion septique antitoxin, 200 units of Bacillus oedematiens antitoxin, 200 units of Bacillus Sordelli, and 25 units of Bacillus histolyticus antitoxin.

Finesilver recommended giving the prophylactic dose subcutaneously if given within twelve hours of injury, and intramuscularly if longer than twelve hours. In extensive, very contaminated wounds he recommends giving two doses. For therapeutic treatment, one to four vials of the therapeutic dose should be given intravenously, depending upon the extent of the involved area, length of time the injury has existed, and the apparent degree of intoxication. The desirable aim is to overcome the toxemia with the first dose. Supplementary injections should then be given every six to ten hours as warranted by symptoms. (43)

Telford and Malone have had rather poor results
with the prophylactic use of this serum and concluded that the prophylactic dose as marketed was lacking in sufficient gas bacillus antitoxin to prevent subsequent infections. They recommended that the therapeutic dose as marketed be used as a prophylactic dose.\(^{(111)}\)\(^{(78)}\) Callender recommends giving a full therapeutic dose prophylactically and when gas gangrene seems likely to occur, a second dose of therapeutic serum should be given.\(^{(18)}\) Carothers had best results by giving huge therapeutic doses of 40,000 to 60,000 units a day both intramuscularly and intravenously.\(^{(20)}\) Craig gives 40,000 units as a prophylactic dose and has given from 120,000 to 250,000 units to a single person therapeutically.\(^{(24)}\)

Since the introduction of the polyvalent serum, reports of its use have been very encouraging and the mortality on an average has been around 15 per-cent, which is a considerable drop from the 45-50 per-cent mortality during the World War. Halloran states, "Improvement following polyvalent serum administration is as remarkable as that seen following the use of diphtheria antitoxin.\(^{(50)}\) The following results of different men give some idea of the value of the serum. Stone in a series of 58 cases, gave adequate serum treatment to 39, and of these, 6 died or a mortality of

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15.3 per-cent. (105) Ghormley at the Mayo Clinic reported 33 cases with a resulting mortality of 13.4 per-cent in those that received serum. Those that did not receive antitoxin had a mortality of 44.5 per-cent. (46) Warthen had 34 cases in a four year period. 9 of these received no antitoxin and were treated only with surgery. One died, giving a mortality of 11 per-cent. 15 cases were treated with serum, and only one died with a mortality of only 6.6 per-cent. (123) Eliason, in collecting 222 cases of gas gangrene, found that in the cases where serum was used the mortality was 17 per-cent, while in those with no serum, a 31 per-cent mortality occurred. (31) Bates ran a series of 32 cases in which 16 were treated only by surgical means, and the other 16 received serum plus identical surgery. In the first group receiving only surgery, the mortality was 50 per-cent, while in those given serum in addition to the surgery, the mortality was 16 per-cent. (4) Veal had good results both when used as a prophylactic and as a therapeutic. 27 cases received no prophylactic serum with a resulting mortality of 48.1 per-cent. 27 cases received prophylactic antitoxin and the mortality was only 7.4 per-cent. When used therapeutically in 49 cases he had a mortality of 20.4 per-cent against 80 per-cent for those receiving no therapeutic serum. (115)
Mitchell reports a mortality of 21 per-cent in his patients receiving serum, and 68 per-cent mortality in those not receiving serum. (88) Holland presents an interesting case of gas gangrene in which no radical surgery except cleansing of the wound was done. No oxidizing agents used nor were there any wide open incisions made to admit air. The main dependence was placed on the antitoxin, and in this case must be given full credit for recovery. (55)

From the above results, we can conclude that the use of polyvalent serum has gained a recognized foothold, and has definitely been of benefit in lowering the mortality rate of gas gangrene.

A few men recommend injection of the serum locally into the wound. Larson injects 50 cc. daily superficially and deep around the wound in the normal tissue so as not to mechanically distribute the organisms into healthy tissue. (70) Searls does not advise local use of serum because it is apt to endanger or further injure muscle and cut down resistance. (102) One man recommends injection of the serum into an artery supplying the wounded area, and Lilienthal has had good results by packing wounds with gauze soaked in serum, especially in cases of gas gangrene of the chest wall. (72)

Serotherapy today forms one of our main lines of
defense against gas gangrene. It should not be depended upon entirely to stop the infection, but should be used as an adjunct to minor surgery and not replace it. Debridement and irrigation still play an important part in the treatment and they should not be sacrificed by the thought that serum is a cure-all. The present day view toward serotherapy is summed up in Bosworth's following words: "Amputation is senseless and harmful, and all reports to date will bear this out. We have an agency which will destroy the infection where it lies, --namely, serum. Debridement or removal of masses of muscle should be avoided. Intramuscular planes should be opened in areas of greatest infection if possible, but unnecessary destructive surgery should not be done. Muscle which appears to be dead, if let alone, will frequently be found viable at a later date."(10)

X-ray Therapy

In 1928, Kelly, knowing that roentgen treatment of many localized infectious processes due to other types of organisms had been beneficial, treated a case of gas gangrene with small doses of x-ray with almost miraculous results. In his article published in 1933, he presented 9 cases of definitely proven gas gangrene with positive cultures which had received x-ray treatment.
Six cases received both serum and X-ray with the result of 100 per-cent recovery. Two cases received serum with no X-ray and both died. The other patient received serum alone and lived. In these cases, three minimal doses of X-ray were given twice the first day, twice the second day, once the third day, and once on the fourth day. All tissues suspected of involvement were irradiated. (61)

With the marvelous results obtained from these preliminary cases, Faust became interested in this type of therapy and in 1934 presented five cases of gas gangrene which he had treated with X-ray, and all recovered. In this series all cases received both serum and X-ray, but the serum used in all cases was specific for only bacillus welchii and Vibrion septique, and two cases showed positive cultures for clostridium tertium. Since the serum was not positive for this organism, Faust concluded that the X-ray may have been entirely responsible for the cures. In one case reported by Faust a little later, the patient received only one prophylactic dose of serum, and X-ray was the only therapy used. The patient made a full recovery. (38)

In 1936 Kelly had treated 40 cases of gas gangrene with X-ray. All cases also received serum. Out of the 40 cases, 5 died, or a mortality of 17 per-cent.
However, Kelly points out that at least three of these deaths were from other causes than gas gangrene, one being due to a slipped ligature, one to a pulmonary embolism after amputation, and one from diabetic complications. Excluding these cases, the mortality was only 10 per-cent. Of all the cases that recovered there was no amputations while all five of those that died had received amputations. At this time Kelly concluded that X-ray treatment was definitely indicated in gas gangrene, and that treatment should be started as soon as the disease is suspected and be given throughout its course, twice each day for at least three days. (62)

By this time other men had become interested in X-ray as a therapeutic measure in gas gangrene. Davis treated four cases with X-ray along with the usual surgery and serum, and two of the four died. Of the two that died, one was a diabetic and the other was seventy years old. Despite his results, he believed that X-ray has a distinct place in the treatment of gas gangrene. (25) Eyerly tried X-ray in a case where the gangrene had spread from the thigh up the trunk to the nipple line, and although the patient died, the local and general condition were markedly improved after X-ray treatments. (36) Warner, in desperation,
tried X-ray on an obviously fatal case of gas gangrene in an amputation stump which had spread to the groin, and the effect was dramatic with an immediate drop in temperature and no further extension of the gas. The patient made a full recovery. (121) Charbonnet reported twenty cases of gas gangrene treated with X-ray and the usual surgical and serum therapy with a mortality of 10 per-cent. He also treated eight definitely contaminated wounds prophylactically with X-ray with no occurrence of gas gangrene in any. (21)

In 1938 Kelly presented 87 new cases of gas gangrene treated with X-ray which he had acquired from questionnaires sent over the country. This brought his total number of cases receiving X-ray treatment to 105 and with the amazing low mortality for the group of 5.7 per-cent. 18 of these cases received no serotherapy either prophylactically or therapeutically, and only one died giving a mortality of 5.5 per-cent. From this it does not seem that serum was essential to recovery, and that the X-ray was the sole factor involved in the cures.

Animal experimentation to determine the value of X-ray has been rather disappointing. Kelly attempted to experiment on guinea pigs, but they were too small an animal, and when real active strains of gas bacilli were used, the infection travelled so rapidly that it

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was soon necessary to treat most of the pig. (63) Erb, using pure washed strains of Bacillus welchii toxin on pigeons, could not find any evidence of the beneficial effects of X-ray treatment when used as either a prophylactic or therapeutic measure. (34)

Explanations as to how the X-ray acts to stop the gas infection have been attempted. Kelly thought that the X-rays might cause some chemical changes in the tissues which would render them unsatisfactory hosts to the anaerobic bacteria. He also thought that possibly the X-ray destroyed the bacteria themselves or that the bacteria do not tolerate a wave length such as that of the roentgen ray. (61) Work on the subject at Stanford University has lead them to believe that the X-rays play upon the nutrient fluids and produce small quantities of hydrogen peroxide, and that the presence of this is fatal to anaerobic organisms. Due to the absorption of the hydrogen peroxide, the X-ray treatments need to be frequent to produce more of the oxidizing agent. Another theory claims that the X-ray causes the tissue to throw out a protein which may be resistant to the toxin of the organisms. (37) At the present time none of these theories have been definitely proven to be correct, and all the above processes are purely theoretical.
The question of whether X-ray will prevent the proper repair of tissue in these cases, has arisen numerous times. So far Kelly has had no complications arise to indicate that the amount of X-ray used was in any way detrimental to the normal process of healing. However, precautions should be taken not to overdose the area. (64)

The technic of the X-ray treatment as put forth by Faust consists of using 88 kilovolts peak gap, 5 milliamperes, 40 cm. distant from target to skin with 0.5 mm. aluminum as a filter for 3 minutes over each area. This single treatment gives 45 roentgen units. (37) Kelly recommends 100 roentgen units per treatment and if treatment is needed longer than three days over the same area, 50 roentgen units is sufficient. (63) Two treatments are generally given the first and second days and one treatment on the third and fourth days, irradiating all involved areas or any suspected of involvement.

The present day opinion of most authors is to include X-ray as a definite part of the treatment of gas gangrene. Kelly recommends X-ray to be used as a prophylactic measure as well as therapeutic measure, as he has proved conclusively that the earlier treatment was started, the more easily the case was controlled.
and the sooner it subsided. With the use of X-ray, the treatment of gas gangrene has become even less radical than that used with serum. X-ray should not supplant the other forms of treatment, but when used with them undoubtedly reduces the mortality rate to a very low figure. Less radical methods, combined with adequate dosage of polyvalent antitoxin, and the therapeutic X-ray, will cure the usual case of gas gangrene with little sacrifice of tissue. The therapeutic value of X-ray in gas gangrene is summed up in Charbonnet's words, "When one witnesses the spectacular effect of the therapeutic X-ray in gas bacillus infections, he will realize that its value has not been overestimated."(21)

Sulfanilamide

The disease of gas gangrene has not been omitted from the massive list of ills that sulfanilamide has been used on. Since its discovery only a few years ago, sulfanilamide and other related compounds have been used in several reported cases of gas gangrene. Although some results are promising, the drug is still in its infancy as far as the treatment of gas gangrene is concerned, and as yet, it has not been used in a large enough number of cases to warrant attempting to evaluate
its place in the treatment of gas gangrene.

Bohlman was the first to use sulfanilamide in cases of gas gangrene. Three cases which had received both minor surgery and antitoxin previously, were started on sulfanilamide therapy. In the first case the temperature dropped to normal and all toxic symptoms disappeared eighteen hours after the first dose of sulfanilamide, while in the other two cases toxic symptoms disappeared on the fourth and seventh days respectively, and all three cases recovered.(7)

Scott reported a single case of gas gangrene treated with sulfanilamide with recovery about one year after Bohlman's report.(100) Fuller presented two cases treated with both prontosil and sulfanilamide in which temperature and pulse dropped to normal within twelve hours after the dye therapy was started, and both recovered.(60) Lacey treated one case with sulfanilamide, both prophylactically and therapeutically with recovery, but did not consider the sulfanilamide to have any prophylactic or therapeutic value as large doses of polyvalent serum were also given the patient. (76) Sewell, during the past year has treated three gas infections with sulfanilamide with one death in a seventy year old diabetic. All three cases also received X-ray, and there was no response directly
attributable to the sulfanilamide. (103)

Kendrick has run a series of experiments on guinea pigs to determine the therapeutic value of sulfanilamide, neo-prontosil and sulfopyridine. He injected the guinea pigs with Bacillus welchii and then gave one series sulfanilamide, one series neo-prontosil and one series sulfopyridine. The results obtained from the three drugs were similar in that none of them provided protection against the infection. The mortality of the pigs treated with the drugs was 89.5 per-cent, while the mortality in a control series of untreated pigs was 94.3 per-cent. He also made a comparison between the relative values of perfringens antitoxin and sulfanilamide in treatment of infected guinea pigs. In those treated with the antitoxin, not one died, while the mortality in the pigs treated with sulfanilamide was 75 per-cent. He concluded that none of the three drugs had any therapeutic value against Bacillus welchii infection. (65) Long, however, with his experiments on mice had more promising results. In mice inoculated with Bacillus welchii and treated with sulfanilamide the mortality was 28 per-cent while in the untreated mice the mortality was 93 per-cent. He says that there is evidence that treatment with sulfanilamide is effective in controlling Bacillus welchii infection. (75)
From his studies, Long is of the opinion that the action of sulfanilamide is directly upon the organisms, and that it reduces their capacity to multiply, thus giving the phagocytes a chance to destroy them. (74) Owens, Kellum, Lawrence Long and others are of the opinion that sulfanilamide acts chiefly on the symbiotic streptococci present in the infection. With destruction of the streptococci, the gas bacilli are more amenable to treatment. (92) (60) (73) If this latter theory is true, sulfanilamide should be a valuable adjunct to treatment in preventing the fatal streptococcus septicemia which is the cause of death after the first week of the disease.

Thus far there has been no indication as to what blood level is necessary for effectiveness. Bohlman determined the blood level of sulfanilamide in one of his three patients and found 8.4 mg. per 100 cc. present on the fourth day of treatment. (7) The dosage, as recommended by Bohlman, should be about 60 grains the first and second days, 40 grains for the next five days, and then 30-40 grains for two additional days depending upon symptoms. (7)

One disadvantage in sulfanilamide therapy in gas gangrene is the time which it takes to establish an effective concentration of the drug in the blood stream.
The disease is so rapidly fatal sometimes that any delay in establishing adequate treatment can easily be disastrous. (103)

While the use of sulfanilamide cannot at this time be recommended in the treatment of gas gangrene, results thus far have been somewhat favorable and in the near future it may play a more important role in the treatment of the infection.

Symptomatic Therapy

Symptomatic treatment is of great importance in cases of gas gangrene. It is the problem of the physician to keep the general resistance of the patient built up all during the course of the disease. He should be kept comfortable and quiet. A nourishing soft diet should be prescribed, and fluids should be given in adequate amounts. If a condition of acidosis is present as occurs rather commonly, doses of sodium bicarbonate should be given either orally, rectally or intravenously. In cases where the anemia has developed to a marked degree blood transfusions are often life-saving procedures, and should be done promptly.

Miscellaneous
There have been many miscellaneous types of treatment introduced by different men throughout the past years, but none have proven successful enough to include it as a regular part of the treatment of gas gangrene.

Fiddian-Greene treated two patients with gas gangrene of the thigh and buttocks by inserting Carrel-Dakin tubes into the wounds and running a continuous flow of pure oxygen from a cylinder into the tubes so that the entire area was subjected to a continuous stream of oxygen. Both patients recovered. (41)

Walker, in England, treated a case with glycerin and ichthyol compresses over the area and with 2 cc. injections of Omnalin, a compound vaccine prepared from non-pathogenic bacteria and containing bile lipids and neutral fats. A slough of the skin around the wound occurred with ulcer formation, but the infection ceased spreading. The patient recovered. (117)

Boothby, in his work on oxygen concentrations at the Mayo Clinic, has discovered that inhalation of between 60-100 per-cent oxygen in air had a definite bactericidal effect on anaerobic organisms present in wounds. This high oxygen concentration of the blood will also remove all the nitrogen gas present in the tissue, thus reducing local pressure on capillaries and therefore relieving the local anoxemia. (9)
Vaccination

In the past few years Penfold and Tolhurst have been working on a toxoid of Bacillus welchii toxin with which they hope to be able to actively immunize man against gas gangrene. They have succeeded in producing an alum precipitated formol-toxoid which when injected into guinea pigs in two doses one month apart, will produce an immunity against subcutaneous inoculations of Bacillus welchii. (93) In the past two years they have tried this formol-toxoid on human beings. They tested the patients immunity by measuring the units of antitoxin present in the blood before and after injection of the toxoid. Their results were fairly promising in that the antitoxin level in the blood was raised in every case after two or three injections of the formol-toxoid, and in one case this level remained at a high level for six months. They conclude at the present time that they have a suitable material for immunizing man against gas gangrene due to Bacillus welchii infection, although as yet they have not determined what level of antitoxin in the blood is fully protective. (94) These experiments bear watching, because if a material does become available which will actively immunize man against gas infections, its importance would be tremendous, and its use in Wars would be a godsend.
Thus we see how the trend of the treatment of gas gangrene has gradually been from the most radical form to the now comparatively conservative treatment.

Whereas fifty years ago, amputation was the only treatment known, today amputation is looked upon by many as a harmful procedure, and is only done as a last resort in those cases which have progressed to such a degree that other therapy has no effect. A set of rules for the present day treatment of gas gangrene infections includes the following: cleansing of the wound, mild debridement, irrigation, adequate serotherapy, X-ray therapy, symptomatic treatment, and possibly the use of sulfanilamide. With the course of treatment veering to the conservative side there has been a corresponding decrease in mortality from around 50 per-cent during the war to 5-10 per-cent at the present time. In the future, with the addition of new treatments and possibly vaccination, the mortality from this devastating disease may be lowered even more.
PROGNOSIS

The prognosis in cases of gas gangrene today is quite different than those occurring twenty five or thirty years ago. From the period during the nineteenth century when the prognosis in these cases was practically nil, we have improved our technic of treatment to such a point that at the present day we can say that practically all of the average cases of gas gangrene can be cured with early and adequate treatment.

Prognosis in this disease is dependent upon several factors. First of all, the condition of the patient at the time he develops the disease is of prime importance. Debilitated persons or those having a chronic disease such as tuberculosis or diabetes, have a low resistance before the infection sets in, and have little reserve with which to combat the added load, and thus prognosis is not so favorable.

The type of organisms present in the wound is a factor. Cases in which aerobic pyogenic organisms are found in symbiotic relationship with the anaerobes have a decidedly worse prognosis than those with only anaerobic organisms, both because of the fact that they tend to hasten the process, and also because of the danger of a fatal septicemia developing. The presence of foreign
material in the wound gives a rather poor outlook as compared with the cleaner cut wounds.

The period of time after receiving the wound to the time when treatment is instituted is probably the greatest factor in prognosis. Wounds seen within ten hours and treatment started within this time have a good prognosis while wounds not seen until twenty-four hours or more after the injury have a correspondingly poorer prognosis.

The part of the body involved and the degree of involvement makes quite a difference in mortality rates. Infections of the extremities are prone to have a brighter prognosis than those of the trunk or organs because of the fact that amputation can always be resorted to in the former if adequate treatment fails to stop the spreading process. (130)

In conclusion we can say that with our present day methods of treatment including serum and x-ray, cases of gas gangrene when diagnosed early before the area involved is very extensive, have a good prognosis when the treatment is carried out adequately and correctly.
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