Gas gangrene

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GAS GANGRENE

BY

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INTRODUCTION
The subject of gas gangrene has emerged from a position of comparative obscurity to one of great prominence as a result of the unprecedented number of cases that occurred during the World War. The alarming prevalence of this sort of infection along the battle fronts in France and Belgium was the occasion for intensive study. It was soon realized that gas gangrene was not a form of cellulitis affecting subcutaneous and connective tissue spaces, but an exceedingly toxic and infectious form of gangrene, produced by the pathogenic gas-producing bacilli occurring characteristically in grossly contaminated wounds, and being characterized by certain objective and subjective findings.

Even today, in civil practice, gas gangrene is probably the most dreaded of all complications occurring in compound fractures or severe injuries of the extremities although it does occur as a complication in other conditions. No one condition so taxes the judgement of the modern surgeon as does the successful management of this condition.

In review of the literature bearing on this condition, one finds it is a long one as is the case of most diseases, being made up of a vast number of irrelevant papers, many case reports and a few path-forming papers. That there is no completely satisfactory treatment for this condition is at once evident by the fact that so many different methods have been set forth. Many more articles and authors could have been quoted but it would have been mainly just a repetition of the information contained in this review. Because of the ever-changing ideas and viewpoints of the present methods dealing with this condition, which is quite hard for the average medical man to keep up with, I have attempted
to cover and assimulate the literature in such a manner so as to give the most widely accepted conception of this condition and the present day treatment.

In this review, I have attempted to deal mainly with the most common form, namely that occurring in the extremity.
HISTORY
Gas gangrene assumed great importance during the World War because of its great frequency. However it is a disease which has been known for many years in both civil and military practice.

Hippocrates, writing of a case of gangrene, though it is not clear that it was of the emphysematous variety, said, "Criton of Thosea 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 and 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. There were frequent evacuations of bilious matter. He died the second day after the onset of the illness---"Celsus is thought by some to have known of the occurrence of gas gangrene in pregnancy, for in his chapter on the extraction of the dead fetus we find, "It may so happen that the child may be distended with a humor, from which there flows a fluid with a foetid odor." (54)

Following these early writings there is a long period which the disease seems not to have been recognized. Avicenna, Guy de Chauliac, J. de Vigo, and Ambrose Pare' do not refer to it. But in Fabricus de Helden's works (Opera Omnia-Frankfort, 1746) we find mention of gas gangrene. "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." (54)

Queanay, in 1745, in a chapter on "Gangrene of putrid dissolution of the humeral mass," gave Peyronnie the credit of being the first to describe and furnish exact observations on gas gangrene, and
spoke of "The subcutaneous emphysema, the erysipelatous color of the skin, and the rapidity of death.--" We find that De la Molte, in 1771, published two observations which have been accepted by some as possible cases of gangrene. In 1786, Thomas Kirkland knew and called it gangrene of the emphysematous type. (54)

Early in the nineteenth Century, Larrey, during the Napoleonic wars, seemed to have known this infection. In some of his observations he spoke of the rapid progress of traumatic gangrene which in a few hours spread from the injured limb and was often fatal in less than ten hours. Boyer, in 1814, mentioned its occurrence in fractures and also spoke of the rapidity of death, while Velpeau, in 1829, stressed it as a complication of fractured limbs, and considered the emphysema of grave significance. In his experiences, death was the outcome in many cases. DuPuytren, in his lectures under the name of "spontaneous emphysema," described a condition occurring in trauma resulting in rapid decomposition, and in 1836, we find Martin de Bazas publishing a case of foudroyant gangrene which followed a crushed foot and in which death occurred in twelve hours. Malgaigne recalls a case of rapid termination after emphysema complicating a fractured limb. He looked for the real cause. "I think," he declared, "that there occurs under the influence of shock and stupor a special change which attacks life just as an extensive 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." For the first time the gas escaping from the emphysema was analyzed. It was found to be inflammable and it constantly showed the presence of hydrogen sulfide. (54)

At the meeting of the Academy of Sciences on October 11, 1849,
Chassaegnac asserted that certain gangrenes with emphysema should be considered as having "a poison far in excess to the mechanical injury."
He described four cases the next year which showed what he called "empoissonnement traumatique." (54)

Maissoneuve really first described gas bacillus infection on September 12, 1853. He reported to the Academy of Sciences two cases of gas gangrene and declared there existed a certain variety of traumatic gangrene to which he gave the name of gangrene foudroyante, in which, first, putrefying gas developed in the interior of veins during life; and second, that this gas circulated in the blood and caused a fatal poisoning. Salleron, a year later, reviewed 65 case histories collecting his material from a study of casualties occurring during the Crimean War. This, it must be recalled, preceded Pasteur's epochal announcement of the relation of bacteria to disease. After infecting animals with putrid flesh, Pasteur discovered in 1876 the organism now referred to as the Vibrion septique. He did not, however, obtain a pure culture. Five years later, 1881, more detailed study of the same bacterium was undertaken by Kock and Goffky who gave it the name of Bacillus edematis maligni. A year later, Molier and Ponget, for the first time, used the term of gaseous gangrene. (76)

Thus far, the vibron septique or the bacillus edematis maligni was the only organism associated with gas gangrene. It was not until ten years later, 1892, that Welch and Nutall (79) described minutely their bacillus isolated from the blood vessels of a patient suffering from aortic anurysem. Working in the autopsy room of the John Hopkins University Medical College, they noticed that the vessels were distended with gas bubbles. This observation was followed by the dis-
covery of the gas bacillus in the barrel of their hypodermic syringe. A year later, 1893, Fraenkel (28), working independently, isolated the same organism, called by Welch the Bacillus Aerogenes Capsulatus, known also as the Bacillus Welchii, and referred to by the French as the Bacillus Perfringes.

The succeeding two decades added very little. With the outbreak of the World War in 1914, however, with its thousands of cases infected by gas bacilli, so plentiful in the oft-manured soil of France and Belgium, the question became an outstanding individual problem. Due to this fact, much interest in this condition was aroused so that the literature appearing during this time is abundant.
INCIDENCE
Since gas gangrene was first described by Maisonneuve in 1853, it has been reported with increasing frequency. Although more than 2700 cases occurred in the American Expeditionary Forces, fortunately it is still one of the unusual diseases except under war conditions. This fact, however, should not delude us into a state of false security. Its occurrence is, in a sense similar to a stroke of lightening, infrequent but sudden and devastating, and no one knows where it will strike next. It is a potential visitor in any case of severely traumatized wound which by virtue of the injury or afterward has had contact with dust or dirt contaminated with animal excreta whether in the street or on the farm. It is especially common in compound fractures, not infrequently occurs after spontaneous gangrene from diabetes or vascular disease and has been reported in association with hypodermic injections, fistulo in ano, ruptured peptic ulcer and appendicitis, bowel obstruction, and bile peritonitis, gall stones, gangrene of the lung, infected abortion, and other diseases. (14)

An idea of the incidence is conveyed by 187 cases summarized by Cramp (16) in 1912 of which there were fifty amputations. In the Bellevue Hospital for a period of two years there was one case to each 644 admissions, at the Mary McClellan Hospital, Cambridge, New York, one case to each 938 admissions: at the East Coast Hospital, St. Augustine, Florida, one case to each 396 admissions.

Miller (54), in his series of 607 cases occurring in civil life, the largest single series ever collected, has subjected these cases to analysis and found that there was a greater prevalence of this condition among males. Also there was no seasonal variation to speak of and the greatest number of cases occurred during the third and fourth decade
of life. In this series of 607 cases, there were 227 bone fractures, 143 of which were compound. From this it can easily be seen that gas gangrene is a frequent complication of compound fractures.

Frank K. Boland (8) in his review of cases collected at the Emory University Division of the Grady (Municipal) Hospital, Atlanta, during the seven years from 1922 to 1929, states that gas gangrene developed in 15 cases out of 80 compound fractures in the negro patients treated, a percentage of nineteen.

Also, during the same period of seven years, among the ninety-seven cases of compound fractures treated in the white division of the Grady Hospital, seven developed gas gangrene, a percentage of about seven. The nature of the compound fractures in both classes of patients seemed equally severe, so that it would appear that the negro is more susceptible to the disease than the white man, or that his resistance is less.

Weintrob and Messeloff (76) in 1927 presented the results of a study of 85 cases from the records of Bellevue Hospital.

Warthen (72) made a study of all cases of gas bacillus infection treated in the Medical college of Virginia hospitals from Jan. 1, 1931 to January, 1936. He found that thirty four cases of gas bacillus infection were treated, or one case for every six hundred and forty seven hospital admissions. Positive cultures for B. Welchii were obtained in twenty eight of the infection, the remaining six were so diagnosed because of unmistakable clinical or pathological findings.

At about the same time Stone and Holsinger, (65) 1934, were collecting and reviewing cases of gas gangrene occurring in the state of Virginia and in their report upon sixty five cases of gas gangrene
along with those reported by Warthen; they drew their conclusions as to the reason for the increased number of cases of gas gangrene occurring in the state of Virginia and thought it was due to the increased number of motor accidents and farm accidents which occurred where the soil was more apt to be more fertile with animal excreta and to the higher number of compound fractures.

Ghormley (32) in 1935, reported upon 33 cases of gas gangrene and gas infection which were encountered at The Mayo Clinic over a five year period showing that compound fractures produced the largest number of infection.

Kelly of Omaha (47), during the years of 1928 to 1936 reviewed 56 cases including his own to determine the value of x-ray therapy for this condition.

As for military incidence, it was found at the end of the war from 1.5 to 3 percent of all wounds were infected by gas bacilli. For a much more detailed review of these statistics which were compiled during the war, one is referred to the Surgeon General’s Report (80) and to the Reports of the Medical Research Committee. (81)
The present state of our knowledge concerning infections caused by anaerobic gas-forming bacilli is one of confusion. This is no doubt due to the fact that any lesion characterized by the presence of gas in the tissues, together with large gram-positive bacilli, is considered to be gas gangrene. Apparently in most cases neither the history of the infection, the clinical course nor the kind of gram-positive bacteria present alters the diagnosis. The great number of unsound tests that are still being used to determine the presence of Clostridium Welchii is another factor that does little to aid in clarifying the present situation.

All bacilli that grow in the absence of oxygen and form spores are grouped in the genus Clostridium, of which at present about 100 members are classified. Nearly all these organisms form gas in certain situations, but this is not a great factor in their classification, since the aerobic and colon group and the streptococci also form gas and frequently do so in infected tissue. Of the 100 species of anaerobic spore-forming bacilli, seventeen are pathogenic for some form of animal life, whereas only seven are in the true sense pathogenic for man. Five of these species of pathogenic organisms constitute the group that is responsible for malignant wound infections attended by edema, necrosis, toxemia and collections of gas, such as were seen so frequently during the World War. Clostridium Welchii is the most important member of this group of five organisms. At present it has eleven synonyms, the most commonly used are Bacillus perfringes, B. Welchii and the gas bacillus. (57)

Attempts have been made to show the the B. Welchii is only one of a number of gas-forming organisms and that it does not merit
the prominent role formerly ascribed to it as the causitive factor in the large majority of cases of gas gangrene. In 1900, Welch (77) stated that "While it has been demonstrated that various bacteria may concerned in producing gaseous affections, it is now evident that the Bacillus which I discovered in 1891 and to which I gave the name of B. Aerogenes Capsulatus is the one whose causitive agent is best established and most frequently in action." This statement is still true and while it is recognized that the Welch bacillus is frequently associated with other aerobic and anaerobic organisms, it is undoubtedly the causitive organism in at least 80 percent of gas gangrene encountered in civil practice. (72)

This above statement fits in very well with The Surgeon General's Report (80) which call attention to the symbiosis of various aerobes and anaerobes. In Base Hospital No. 15, A. E. F., in 73 cases of gas gangrene with death, activity of the gas bacilli was self-limiting and practically confined to the first week after the wound was received, with a drop in anaerobes from 38 to 7 percent during the first seven days, as the common pyogenic streptococcus and staphylococcus accumulated rapidly in the wound. The symbiotic effect was particularly prominent in fatal wounds. Infections with anaerobes alone showed a high death rate but a short period of danger to life. A streptococcic bacteremia was by far the most important cause of death, especially in patients living beyond the first week, which was roughly established as a self limiting period of gangrenous process and many deaths attributed to the anaerobes were in reality deaths due to streptococcus in the process of replacing them. (7)

Also from a series of Surgical cases from Evacuation Hospital,
No. 8, A. E. F., 1918, it was shown that many cases did not develop
gas gangrene although gas gangrene was clinically evident at the time
the wound culture was made. It was thus seen that more than two thirds
of the severe, non-transportable wounds contaminated by anaerobic
bacilli failed to develop gangrene, all of these cases being under
observation for at least 5 days, and many of them as long as two weeks.
This fact involves a very important pathological principle. These
bacteria are incapable of producing gas gangrene by their presence alone
and must be accompanied by the failure of circulation, the extensive
cellular damage of large quantities of muscle, and in all probability
by constantly progressive increase of this series of factors. (7)

Experimentally, injection of large quantities of washed B.
Welchii failed to produce lesions in laboratory animals, but lesions
would develop if either acid or powdered glass was injected with the
bacilli or if slight injury to the muscles preceded the injection.—
"In other words, the Welch Bacillus is not a true parasite but a
saprophyte that cannot grow in healthy tissue, it is able to thrive
only if the body cells are first injured by some chemical or mechanical
means. The lesions involve the muscles, the blood vessels and the fat
of the subcutaneous connective tissues." (7)

Anyone who is called on to treat injuries incurred in such
a manner as to permit the entrance of soil into the wound is probably
more or less familiar with the condition commonly known as gas gangrene.
The presence of the organism or organisms causing this condition should
always be suspected, and, in the event of evidence of such infection in
a compound fracture or other wound, it would seem wise to regard it as
a possible etiological factor.
11.

Gas bacillus infections are seen usually in wounds of the extremities, in which a foreign body has been introduced, causing a disruption of the anatomical continuity of the structure, or in those conditions in which the distorted anatomical continuity of the structure has been brought into contact with a foreign substance which is of such a nature as to cause the propagation and growth of the various gas forming anaerobic bacilli. The causitive organism of first importance in this group of infections as stated before is the Clostridium Welchii. Davis (17)

The common habitat of the various anaerobic gas bacilli is thought to be cultivated soil and animal excreta, and it may be that the apparent susceptibility of negroes is due to uncleanliness. Boland(8) On the other hand, Gage (29) believes that all kinds of wool and woolen goods harbor the microorganisms. He not only found gas bacilli in the wool pads interposed between powder and shot in ordinary bullets, but also grew them in culture taken from woolen clothes just returned from a pressing club, and in samples of unused cloth taken from a tailoring establishment.

The bacilli are straight or slightly curved rods with rounded or sometimes square cut ends enclosed very frequently in a transparent-like capsule. Spores are usually absent in tissues and often in cultures. Dunham (56) showed that the culture isolated by Welch formed spores when grown on blood serum; and some strains, since isolated, formed spores very readily. They are anaerobic, non-motile and gram positive, but more easily decolorized than any other gram-positive bacteria. Growth is rapid at 37 degrees Centigrade, in the usual culture media containing sugars, and is accompanied by the
production of gas. Nutrient gelatin is not liquefied, and on agar plates colonies are developed which are from one to two millimeters or more in diameter, grayish white in color, and in the form of flattened spheres, ovals, or irregular masses covered with hair-like projections. Bouillon media is diffusely clouded and a white sediment is usually formed. Milk becomes rapidly acidified and coagulated, assuming a worm-eaten appearance which has been called "stormy fermentation." A large amount of butyric acid is produced. The bacilli ferment most sugars, and they have been divided by Simmonds (63) according to their ability to ferment either insulin or glycerol, or both or neither, but they apparently all produce the same toxin. (17)

When quantities up to 2.5 cc of fresh bouillon cultures are injected into the circulation of rabbits and the animals are killed shortly after the injection, the bacilli develop rapidly, with an abundant formation of gas in the blood vessels and the organs, especially the liver. The material suspected of containing the bacillus alone, or associated with other bacteria, is injected intravenously into the rabbits, which are killed five minutes later, and kept at 37 degrees Centigrade for 16 hours, and the cultures in milk made from the liver and heart blood; if "stormy fermentation" occurs in the milk after incubation, the test for B. Welchii is positive. (17)

In War wounds the B. Welchii is usually accompanied by B. Sporogenes, which is a markedly proteolytic anaerobe which is non-pathogenic in itself, but which probably stimulates the pathogenicity of other anaerobes. The presence of this anaerobe makes the isolation of B. Welchii in pure cultures often a difficult procedure.

Its pathogenicity is usually not marked in healthy animals, although Dunham (56) found that the bacillus taken freshly from human
infection is sometimes very virulent; bacilli of this type are one of the frequent infections after irregular unclean wounds, such as those received in war or in civil practice where much tissue is destroyed or crushed. In these infections there is a marked destruction of tissues, especially in the muscles and this is supposed to be due to one or more of five conditions:

1. To the large quantity of butyric acid produced from the glycogen of the muscles.

2. To pressure due to the amount of gas produced.

3. To the presence of a foreign protein.

4. To a specific toxin.

5. To the presence of a soluble, ionizable calcium salt, which according to Bullock and Cramer (13) produces a local breakdown of the normal defense mechanism against spore-bearing animals.

Other organisms of the gas forming anaerobic group which are either associated with or cause similar types of infections are Bacillus Novii which secretes a very active soluble toxin; B. Fallax which is only slightly pathogenic, and B. Histolyticus which is intensely proteolytic, digesting tissue down to bone in test animals; B. Putrificus, not pathogenic, and the bacillus of malignant edema, Clostridium Oedamatis Maligni, or Vibrion Septique, which causes an extensive hemorrhagic edema of the subcutaneous tissues, at the site of the wound, so that subsequently there is a serious effusion which is frothy from gas formation and has a foul odor. (17)

Barney and Heller (2) have shown that as many as four anaerobic organisms capable of rapid invasion in the guinea pig body were isolated from an amputated arm in 1922. Weinberg in 1916 (73) and
Bull and Pritchett in 1917 (11) demonstrated that B. Welchii forms an exotoxin which is neutralized by an antitoxin.

According to Reeves (57), probably the most reliable single laboratory procedure is a capsule stain, since Clostridium Welchii is the only pathogenic anaerobic organism bearing a capsule but even this type of stain is sometimes extremely difficult to make.

Medical literature, particularly in the last twenty years, contains many reports giving Clostridium Welchii as the etiologic agent in a wide variation of clinical conditions. Torrey and Kahn, (68) on the basis of experimental anemia in rabbits, produced by intramarrow injections of Clostridium Welchii toxin, claimed some similarity to primary pernicious anemia in man. Gordon (35) and Taylor (66), after a study of fifty cases, concluded that Clostridium Welchii is usually associated with acute cholecystitis. They also found the organism in 13 percent of all gall-stones removed at operation. Jennings (44) in 1931 states he found Clostridium Welchii in the lumen of the appendix in 90 percent of cases. Clostridium Welchii was reported by several to cause the toxemia of intestinal obstruction. Most of this forgoing work has been disproved now because most of the experimental evidence and clinical conclusions linking Clostridium Welchii with conditions other than true gas gangrene have been based on unsound tests for the presence of this organism. (17)

In 1931 a committee at the New York Hospital for Bone and Joint Diseases (31), appointed to determine why gas infections appeared so frequently in amputation stumps after clean surgery, brought forth some interesting facts. The committee considered that all the gas infections were caused by Clostridium Welchii and then discovered that
most of the infections appeared in arterio-sclerotic individuals or patients past the age of fifty, some of whom had thrombo-angina obliterans. These infections were mild, and recovery was the rule when the patients were in fairly good physical condition. As stated before, all series of cases that the author studied, (57) one third arose in patients past fifty years of age, in diabetic patients, in arterio-sclerotic patients, and in patients with thrombo-angina obliterans or generalized circulatory failure. These infections may be spontaneous, follow amputations for dry or moist gangrene, and appear after the parenteral injection of drugs and solutions and after bruises in which the skin is not broken. The clinical picture though as compared with true Clostridium Welchii infections, is relatively mild.

The various pathogenic organisms that cause true gas gangrene are distinct species, belonging mostly to the saccrolytic group; they are similar in morphology to one another and to numerous species of putrefactive proteolytic bacilli, only a few of which have so far been classified. There are myriads of these putrefactive, gas-forming, anaerobic bacilli lying dormant in the soil, periodically growing on bits of decaying organic material and thereby maintaining their numbers. These organisms constantly contaminate food and it has been shown experimentally that they utilize the tissues and organs of animals to continue their existence. Evidence has been and still is being collected and accumulated by this author in his laboratory to show that in the latter decades of a human existence, the organs and muscles may become contaminated by these saprophytes and that under certain conditions they can begin the destruction of the tissues before death. The author believes that the type of putrefactive gas gangrene
appearing mysteriously in older people, and those suffering from diabetes, arterio-sclerosis and circulatory failure, is caused by those saprophytic bacteria already present in the tissue injured or deprived of its blood supply. All that is necessary for their growth is death of tissue. (57)

According to all the later authors upon this condition, namely Wharthen (72), Ghormley (32), Stone and Holsinger (65), Kelly (47), Weintrob (76) and others, they agree that the gas bacillus can be demonstrated in approximately 80 percent of cases and is the most important one from the standpoint of an etiological role although one can practically always demonstrate the presence of other aerobic and anaerobic organisms as a complicating factor. They also agree that compound fractures accompanied by severe lacerations of the extremities is the most common predisposing factor to the infection although it can occur in a wide variety of conditions.

As a cross-section for all later series of cases reported, I have analyzed and presented the series of Ghormley to show the variety of predisposing factors. (32)

Cases of Gas Gangrene and Infections with Gas Bacilli (Clostridium Welchii) encountered in a five year period.

Causitive or pre-disposing factors: No. of cases.

Following trauma:

1. Compound fractures-------------------9
2. Injuries to soft parts-------------7 16

Metastasis-primary source unknown 3

Following amputation:
1. Thrombo-angina-obliterans------------------3
2. Arterio Sclerosis (with diabetes)---------2

Following operation:
1. On stomach---------------------------------3
2. For intestinal obstruction-----------------2
3. Colostomy and resection--------------------1
4. Cystostomy---------------------------------1
5. For perinephritic abscess-------------------1

Abortion

These 33 cases of gas gangrene and gas infection which were encountered at The Mayo Clinic in a five year period represent a variety of causitive factors. As would be expected, compound fractures produced the largest number of infections, although wounds of the soft parts were not far behind. Either of these may be said to be the commonly known types of trauma from which gas infections may develop. Anyone doing many amputations for gangrene due to thrombo-angina obliterans, or for gangrene due to arterio-sclerosis with diabetes, has probably seen the occasional instance of gas infection in the stump. It is a disturbing complication which may take place frequently enough to justify administration of a prophylactic dose of gas gangrene anti-toxin before amputation is undertaken. (32)

SUMMARY

1. Although the gas bacillus is now accepted as the most important etiological agent in this infection, no cases that have been reported in later years that do not show the presence of other aerobes and anaerobes. These different strains have varied symbiotic relationships.
2. Later experiments have definitely proven that the gas bacillus alone is not capable of producing gas gangrene but that this symbiotic relationship with other organisms plus the presence of necrotic muscle or other tissue seems essential for the multiplication of these anaerobes and the elaboration of their toxins.

3. The anaerobic bacteria cause pathological changes through the medium of toxins which they elaborate.

4. Many of these micro-organisms elaborate a proteolytic ferment which destroys tissue and thereby favors the growth of bacteria.

5. All of the gas-producing bacteria except Bacillus histolyticus, have a saccharolytic ferment which gives rise to the formation of gas within the tissues. The gas itself is not toxic, but aids in producing ischemia by pressure upon and occlusion of veins, capillaries and smaller arteries.

6. The incubation period is from one to four days or even longer, depending upon the virulence of the organism and the amount of devitalized muscle.

7. Approximately 30 percent of cases reported and treated as Clostridium Welchii gas gangrene are caused by other anaerobic organisms which is due to inadequate methods of bacterial diagnosis or in inexperienced hands.

8. This 30 percent of cases should be classified as putre-gangrene and treated conservatively by systemic supportive treatment, debridement and irrigations. Clostridium Welchii antitoxin is not indicated and may be injurious in some cases.

9. Putrefactive gangrene is more likely to appear in patients
past the age of 50 years who are constitutionally below normal. Cases appear notably in patients with circulatory failure, arterio-sclerosis, thrombo-angina obliterans and diabetes mellitus.

10. Patients suffering from wounds, fractures, particularly of muscle tissue, which have been contaminated with soil or street dirt, should be regarded as suspected cases which might tend to develop gas gangrene in a short while since the above described set-up is regarded today as the most important pre-disposing factor to gas gangrene.
The study of the pathology of infection by the group of B. Welchii had followed from several fortuitous circumstances. First, there was the insistent problem, only partially solved by the improvement in the antiseptic treatment of wounds, of gas bacillus infections, following shell and bullet wounds everywhere in the War; second there was available to these men several cultures of B. Welchii isolated during the summer of 1916 on the Western battle front by Dr. Simonds (63); and finally and especially Dr. Flexner's wish that with these cultures the subject of gas bacillus infection of the pigeon which he had observed many years before at the Johns Hopkin's Hospital should be reinvestigated, as, in his opinion, the process in that species of animal epitomized the pathologic effects occurring in gas gangrene in man, and because he believed that a better understanding of the one condition would serve to explain many still obscure points in the other. (11) Bull and Pritchett-1917.

From this group of experiments which would be too lengthy to describe in detail and from reading brief extracts of the opinions of other men having experience in this field and type of work, they found a wide diversity of opinion held by recent students of the pathogenesis of gas bacillus infection in man. It also showed how remote the conceptions were from that of a specific pathogenetic process, due to the action of particular toxic substances, which was the basis of conviction derived from their experiments. According to the view of Bull and Pritchett (11), infection by B. Welchii, like infection by B. Tetani, essentially resolves itself into an intoxication, in which an exotoxin yielded by the multiplying organisms constitutes the chief danger. The two conditions differ, however, with respect to the local effects pro-
duced on the tissues, since the tetanus toxin does not possess inflammatory and necrotizing properties. The Welch bacilli, therefore, grow more abundantly and produce wide destruction of tissue, in which process they are soon assisted by the usual pyogenic micro-organisms, which quickly attain a foothold in the dis-organized structures. (11)

In discussing the pathology of gas gangrene, especially of the muscle, one is confronted with a manifold clinical syndrome which if not handled systematically will further confuse the individuals interested in this problem. I have found that the report by Emrys-Roberts and Cowell, of the Royal Army Medical Corps (23), is a very excellent study in the morbid anatomy of gas gangrene of muscles. Their experience was obtained from cases observed on the Western Front during the World War, and with a wealth of material at hand and with keen clinical and laboratory observations, certain points of significance were of aid in further understanding the morbid processes in gas gangrene of the extremities. I shall freely quote from their excellent work.

A very brief reference to the clinical side of this infection will make it easier to follow the sequence of events described in the study of the morbid anatomy and histology. As a result of studying a large number of cases of gas gangrene, Emrys-Roberts and Cowell recognized three main clinical types:

A. The common type—which occurs in wounded lying out 12-24 hours, or which develops a few hours after the first operation.

B. The fulminating type—where the patient, if untreated, may be dead in a few hours.

C. The delayed type—with a slow onset, so that the condition
only becomes established several days, or even weeks, after the date of wounds.

Grossly the naked eye appearances of the infected muscle will be described:

A. At the wound surface.
B. In the area of dead muscle.
C. At the spreading edge.
D. In the contractile part beyond.

The variations in appearance at these different levels, and after different lengths of time have elapsed, depend on the following factors:

1. The extent of local trauma.
2. The degree of chemical changes in hemoglobin resulting from the acid produced locally.
3. The presence of gas in the tissue.
4. The amount of myolysis produced by the bacterial "toxins".

A. At the wound surface---There are two types of wound of muscle in which gas gangrene is especially liable to develop. Firstly, in deep penetrating wounds, with or without fracture of the bone, in which the main vessels may or may not be involved; and, secondly, an extensive surface wound, where gross laceration of the muscles has been produced, and where large amounts of infective material, such as dirt and fragments of clothing have been carried in. (23)

In examining the early cases of the first group, the damaged and infected fibers along the track of the injury may be seen pale in color and non-contractile, while the wound surface is covered with a thin film of a viscid greenish-yellow fluid. On close examination faint pink
lines, indicating the spread of infection into the muscle, run along the course of the peri-vascular tissue. In other cases, where laceration is more superficial, the wound surface is at first a dusky red, later becoming paler, then green, and finally black. This is due to the local contusion producing interstitial hemorrhages, the blood from which is soon attacked by the products of bacterial growth. Frequently, here, may be seen small dark-colored blood-clots half embedded in the torn muscle substance, or attached merely by a thin fibrinous pedicle. These clots may be a factor of importance if not wholly removed at operation, since several examined by these men were found to be swarming with anaerobic bacilli. (23)

In the earliest stages the surface is hard to the touch, especially to the ungloved finger. The surface of the dead muscle is coated with a thin white fibrinous layer. There is no actual pus exuded from the wound surface, although a clear, foul smelling fluid escapes. Underneath the fascial sheaths a layer of thick greenish turbid lymph is found, a similar fluid may often be observed spreading around the nerve sheaths.

As the infective process continues to develop, softening occurs. The surface becomes crepitant to the finger, and soon reaches the final stage of black deliquescence.

B. In the area of dead muscle.—In the very earliest cases, if the muscles is examined immediately below the wound surface, it is found to be firmer than normal and no longer contractile. There is no change in color, but there is a distinct lack of lustre and translucency. Soon, however in advanced cases, the sequence of color changes already noted begins.
Gas production begins at a variable time after the death of the muscle, usually it does not occur until many hours have elapsed, so that it must be regarded as a late manifestation. At first minute bubbles are found, these coalesce and rapidly increase in size, giving the dead muscle a spongy or honey combed appearance. As gas is produced in greater quantities it forces its way along the planes of least resistance, till it bursts through the surface of the dead muscle. In this way the fascial sheaths become distended with gas, and, in the case of a long muscle, the presence of the gas becomes an additional factor, as a mechanical ischemia is produced from the blood-supply thus obstructed. In a muscle, such as the tibialis posticus, the pressure exerted in its rigid fascial compartment is sufficient to partially occlude the main vessels, and thereby accelerate the spread of gangrene. From the fascial sheath the gas soon finds its way into the cellular tissue and becomes subcutaneous, extending in some cases over the whole body, just before death.

They made a number of observations on the specific gravity of gas gangrene muscle in all stages and found, that as the presence of interstitial gas becomes apparent, so the specific gravity decreases, until, in the later stages, the muscle is found to float in ordinary water. (23)

In this dead muscle area they investigated the extent of possible arterial thrombosis, having in mind the fact that in gross inflammatory lesions in general thromboses are common. As a typical example they quote the case of an advanced gas gangrene of the leg where the whole limb was distended, cold and pulseless, and where one might expect to find a measure of thrombosis. But by injection, they found it had
penetrated perfectly. They therefore conclude that massive thrombosis, apart from that resulting from trauma, is not a concomitant of the process of gas gangrene. Absence of circulation is this case was undoubtedly due to the mechanical pressure of the contained gas.

C. The spreading edge.—In advancing cases, as you proceed away from the wound, a point is at last reached where non-contractility ceases and the muscle again reacts to stimuli. This line of junction is found to proceed across the muscle in an extremely irregular fashion.

D. Lastly, they have examined the contractile muscle in advance of the spreading edge for evidence of vascular lesions. These, in the absence of direct evidence of trauma, and its resulting bruising effects, have never been encountered. It must be noted however, that traumatic interstitial hemorrhage is quite commonly met with at a considerable distance from the site of the wound.

Mode of Spread.—The process of gas gangrene is seen to spread, within the fascial sheath, in the direction of the fibers of the affected muscle. Thus the infection is confined to the affected muscle to the exclusion of neighboring muscles, unless the main blood supply is interfered with, either by trauma or by pressure of gas from the affected muscle, or groups of muscles as the case may be, or unless the infective exudate which has been previously described, tracking along the sheaths of such structures as arteries, nerves, and tendons, extends the process from one segment of a limb to another. (23)

HISTOLOGY

The micro-pathological changes noted were remarkably consistent, and the type of organism present did not appreciably affect the general character of the morbid process. An outstanding factor governing the
histological picture was undoubtedly the presence or absence of bruising, with its concomitant blood extravasation and thrombotic changes.

Bearing these points in mind they again outline the changes met with in the following areas—

A. At the wound surface.
B. In the area of dead muscle.
C. At the spreading edge.
D. At the site of resistance or recovery.

A. Site of wound—In dealing with a typical case of advanced gas gangrene, the superficial, obviously necrotic, muscle will be found to be composed of distorted, swollen, fragmented fibers, with separated peri-fibrillar sheaths imbedded in a mass of fibrinous reticulum, in whose meshes are large numbers of polymorpho-nuclear leucocytes, especially on the actual surface,--together with varying numbers of both aerobic and anaerobic organisms and extravasated blood cells, and cell debâres. Phagocytosis of both bacteria and pieces of dead and lysed muscle is well seen. The vessels at the surface are damaged, and thrombosis quickly occurs. As the muscles fibers of the vessel walls also undergo lytic changes, in the immediate surface area no definite vessel remain.

The characteristic fibrinous reticulum, by effectively binding the leucocytes and pieces of dead muscle, prevents the formation of pus and accounts for its absence in gas gangrene. (23)

If one examines the site of a wound in a less advanced case, the first thing to attract notice is the filmy white fibrinous exudate on the surface, which also extends downwards for varying depths into the subjacent infected muscle. The deposit is identical with the fibrinous reticulum, suffused with leucocytes just described. In extremely early
cases of gas gangrene the fibrinous deposit, though invisible to the naked eye, is readily seen under the microscope. The presence of leucocytes, then, on the wound surface is quite characteristic. Although, as we shall see later, leucocytes are the more rarely seen as we approach the spreading edge, indicating the anti-chemostatic properties of the anaerobic "toxins", it should not be forgotten that in its original manifestation the infective process consists invariably in a mixture of the effects of both aerobic and anaerobic bacteria.

This superficial fibrinous reticulum, though characteristic, is not peculiar to gas gangrene. It can, and does, occur in massive aerobic infections, where the underlying tissue response has become too enfeebled.

The inference drawn here is that in gas gangrene a similar enfeeblement has occurred, indicating a state of lack of resistance.

B. The area of dead muscle.--As one proceeds from the actual site of the wound into the area of dead muscle, the presence or absence of bruising more than ever dominates the histological picture. When the bruising of the muscle is slight, examination of the dead tissue reveals only a moderate degree of extravasation and thrombosis. (23)

The specific action of the anaerobic "toxins" appears to be myolytic in character. Hence in muscle fibers already killed or injured by the force of the blow and this applies equally to the muscle fibers of vessel walls--the process of myolysis is hastened, and the hemorrhages, extravasations, and thromboses are thereby aggravated.

The muscle fibers themselves in this dead area, except in very early cases, where occasional striated fibers, may be seen extending almost to the wound surface, have completely lost all normal characteristics
of striation and staining properties. They are frequently swollen, distorted, and fragmented, present longitudinal splitting, and are separated from the surrounding interstitial tissue by distinct peri-fibrillar spaces. Many of these fibers, and also particles of lysed fibers, nearest the wound surface, are in process of active phagocytosis. Myolysis frequently proceeds to such a degree as to produce entire disappearance of the portions of fibers involved.

The fibrinous reticulum, previously described on the wound surface, is here observed to extend both between muscle bundles—in perifascicular fashion,—and between muscle fibers—in perifibrillar fashion,—to a slight degree and for a short distance. The enmeshed leucocytes decrease rapidly in number as we proceed in the direction of the spreading edge, the fibrinous reticulum becomes more attenuated, its place being taken by fluid. In this fluid are suspended the "toxins" of the anaerobic bacilli, occasional leucocytes, and from time to time extravasated blood cells. The bacteria are present in ever decreasing numbers the further we proceed from the wound surface, and are found lying both in the perifibrillar and perifascicular areas. The fluid is presumably produced by exudation from the capillaries; its accumulation accounts for the well-recognized hardness and solidity of the muscle as previously described, and its outpouring through the wound surface provides the familiar discharge associated with gas gangrene.

As we advance further towards the spreading edge, the muscle fibers become singularly intermingled, the living with the dead and dying. So far from there being any hard-and-fast line between affected and unaffected fibers, there are seen to exist side by side and in every plane. The same may be said even of bundles of fibers, so that, while the line
of demarcation between contractile and non-contractile muscle may be assigned to a given spot it must be understood that contractility is a relative term, and that muscle which contains a due proportion of dead fibers may yet be contractile by virtue of the power latent in the still living fibers. (23)

The lytic changes, described as occurring in vessels subject to trauma, may also be demonstrated as occurring in vessels not so subjected. Thus the stages between normal blood vessels on the one hand, and vessels whose walls have been completely lysed on the other, can be seen. We find that these changes in the blood vessels are due to the myolytic action of the "toxins", and do not appear until the changes in the muscle fibers have become established. In the case of the capillaries-owing to their free anastomosis and to the absence of muscle elements lytic changes do not take place until a late stage of the process is reached, and they continue to supply this area with blood particularly up to the wound surface. In this way the supply of active leucocytes, which is so marked a feature at this spot, is accounted for.

While examining the muscle fibers, they frequently found, running alongside, a row of nuclei which would at first sight appear to be proliferated sarcolemmal nuclei. They are not, however, sarcolemmal in origin, but are the nuclei of endothelial cells of the capillaries, which can be demonstrated both coursing alongside muscle fibers, and crossing them in an interlacing manner. (23)

C. The spreading edge.--The spreading edge is perhaps the most interesting stage of all. Here the proportion of dead to living fibers is reversed—until one finds occasional dead or dying fibers in the midst of living ones. In the present state of our knowledge, a fiber
provided with striations may be said to have been unaffected by "toxins" at the time it was fixed. Conversely, loss and blurring of striation may be taken to indicate that the fiber has been killed or has reached the dying stage. One can trace the individual fiber from the area of dead muscle into that of the living through the following stages. At first the fiber is swollen, has lost its striation and staining characteristics and is surrounded by the fluid containing perifibrillar space. As one proceeds, it gradually loses its peri-fibrillar space, its swollen appearance, and longitudinal splitting, until it approximates to the living fiber in all save its possession of striae. In this condition one can trace it onwards until at last well-marked striae appear, and one is able to say, "Here is the spreading edge." (23)

At the spreading edge there is no indication whatever of vascular change in those cases where the effects of bruising can be excluded. Vascular changes, dependent to a greater or less degree on the myolytic properties of the anaerobic "toxins", are comparatively late phenomena, since the muscle fibers of the vessels are not at first exposed to the action of the "toxins" to the same degree as are the fibers of the muscle proper.

The demonstration, histologically, of anaerobic bacilli as we approach the spreading edge is a purely fortuitous occurrence. They know that they exist there—and beyond it—because their presence can be proved in cultures made from pieces of muscle taken for this purpose.

These bacilli at and beyond the spreading edge are eventually destroyed. Only in grave infections, with profound loss of bodily resistance, do such bacilli become a source of danger. They know how in these cases secondary foci of gas gangrene may develop well away from
the original site of infection, in such spots as where saline injec-
tions have been given subcutaneously, or where pressure from a
splint has taken place. The bacilli at and beyond the spreading edge
are so few in number, that it may be safely stated that the "toxins" they
evolve are negligible. How, then is the continuous and advancing death
of the individual muscle fibers to be accounted for? The explanation
is that the soluble "toxins" of the anaerobes exist in the peri-
fibrillar spaces, are here absorbed by the muscle fiber, travelling in
the direction of its long axis, and kill the fiber as they advance.
Heavy bacterial infection, combined with inefficient drainage at the
wound surface, leads to increased absorption of the "toxins", and so
hastens the advancing death of the individual fibers. Similarly the more
damaged the tissues and the greater the degree of blood extravasation
and thrombosis, the less the resistance there is to the lethal process.
Hence the astonishing rapidity of the advance in certain cases, more
especially if, together with the local loss of resistance, we have a
lowered general resistance resulting from fatigue, shock and hemorrhage.

D. Area of resistance or recovery.--Following upon operative
interference, where either the wound has been thoroughly opened up,
amputation performed, or muscle excised, one might be in the position to
demonstrate the tissue reaction that accompanies the checking and
eventual overcoming of the process of gas gangrene.

This process is marked by the further development of the
fibrinous leucocytic layer, in such a manner as to form a distinct line
of demarcation between this layer and the underlying contractile muscle.

Occasionally, arrest of the process occurs spontaneously, and
a similar line of leucocytic infiltration is formed at the wound surface.
Microscopically, there is usually a sudden transition from the infiltrated layer to the healthy muscle, while within the layer of fibrinous exudate the muscle fibers, where recovery is taking place, are found to be dead and in process of phagocytosis. Living fibers can be met with, however, at quite a short distance as we proceed inwards, indicating the cessation of the myolytic process. Here, in contrast to the generally long drawn-out process of muscle fiber disintegration associated with advancing gas gangrene, the change from the living striated fiber to the swollen and lytic stages is usually accomplished abruptly. (23)

The peri-fibrillar and peri-fascicular spaces contain the anaerobic "toxins" which by reason of their anti-chemiotactic properties repel leucocytes. Hence if, as we near the wound surface, these spaces are seen to contain an increasing number of leucocytes, we may regard it as a measure of the neutralization of the "toxins" by the anti-substance evolved in the tissues and conveyed to the spaces by the capillaries. Hence also, if, at the wound surface and for a certain depth into the subjacent muscle, we meet with pronounced leucocytosis, we know that the presence of these leucocytes demonstrates the actual degree of the neutralization of the "toxins"; otherwise these cells would cease to be attracted to this area, and could certainly be inhibited from exercising their phagocytic properties. We are, therefore, justified in saying that the greater the mass of leucocytic aggregation at and near the wound surface, the better the fight is proceeding. (23)

The fibrinous character of the leucocytic exudate, with its binding effect, is an indication that the underlying tissues are in an enfeebled condition, as we have already stated. When the stage of re-
sistence or recovery is reached the fibrinous exudate still exists, though now superimposed upon living muscle. Later, when the stage of recovery is still further advanced, this exudate, together with dead muscle, is shed in the form of sloughs; revealing beneath, the establishment of true granulation tissue, with loops of new capillaries and remains of muscle fibers undergoing absorption. This is a sign that the underlying tissues have fully regained their vital properties. (23)

Regeneration of such a highly specialized structure as muscle fiber must necessarily be of a very imperfect character, and they question the possibility of any real replacement of lost muscle tissue.

In view of the many possible causative agents and the several factors affecting the pathology, it is not surprising that the clinical manifestations of gas gangrene vary within the widest possible limits. It is, however, unexpected that pathogenic anaerobic bacilli can be grown from the discharge of wounds which heal without giving clinical indications that these organisms are present. Yet such is the case. Still further evidence that these particular species of bacteria may remain dormant and inactive for many months in traumatized tissues is afforded by the incidence of serious gas gangrene following some simple plastic operation on a wound which previously had given no evidence of such an infection being present. (5)

In 1916 Wallace (71) gave forth his observations concerning the naked-eye appearance and color changes occurring in gas gangrene which were confirmed by Emrys-Roberts and Cowell. (23) Also in 1916 Taylor (66) thought that the chief agent at work was the evolved gas, which by its pressure inhibits the blood supply, devitalizes the tissues, fragments the muscle and scatters the infection. Henry (40) in 1917
also emphasizes his contention, after a study of the main groups of anaerobes, that the first active phase of the infection is the truly production of gas. Emrys-Roberts and Cowell do not agree with these two latter men. They say that while this may be said of the fulminating type of case, they hold that, generally speaking, gas-production occurs late.

**SUMMARY**

1. Gas gangrene of muscle is essentially a manifestation of anaerobic infection. Extensive trauma is an important etiological factor, as is also the symptom complex of shock, hemorrhage and exhaustion.

2. The "toxins" involved by the growth of the anaerobes contain a myolytic substance—an acid, and, possibly also, deleterious disintegration products; in addition, they possess antichemiotactic properties towards leucocytes.

3. The lytic changes in individual fibers are traced through the following stages during the process of advance:—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 peri-fibrillar spaces, in which are suspended the "toxins" and bacilli; fragmentation of the fibers, with marked lysis (which may proceed to complete disintegration); and finally, phagocytosis by the leucocytes at and near the wound surface.

4. Lytic changes also take place in the muscle fibers of blood vessels, though these are comparatively late phenomena. The capillaries owing to their lack of muscle constituents escape, and, as the result of free anastomosis, the blood supply is generally maintained, and
diapedesis of leucocytes provided for.

5. The formation of a fibrinous leucocytic layer at the wound surface is characteristic. The greater the number of leucocytes present, the greater the degree of neutralization of the "toxins", and visa versa. The presence of this layer is associated with the absence of pus.

6. When the stage of recovery and arrest of the process is reached, the fibrinous leucocytic layer assumes the character of a white line of demarcation, separating dead muscle on the one hand from living muscle on the other. Subsequently this layer is cast off in the form of sloughs and true granulation tissue takes its place.

7. During the stage of arrest of the process the lytic changes already described, are so abbreviated or compressed in the case of individual fibers, that the change from living striated fiber to the last stage of lysis and phagocytosis is abrupt.

8. The production of gas is always a late phenomenon, except in the fulminating type of case. Its action is purely mechanical, and may lead to ischemia by compression within fascial sheaths, thus assisting and hastening the infective process.

9. Although anaerobic bacilli can be demonstrated in apparently normal muscle well ahead of the process of gas gangrene, they do not assume a pathological role except when, in cases of very grave infection, they are associated in the process of a bacteremia and may give rise to secondary foci.

10. Vascular changes, apart from the effects of trauma, are absent in the advancing edge of the gas gangrene process.

11. Regeneration of muscle fiber is extremely improbable.
CLINICAL SYNDROME
The symptoms and signs arising from limited foci of infection with anaerobic gas-producing bacteria are well in keeping with the pathological changes already outlined. The disease occurs a variable time after the reception of a wound, particularly if this is lacerated and associated with much trauma and hemorrhage into the tissues, or with fracture of a bone. Loss of blood leading to shock, and any previous disease tending to impair the blood supply to the part (e.g., diabetes or arterial diseases), are pre-disposing factors. It is most common after street accidents, but may occur in any wound contaminated with dirt or fecal material.

One of the earliest symptoms is pain coming on about 36-48 hours after the injury, and becoming progressively more severe. A marked rapid rise of pulse rate about the same time is to be expected. Such a combination of symptoms should lead one to a careful inspection of the injured part. The area does not have the physical characteristics of a pyogenic abscess. There is no redness or increased surface temperature. The skin overlying the lesion is exceedingly tender with alternating anemic and discolored reddish-black patches. The discharge from the wound is not purulent but an irritating brownish watery fluid with a sickly foul odor. Later, as the edema increases and the gas develops, it becomes dusky and bronzed in appearance. The systemic signs accompanying such an infection afford a strong contrast to those of other types of localized infection. Uncomplicated gas bacillus infection causes an extremely rapid and easily compressible pulse. There is an alarming fall in blood pressure and all the signs of complete collapse are noted. The degree of fever is incommensurate with the rapidity of the pulse rate. The patient is listless and apathetic. The customary malar flush
associated with a pyogenic infection is replaced by a striking pallor. Furthermore, when the infection spreads, it is more likely to do so into adjacent muscle rather than to produce a general bacterial infection of the blood stream with multiple abscesses. (5)

In virulent cases, the initial symptom is usually spontaneous pain or a sudden increase in the intensity of pre-existing pain. This comes on from 18-24 hours after the injury occurs. Shortly thereafter, or in a few cases before pain is felt, a distinct and rapidly developing distention appears about the traumatized tissues. This is not due to the formation of gas, but rather to the outpouring of a serous exudate. Accompanying these are an alarming rapidity and feebleness of the pulse, a peculiar grayish pallor, vomiting and weakness. The circulatory collapse is abrupt, progressive and so severe that one might suspect an internal hemorrhage. It is out of all proportion to the local injury. The temperature is rarely above 102 degrees F. As the swelling about the wound increases, the overlying skin becomes tense and blanched. The discharge from the wound is at first a dirty brown fluid, which saturates the air around the patient with the foul odor of rotting meat. In a few hours the formation of gas within the deeper tissues increases the swelling of the part. The overlying skin becomes raised and consequently dusky and discolored, vesicles appear on its surface as lymphatic channels and venous channels become occluded. The discharge from the wound forms a gelatinous mass in which bubbles of gas can be seen. The portion of the limb distal to the infection becomes engorged, discolored, and cold as its circulation is obstructed. In the meantime the patient's pulse rate has become increasingly rapid and the amplitude of the pulse steadily smaller. The mental state is one of apathy and torpor, the patient is quite conscious
but fails to apprehend the seriousness of his condition. If untreated, the skin over the necrotic tissue sloughs and the distal portion of the limb becomes gangrenous. These patients succumb within 18 to 24 hours after the onset of the symptoms, unless heroic measures are instituted immediately. (5)

Emrys-Roberts and Cowell (23) consider three main clinical types in a discussion of the symptomatology of gas gangrene infections.

A. The common type which occurs in neglected wounds 12-24 hours after the injury or a few hours after the 1st operation. Occasionally a patient comes before the surgeon with the condition well established. Clinically the patient may exhibit much suffering from an anatomically trivial wound, he looks ill; he is flushed, has 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" increases, the flush is replaced by a pallor, finally a pale lemon color of the skin appears, and sclerae become distinctly icteric.

The patient is now profoundly ill. His tongue is dry and foul the pulse is running and soon imperceptible, respiration is rapid and shallow. Vomiting is usually a distressing feature, and in the last stage, becoming black from petechial hemorrhages. Mentally these patients are perfectly clear, and it is not uncommon to see a man smoking a cigarette or reading a newspaper a few minutes before death. Mild deleriums may be frequent but not common. In cases of a deep penetrating wound, as for instance in the calf of the leg, the seriousness of the general condition gives rise to the suspicion that deep gas gangrene is established. It is in such wound of the lower extremity where the main blood
vessels are especially liable to injury, that the massive or vascular type develops. The ischemia thus produced favors the growth of the organisms, and once gangrene is established, the feeble, collateral circulation is progressively impeded until the whole limb is dead.

In the later stages of an infected penetrating wound changes in the overlying skin occur which indicate the site of origin of the toxemia. The pallor of tense skin is followed by a reddish blush, soon becoming a dusky violet, which spreads rapidly from the edge of the wound. The coloring may be uniform or mottled. At this stage, if the dead and infected tissues are removed, as by amputations, the color soon fades and after 24 hours leaves nothing but a slight desquamation; otherwise blisters next appear and increase rapidly in size. Finally, as the tissues begin to undergo lytic changes, the green and black colors of decomposition appear. The presence of gas may be appreciated after a few hours, but should always be regarded as a late phenomenon. If such cases are untreated, the infection runs its course and ends fatally in 12–24 hours after the date of injury.

B. The Fulminating type—In the common type the rapidity of the spread of infection is striking; but in the fulminating type the spread of the sequence of events is even more dramatic. The patient is admitted to the hospital in the gravest possible condition with well-developed gas gangrene a few hours after being injured. This is especially likely under the following conditions where both shock and loss of blood are present:

1. In cases of gross gun shot injuries of bones with extensive laceration of muscles.

2. In multiple wounds of the trunk and lower extremities.
3. In penetrating wounds of the limbs completely involving
the main blood supply or in rare cases where a tourniquet has been
applied and over-looked.

In these cases before the initial shock has had time to pass,
and the patient has recovered from 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 infections, that combines to produce these fulminating cases.

Such patients when seen on admission are cold, pale, restless,
and probably vomiting. The mucous membranes and extremities are cyanosed;
the pulse is imperceptible at the wrist, and the systolic blood pressure
is about 50 mm. of mercury. Locally, the wound exhibits the character-
istic odor and signs of dead muscle, with the surface color changes al-
ready described. In these cases extensive gas formation may occur after
a very short space of time. When in this state, the patient cannot stand
much surgical interference and death takes place in 10-24 hrs. or even
less, after the time of injury.

C. The delayed type—With a slow onset so that the condition
only becomes established several days, or even weeks after the date of
the wound. Here both the local and general resisting powers of the
patient have succeeded up to a point, and the latent infection is at
first limited to the surface of the wound. At the original operation the
wound was freely laid open and cleaned up. After a day or two the surface
does not granulate as it should, and soon after constitutional symptoms
develop, showing that that the latent period has come to an end and the
infection has began to spread inwards. This process may occur several
weeks after the original wound.
The diagnosis of gas infections must depend not only on one's ability to judge clinical findings, but on the laboratory aids as well, since positive cultures from the wound and positive blood cultures can be obtained. If one were to tabulate, in the order of their importance, these diagnostic aids, they would be as follows-

(1) Pain, which is the most common symptom; (2) Swelling, which is the most common sign; (3) Elevation of pulse rate; (4) Bacteriological findings—that is, smear from the wound and cultures of the blood; (5) Discoloration; (6) The presence of crepitus in the tissues or of gas in the exudate; (7) A bad odor, which is said to be characteristic, but which again is not a constant sign; (8) Elevation of temperature, which at times, however, is not important; and (9) The presence of gas bubbles in the roentgenogram of the affected part.

Nearly all who have written on this subject agree that pain of severe degree is probably the earliest, if not the most common symptom found in cases of gas gangrene or gas infection. Accompanying this pain is swelling, which is usually of a firm type, without much fluctuation, until necrosis is well established. Probably one of the most significant of the early signs is elevation of the pulse rate. While this is, of course, not diagnostic of gas infections alone, yet it is one of the earliest and most definite signs of a change in a patient's condition. As a rule, elevation of the pulse rate is out of proportion to the elevation of temperature. When this is observed to be the case, some infection should be suspected, and a smear and a culture of the wound should be taken. If the smear shows organisms of suspicious appearance to one familiar with the examination of such smears, the author feels that institution of treatment by administration
of gas gangrene antitoxin is justified. The report of the culture will
necessarily be delayed and one should not wait to receive it before
commencing treatment when gas infection is suspected. (32)

Discoloration of the skin is at first reddish; it later be­
comes grayish yellow, and finally cyanotic. Crepitus is one of the signs
looked for most frequently and considered as characteristic. It is
characteristic of gas infections, but may not be present in all
anaerobic infections, as it has already been pointed out that some of
them are not gas producing and yet are as pathogenic. Bubbles of gas in
the exudate or pus are usually looked for and, in most instances, are
found, but again it should be emphasized that, in spite of the name
"gas gangrene", there are allied conditions just as pathogenic which do
not produce gas.

The odor is said to be characteristic; it is interesting to
read the various attempts to describe it. One author says the odor is
"that of rotting meat"; another declares "It smells something like a
mouse"; a third states "The odor is putrefactive, offensive, almost
indescribable but once encountered will never be forgotten. It is ob­
vvious that an attempt to describe the odor so that anyone can recog­
nize it is out of the question. From what already been said, it must
be clear that in some cases the odor may not be so characteristic and
he who diagnoses the condition on odor alone may come to grief. (32)

Elevation of temperature as has already been pointed out, is
not in proportion to the elevation of the pulse rate; as in the case
of infection by Vibrion Septique reported by the author, the temperature
was elevated one day only and throughout the rest of the fatal course
of one week remained normal or sub-normal.
From the foregoing account it is seen that in established cases the clinical picture is so striking that the pungent smell, color changes of dead muscle and grave constitutional changes never remain long in doubt. It is in the earliest stages of the common type that the importance of immediate diagnosis lies. Here, if attention is paid to the local physical signs found in the wound, a diagnosis can be made before the general symptoms have had time to develop.

Davis (18), in 1916, brought out the value of Roentgen ray diagnosis in gas and pus infections in which a "halo-like" shadow was usually present, either locally around the foreign body in the substance of the tissues or a regular or elongated expanding halo along the track of the foreign body or in the fascial planes. The value of this added armamentarium to the diagnosis of gas bacillus infection can not be too strongly stressed.

Sprague (64) and Schneider (62) recently re-emphasized the importance of roentgenography in diagnosis of gas gangrene of the extremities.

Air emphysema of the extremities is differentiated by the lack of local tissue changes and uncomplicated clinical course. (17)

Twenty years ago Davis (18) described the x-ray findings of gas as follows:

It was a routine procedure at the Twenty-third General Hospital to Roentgen ray all bullet or shell wounds, when the missile was suspected of remaining in the body. Also it was their custom to have two views; an anter-posterior and a lateral, before starting any surgical interference aiming to remove the foreign body.

As a large percentage of these cases were bullet or shell
injuries, they had an excellent opportunity of studying and drawing conclusions from their Roentgen ray findings.

In all cases where the Roentgen ray showed a "halo-like" shadow about the missile, they also found clinically, at the operating table and in the laboratory, evidence of an infection caused by gas and pus-forming organisms. (18)

The Roentgen ray pictures of these cases may best be described by dividing them into two groups: In the first the gas and pus infection is local or limited and a single "halo-like" shadow is noted about the bullet, sometimes encircling it like a halo, or more often extending in one or more directions from it, either above or below or laterally. This shadow may have a diameter of half an inch or as large as two inches. The local picture may be composed of a number of small irregularly round or elongated shadow areas in close relation to the bullet or extending along the track of the missile.

The Roentgen ray picture in the second group of cases, that is in those cases in which the gas and pus infection is more or less extensive, shows a shadow similar to that noted in the first group, plus shadows extending upward and downward for a considerable distance, according to the extent of the infection.

Clinically these cases early manifest definite symptoms. The patient complains of severe pains in the region of the missile. He feels sick, weak, and is very restless. There is a marked rise in temperature and increase in the pulse rate. Locally one finds a swelling which may be confined to the area about the missile, or in more severe or extensive cases, the entire diameter of the limb may be increased and indurated. A point of exquisite tenderness will at times help the operator
to localize the missile. On palpitation with moderate pressure, a crackling sensation—crepitation—is imparted to the examining hand, and gas bubbles may be seen to escape through pus at the wound of entrance of the missile.

At operation one finds along the entrance wound and about the missile, a generous pocket of thick pus, which has a pinkish color and gives a characteristic gas odor. This may be localized about the missile or in more severe cases extend up along the muscular planes.

The laboratory examination of the pus shows in about 95 per cent of the cases the B. Welchii, with accompanying pus organisms; namely the staphylococcus, streptococcus, colon bacillus, tetanus bacillus, etc.

They found the Roentgen ray picture here described so constantly in cases which gave this same clinical, laboratory and operating room findings that they believe it to be of considerable value. (18)

In cases where the missile has been allowed to remain in the body and clinical symptoms develop, they request a Roentgen ray to see if this finding has developed. If this picture is encountered when raying to localize a missile, it is an indication for urgent surgical interference.

Today the presence of gas bubbles in the roentgenogram of the affected part is regarded by some as of great value in diagnosis. This may no doubt be regarded as a valuable aid in diagnosis but it cannot be pathognomic. Ghormley(32) states that air bubbles are often seen in the roentgenograms of cases of compound fractures, as well as in those cases of interstitial emphysema. He feels that unless roentgenograms are taken repeatedly and an increase in the number or size of the gas bubbles can be demonstrated, the observation cannot be said to carry much weight in
making the diagnosis as far as traumatic lesions are concerned.
TREATMENT

PROPHYLAXIS
The treatment of gas bacillus infections of the extremities resolves into an early recognition of the symptomatology and the immediate institution of prophylactic and active therapeutic measures available. The ever increasing number of cases of gas bacillus infections being seen in civil life today may be attributed to a certain extent, to the hesitancy to utilize proper measures available or to sheer ignorance of the morbid prognosis of crushing injuries of the extremities. The anticipation of complications of any "dirty" wound will serve as a reminder for instituting prophylactic measures.

**PROPHYLAXIS**

The prophylactic treatment for gas bacillus infections of the extremities resolves itself into the evaluation as to what wounds are apt to give rise to gas gangrene. After a careful physical examination and history is taken relating to the manner in which the injury was sustained, and eliciting such criteria as whether the patient was injured near soil contaminated by excreta of farm or domestic animals, the examining physician should be on guard for the possibilities of B. Welchii and other anaerobic infections. If there is much maceration and crushing of tissue, with or without fracture, an extensive debridement operation is immediately performed under either local or general anesthesia, (the type of general anesthesia will be discussed in a subsequent paragraph). The wound should be irrigated with oxidizing agents such as hydrogen peroxide, potassium permanganate solution 1:500, Dakin's solution, potassium chlorate 2 per cent, and other similar solutions. (17)

Intravenous infusion of 2.5% of glucose and .45% saline solution will sustain the patient during the immediate shock. External heat is advisable, and morphine, grains one-sixth to one-fourth should be used p.r.n.
The use of commercial prophylactic tetanus and gas gangrene antitoxins is to be highly commended, since the usual dose contains 1500 units tetanus antitoxin, 2000 units B. Welchii antitoxin, and 2000 units Vibrion Septique antitoxin. This is given in one dose, and usually suffices in the less extensive injuries. However, it may be repeated every other day for three days, if in the judgement of the surgeon the extent of the injury warrants it. Careful precautions must be used to guard against horse serum reactions, and the usual inter-dermal tests should be performed before each injection, and any manifestation of anaphylactic reaction should be treated with Epinephrine hydrochloride 1-1000 solution. An ounce of prevention in these types of injuries is worth a pound of cure.

Hanchett (39), in a paper before the Western Surgical association in 1934, re-emphasized the value of effective prophylaxis, debridement and delayed suture in all massive contused and lacerated wounds, and compound fractures; polyvalent serum associated with active surgery seem to give the best results in his cases.
ACTIVE TREATMENT

SEROTHERAPY PLUS SURGERY.
The active treatment of gas gangrene of the extremities must be instituted as soon as the earliest symptoms arise; diagnosis already established by methods indicated in previous paragraphs. One should then proceed unhesitatingly to administer the proper serum and surgical procedures which today have been very effective in decreasing the mortality and morbidity of the anaerobic infections.

During the World War the treatment of this condition was primarily surgical since no effective anti-serum had as yet been manufactured commercially. Albrecht (1) in 1917 says that in established gaseous gangrene the best remedy is operation as quickly as possible. Incisions should be long and deep, not only in the apparently affected tissues, but also into apparently healthy tissues. Or, instead of a single, very deep incision, several smaller incisions may be made. This course is necessary in healthy tissue, because the gas accumulations are signs of an advanced process and beneath these gas accumulations there is a large zone of tissue without evident alterations, but in which active bacilli are widely diffused.

If necrosis is extensive, amputation may be necessary, and if the amputation is not made in safe healthy tissue, wide and deep incisions will have to be made in the stump.

Some refractory cases resist even the most radical treatment. Such show the typical yellow pallid tint; anguished facies; pale cyanotic coloration of the lips; a strong halo in the eyes; profound general agitation; and with terrible pain death comes rapidly. Albrecht holds that death is due to the direct action of the toxin on the heart. Regarding the similarity of the syndrome is these lethal cases with the syndrome of complete cessation of the suprarenal function, Albrecht
has examined the supra-renal organs in many of the cases and found them profoundly altered, especially there diminution and disappearance of supra-renal lipoid substance. Hence, Albrecht (1) has proposed that in the surgically treated cases subcutaneous injections of half to one mg. of adrenalin be made before or immediately after operation; the dose to be repeated on successive days. He believes that he has saved some lives by this method.

Van Buren (69) in 1917 enumerates the important point used in the treatment directed towards the prevention of gas gangrene at that time as follows: (1) Operate as soon as possible; (2) Use nitrous oxide anesthesia if possible; (3) Prepare the part with the minimum amount of delay and trauma; (4) Avoid the use of tourniquets; (5) Make incisions longitudinally both in skin and fascia; (6) Go between, rather than through normal muscle and do not cut across them unless you have to; (7) Open the wound as thoroughly and freely as you possibly can; (8) Excise all torn, crushed, discolored, non-contractile muscle until you have left only that which is firm, of normal color, actively contractile and which bleeds easily; (9) Make a careful search for and remove all loose bone and foreign bodies and blood clots; (10) Stop the bleeding, leave the wound wide open and separate the walls with gauze laid in, not packed in; (11) Spray the wound with one percent aqueous solution of genetian violet every two hours until granulation tissue makes its appearance.

It was not, however, until 1917 that Bull and Pritchett (11) made their remarkable discovery of an anti-toxin for the exotoxin of the gas bacillus which they had previously had discovered and reported. Even though their solutions of anti-toxin were quite crude, even today
changes are being made to increase its potency. However, since the
time of their discovery of the antitoxin, sera therapy has been
combined with surgery as a more active and widely accepted form of
treatment.

Glotowa, Ostrowski and Ssilanowa (33), in 1935, in an eval-
uation of gas gangrene sera state "that in the therapeutic treatment of
gas edema disease the B. Welchii and Oedematien sera are of especial
importance since the B. Welchii as the gangrene stimulus (or excitant)
plays the chief part and the B. Oedematiens of more common occurrence
accordingly has second place, yet it builds up the most toxic microbial
irritation in gangrene and therefore causes the worst course of all the
gas edema diseases. But also the Vibrion Septique and the B. Histolyticus
are very significant in gangrene pathogenesis, although much less en-
countered in the wounds of patients. For these reasons the preparation
of excellent curative sera and the possibility of their evaluation are
of the greatest importance."

The authors summarize their report with the following:

1. The evaluation of gas edema sera (anti oedematiens, vibrion
septique, and histolyticus) through intravenous incorporation into
white mice, analogous to the international standardization method for
B. Welchii anti-serum, gives exact results.

2. An international simple proportional evaluation method for
all gas edemas (oedematien, vibrio septique, and histolyticus) analogous
to the international titration for B. Welchii serum is very urgently
called for. Also the production of international standard gas gangrene
sera and its taxation for all countries undertaking its manufacture, are
extremely desirable.
Bearing in mind these things, one should use only those commercial preparations available which contain the aforementioned types of antitoxin. The usual combined gas gangrene antitoxin available today contains 10,000 units B. Welchii antitoxin and 10,000 units Vibrio Septique, and does not contain the other two mentioned organisms. Davis (17) feels that this is an unfortunate situation and it is hoped in the near future a polyvalent gas edema antitoxin will be made available according to the standards as brought out by Glotowa, et al.

The antitoxin should be given in massive doses, since the toxemia and local tissue reaction is very great. The use of 50,000 to 100,000 units is obligatory. Here again we wish to caution the surgeon against hesitancy as to the intensive therapy. In some cases, the cost of administration is so exorbitant that in many cases patients will be unable to afford this excellent therapeutic measure. Davis, therefore advocates that in those cases in which the patients financial means prohibit him from obtaining the benefits of antitoxin therapy, the local or state health Depts. should have antitoxin available in much the same manner as for diphtheria, and other infectious diseases.

The exact surgical procedure to follow in any given case is a difficult thing to determine until the presenting symptoms indicate the course of treatment.-

1. Where there is much distortion of anatomical continuity of the structures one is more or less forced into radical procedures to preserve the life of the patient rather than the limb, therefore, where there is extensive crushing of the soft tissue parts, accompanied with or without fracture of the bone, a guillotine amputation under scopolamine, morphine and gas anesthesia is indicated. It has been the ex-
perience of Davis (17), that ether anesthesia has a deleterious effect upon the operative course of these patients. The exact nature of this is hard to determine, but the ether effect appears to be synergistic with the disseminated toxins of the infective organisms. Therefore, he advises amputation of the guillotine type, high above the level of spreading infection which can be readily ascertained by the use of the Roentgen ray. When the Roentgen ray picture shows the gas formation in single or isolated halo-like areas or about a foreign body which might be compared to a local staphylococcus like type of abscess in extent, local surgical procedures as debridement, excision, etc., with drainage are indicated. When the Roentgen ray picture shows the gas an extensive honey combing generalized, streptococcus-like in extent involvement, a guillotine amputation is indicated. Secondary prosthesis may be done at a later date when all signs of infection disappear and the patient is entirely recovered from the effects of the toxemia and surgery. The viable stump should be carefully preserved and guarded against secondary trauma since it has been shown that recurrences of the gas badillus infections may occur after surgery.

2. Where there is not much destruction of the tissues due to the injury conservative surgical measures are indicated. Numerous methods of therapy have been advocated and they feel that too much stress cannot be placed upon the free incision of the wound along the fascial planes and nerve sheaths, followed by the continuous irrigation of the wound with hydrogen peroxide, potassium permanganate 1-500 or Dakin solution. (17) Fidean-Green (26) advocate the use of O2 gas in the form of a continuous irrigation. Physiologically this method is very logical.
Warthen (72) in his account on the present treatment at the Medical College of Virginia Hospitals gives what I think to be about the most widely accepted viewpoints as to the general management of these types of cases. From his account I will again quote freely as it agrees with practically all modern day writers upon this infection.

All penetrating or crushing injuries, especially when contaminated are treated as potential gas bacillus infections. The wounds are excised, preferably under a general anesthetic, all foreign material is sought and removed and light dressings are applied which permit frequent inspection of the part. After testing the patient for sensitivity to horse serum, a prophylactic injection of five cubic centimeters of gas gangrene antitoxin is given intra-muscularly. This contains 1,500 units of antitetanic serum and 1,000 units each of B. Welchii and Vibrion Septique anti-toxin. A secondary prophylactic injection is frequently given 12 hours later and in very extensive injuries a therapeutic dose of twenty cubic centimeters, containing 10,000 units each of B. Welchii and Vibrion Septique antitoxin, is injected intra-muscularly. The patient is closely observed during the next few days for local or general manifestations of gas gangrene. Excessive pain in the incision or tenderness over the large vessels supplying the part is suggestive of a beginning gas bacillus infection. An increasing pulse rate is frequently the first sign of an early infection and always calls for an inspection of the wound. A markedly elevated temperature is sometimes present at the onset of the infection but the absence of fever is never reassuring, as well advanced gas gangrene may be accompanied by a normal or even subnormal temperature. Careful palpation over a suspected incision with the hand encased in a sterile glove is the surest method of determining the
presence of an early gas infection. If air trapped in the incision at the time of operation and subcutaneous emphysema from pulmonary injury can be excluded, the characteristic fine creptus is virtually pathognomonic of an underlying gas bacillus infection. The removal of sutures and demonstration of large square cut Gram-positive bacilli in the thin brownish offensive discharge completes the diagnosis for all practical purposes. Valuable time will be lost if operation is withheld until positive anaerobic cultures are obtained and only in exceptional cases is this delay justified.

A debridement under spinal or general anesthesia is immediately done through a generous skin incision with excision of all diseased muscle and thorough exposure and drainage of all involved portions of the wound. Bleeding is carefully checked, the margins of the incision are spread apart and dry gauze is loosely packed throughout the wound. The dressing is moistened at hourly intervals by one of several solutions. Dakin's solution is used when large vessels are exposed, but the danger of secondary hemorrhage frequently necessitates the substitution of potassium permanganate 1:5000 or 1/2 strength hydrogen peroxide. The latter solution is avoided when the margins of the wound are undermined, as further extension may result from bubbles dissecting beneath the tissues. Therapeutic doses of gas gangrene antitoxin are injected intramuscularly or intra-venously at intervals of four to eight hours, depending upon the extent and virulence of the infection. Twelve hours after operation the gauze is removed and the wound is inspected. Any suspicious areas are carefully palpated with the gloved hand. If the infection is still present a further debridement may be done, and only in the exceptional case is it necessary to resort to a guillotine
amputation in order to check the spread of infection. In the majority of cases the primary debridement results in an immediate local and general improvement. If the wound appears satisfactory, compresses are begun or carrel tubes are inserted and irrigations are continued until all slough has separated and healthy granulations appear.

The blood destruction incident to gas gangrene rapidly produces a profound anemia and frequent blood transfusions are necessary. Whole blood is usually given by the multiple syringe method, especial care being taken that the syringes are used only once, other-wise infection may be carried from the recipient to the donor.

This method was followed in his their last fifteen cases of gas gangrene with considerable success. Only one fatality occurred in this series, and only 3 amputations were necessary. A comparison with the earlier non-antitoxin cases of which there were 8 amputations done out of nine cases, shows or indicates that these favorable results have been due in a large measure to repeated injections of therapeutic doses of gas gangrene antitoxin. Prophylactic doses of the antitoxin are not always preventive, but appear to be of definite value even in the case which subsequently develops gas gangrene, for gas bacillus infection which develops following prophylactic injections appear to be milder and more amenable to subsequent specific treatment.

Ghormley (32) in his series of cases of cases reported from The Mayo Clinic in 1935 used an average of 2 doses of the antitoxin in each case of 33. In many instances, the intra-venous dose was followed in a few hours by an intramuscular dose. He states that no less important than the use of antitoxin is the use of the proper surgical procedures. The state of progress has not yet been reached where these
patients can be cured by antitoxin alone, and one must not expect it. Surgical judgement and execution must play a very important part in the treatment. (32)

Boland (8) in his series of cases reported from the Grady Hospital, Atlanta, also used the combination of serum therapy and proper surgical procedures in all of his cases. He states that the treatment of a compound fracture complicated with gas gangrene resolves itself into treating the gangrene, and treating it as promptly and vigorously as possible. If its spread is not controlled, death from septicemia, toxemia, or possibly gas embolism, is almost the invariable outcome. The alignment of the broken bones can be taken care of later, and the patient will be fortunate indeed if, after he is rid of the lethal infection, there are bones to be aligned. More than likely the fracture will disappear in an amputation. He further states that simple fractures require more consideration from the surgeon than reading an x-ray report and the application of splints; compound fractures demand unremitting care to avoid serious contamination and give the best possible end result, while the attention and judgement necessary to save a limb or life in a compound fracture infected with gas bacilli equals that of any problem in surgery.
X-RAY THERAPY PLUS SERUM
Recently Kelly (47) and Faust (24) have reported the successful use of x-ray irradiation in the treatment of gas gangrene. Faust states that there are several possible theories in the action of the x-rays but as yet no one knows the exact mechanism. But since the results obtained were favorable it is believed the methods of therapy should be given publicity for the good that it may do.

One explanation of the action of the x-ray is that when x-rays are played upon nutrient fluids they are deadly to protozoa by producing small quantities of hydrogen peroxide; the presence of hydrogen peroxide would be fatal therefore to the B. Welchii and other anaerobic organisms. Due to the absorption of the hydrogen peroxide the x-ray treatments need to be frequent in order to produce more of the gas.

Another theory of the action of the x-ray is that it causes the tissue to throw out a protein which may be resistant to the toxin of the gas gangrene organisms. The x-ray may act as a catalytic agent by aiding the serum to act on the toxin in those cases in which the antitoxin therapy is given.

The present status of the X-rays as an aid in the treatment of gas gangrene as given by Kelly. (48)

In 1928 the author was called in and asked if he had anything in the x-ray or physical therapy department which might help in treating a severe case of gas gangrene. At this time any surgical procedure was deemed unwise as the infection had spread to the groin and the patient was delirious.

He was given small doses of x-ray twice a day which almost seemed as it would do no good, yet the response was so remarkable
and the recovery so rapid that the incident remained in his memory and, in a few cases following this, similar treatment was given with the same startling results. In all, over a three year period, eight cases were treated which is called the first series.

In the first series, there were eight cases in which x-ray treatment and gas bacillus serum were given. In this series there were two deaths. Further analysis showed that both of these deaths occurred in the cases in which the trunk was involved. Recovery occurred in all six cases in which the extremities were involved.

The conclusions drawn after analyzing the results in the first series were that the x-rays were very probably of definite value in the treatment of gas bacillus infection, when the extremity was involved, but since death occurred in both cases in which the trunk was involved, certainly there was no evidence of its value in these cases. However, realizing that they used a very low voltage type of radiation, they thought that by increasing the voltage and depth dose they might be more successful in the future when the trunk was involved if they gave a heavier type of radiation. The recommendations they then made to the Radiological Society of North America in 1931 was that more cases be treated with x-rays when the opportunity presented and if the trunk were involved, to give heavier doses. After a period of three years during which time they treated 2 cases, one in which the trunk was involved and one in which the extremity was involved, both patients living, they wrote a letter to several colleagues who had treated cases and collected as much data as possible on their work. To their two cases they added thirty more. These 30 plus the two making 32 they put in a second series.

In the second series, of 32 cases treated with the x-rays, serum
was administered in only thirty cases. However they were more anxious
to know the effect of the x-rays in the trunk cases as compared with the
extremity cases, so they divided them accordingly. There were eight cases
with trunk involvement and all eight patients lived, while of the 24
with extremity involvement, five died. These results were somewhat
contrary to the results in the first series. The results in the first
series would lead one to believe that recovery should occur in all cases
in which an extremity is involved and that death should occur in all
trunk cases, while results in the second series would lead one to believe
that recovery should occur in all the trunk cases and that death should
occur in at least some of extremity cases, since there were five deaths
in this group.

Further analysis of the extremity cases in the second series
brings out these facts; namely, that there were thirteen cases of the
twenty-four in the extremity group in which amputation was not done and
the thirteen patients lived, and out of the remaining eleven extremity
cases in which amputation was done only six patients lived and five died.

The proportion dead in this small series who had amputation
was 45%. They then combined all the cases in the first and second series
and they are shown in the table below:

| Total cases--------1st and 2nd series |
|-----------------|----------------|--------|--------|--------|--------|
| Trunk cases     | No amputation  | Amputation | Living | Dead   | % dead |
| 10              | 10             | 0         | 8      | 2      | 20     |
| Extremity cases | No amputation  | Amputation | Living | Dead   | % dead |
| 30              | 17             | 17        | 17     | 0      | 0      |
|                 |                | 13        | 8      | 5      | 39     |

The figures in this table above show the relative mortality
in the trunk and extremity cases of the first two series of 40 patients.
The table shows ten trunk cases and thirty extremity cases. The two dead in the trunk group occurred in the first series and they believe that as far as x-ray therapy is considered the result may be attributed to inadequate treatment. The next fact evident is in the no amputation group and this is indeed startling. In the extremity group of seventeen cases in which amputation was not performed there were no deaths, 17 cases of gas bacillus infection with 100% recovery. In the extremity group in which amputation was performed the result was not so good; there were 13 cases with five deaths, or a mortality of 39%; and this about the usual mortality in other series reported in the literature.

The reason for the high mortality in the second series in the extremity cases led them to investigate the hospital records of the five patients who died and it brought to light these following facts-1st man died on the ninth day after a ligature had sluffed off of a large vessel; he was apparently over his gas gangrene. The second man died of pulmonary embolism on the 23rd day. The third, fourth and fifth persons died from shock of amputation. They did not, however, receive sufficient amount of x-ray therapy.

In a final analysis of these five deaths in the second series, one might honestly eliminate 2 of the 5 cases in which death occurred, as far as gas bacillus infection as a cause of death is considered—due to the fact that one patient probably bled to death while the other died of a pulmonary embolism on the 23rd day following some work on the stump. In the other three deaths in the amputation group gas gangrene cannot so easily be ruled out as a factor, and these 3 deaths with the 2 deaths in the trunk cases in the first series make a total of 5 deaths due to gas gangrene in the first and second series.
Encouraged by the results obtained using the x-rays as an aid in treating gas bacillus infection in the first 2 series, they decided to send a questionnaire to radiologists and surgeons throughout the country who they thought might have had some experience with the work and in answer to this questionnaire they received data on sixteen additional cases. All of the sixteen patients lived and that is the result they hoped to attain at the time they reported their first series; namely, that others throughout the country would treat gas bacillus infection with the x-rays when the opportunity presented itself and by this means the results of the x-rays would more quickly be determined. They hope of course that the day will come when all patients with gas gangrene, when an adequate dosage of x-rays is used as an aid in treatment, will recover.

The results obtained in the third series are shown in the table below:

<table>
<thead>
<tr>
<th>Series:</th>
<th>No. of cases:</th>
<th>X-rays:</th>
<th>Serum:</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>16</td>
<td>16</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Extremity</th>
<th>Trunk</th>
<th>Living</th>
<th>Dead</th>
<th>% Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>2</td>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No serum</td>
<td>Living</td>
<td>Dead</td>
<td>% Dead</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

All sixteen patients had x-ray treatments but only 11 had serum. All lived so evidently the five in this group who received no serum recovered.

As regards to the status of amputation, this series adds definitely to the opinion they have held for some time; namely, that it is an unnecessary therapeutic procedure. There were 12 patients who did not receive amputation and all 12 lived. Two patients in the series received amputations and lived regardless of that fact.
Mortality rate in the three series.

<table>
<thead>
<tr>
<th>Series</th>
<th>No. of cases</th>
<th>Living</th>
<th>Dead</th>
<th>% Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>2.</td>
<td>32</td>
<td>27</td>
<td>3</td>
<td>9.3</td>
</tr>
<tr>
<td>3.</td>
<td>16</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

In the above table the mortality rate of the three series is compared. In the first series the death rate was 25%. In the second series it was 9.3% and in the third it was 0%.

The question of the use of serum is still undetermined. In the first series all patients received serum. In the second series 2 patients received no serum and recovered. In the third series 5 patients received no serum and recovered. So it can be seen that the seven patients in the three series who did not receive serum lived. However, in spite of this fact, they do not see fit to recommend the omission of the use of the serum at this time.

With regard to amputation, they are very emphatic in their belief that amputation is not a therapeutic procedure for gas bacillus infection.

There were 44 cases in which the extremity was involved. There were 29 in which amputations were not performed and all 29 patients lived. Out of the fifteen who had amputations, 5 died or a mortality of 33%.

In the table below, the mortality rate for the three series is tabulated.

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Living</th>
<th>Dead</th>
<th>% Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>56</td>
<td>51</td>
<td>5</td>
<td>8.9</td>
</tr>
</tbody>
</table>

Of 56 patients, 51 lived; 5 died of gas bacillus infection giving a mortality of 8.9%. They feel that this mortality rate compares favorably with any series of gas bacillus cases for far reported in the literature.

In concluding, it seems fair to state that the x-rays up to this
time seem to be definitely established as an aid in the treatment of gas gangrene both in extremity and trunk cases, but it seems desirable to use serum and other measures and refrain from amputations until the patient has recovered from shock and gas bacillus infection. Amputation may then be necessary in a badly damaged extremity. In one case of this series, this was done and gas gangrene recurred after amputation. The area was immediately treated and the gas infection subsided. Since there is so much shock connected with amputation and furthermore since the diseased area is not all eliminated by some of these amputations, it again seems worth while to omit amputations as an absolute therapeutic procedure for gas bacillus infection.

X-ray Technic:—The x-ray treatment should be given morning and evening over a period of at least three days and of sufficient voltage to insure penetration of the involved tissue—from 90 to 100 kilovolts on an extremity, 1 mm. aluminum filter, from 130 to 160 kilovolts on the trunk with increased filtration; about 100 roentgens per treatment over each area. (48)

Finally:—

1. Use x-rays in all cases.
2. Use serum unless contra-indicated.
3. Use tetanus antitoxin.
4. Use local surgical procedures and antiseptics as indicated.
5. Do not amputate for gas gangrene until all other therapeutic procedures have been tried and it is deemed absolutely necessary to save the patient's life.
In 1937 Bohlman (7) reported the use of sulfanilamide in the treatment of gas gangrene. Search of the literature fails to reveal the use of sulfanilamide heretofore in the treatment of gas gangrene. It appears to be a valuable adjunct in this respect and offers great promise with regard to saving limb and life.

Cases: W. C.-Negro youth, aged 15 received a transverse fracture of right femur in mid third and compound of left femur in lower third. Wound treated, dressed and reduced-1,500 units of tetanus antitoxin given-10,000 units of combined gas bacillus antitoxin were given-temperature to 102 degrees the 2nd day and fluctuated in an irregular manner-5th day leg greatly swollen, very much pain-dressing removed and gas heard to escape-crepitation felt from 4 inches above ankle to 3 inches of groin. No pus-patient very ill-showed extreme signs of toxicity. A wide incision was made from greater trochanter to just above ankle. Because of great distention and extreme toxicity, amputation offered little hope. So sulfanilamide therapy started immediately. Three 5 grain tablets every 6 hours for 2 days-2 tablets every 6 hours for 5 days and then 1 tablet every 3 hours for 2 days. 18 hours after first sulfanilamide given, patients temperature normal, no toxic symptoms. Excellent union was gotten in both legs after necrotic gangrenous areas sloughed and were expelled.

Case: A. C.-Negro, age 42, received extensive, multiple comminuted fractures of left tibia and fibula with similar injuries to the right lower leg and a compound wound over upper anterior third of right tibia. Considerable soft tissue damage; given prophylactic dose of tetanus and gas bacillus antitoxin. Third day temperature and pulse rose. Crepitation felt. The patient received 25 grains the first day, 75 the 2nd, then 30, 45, etc. The 2nd day after treatment started temperature
dropped to normal and toxic symptoms disappeared.

Case: - Miss M. C., age 21, received such severe injuries of right femur in an elevator accident that it warranted guillotine amputation as soon as her condition warranted it. Given usual prophylactic doses of gas bacillus and tetanus. Developed gas gangrene of the stump with severe signs of toxicity. Culture revealed B. Welchii. Sulfanilamide started-60 grains the first day-then 85-60-40-60-40 and so on, on successive days, then discontinued. Temperature and pulse dropped almost to normal. Patient progressed toward complete recovery.

Long is at present time conducting experiments with B. Welchii to determine the effect of sulfanilamide on their growth and phagocytosis. He believes that phagocytosis is not inhibited or enhanced by this drug, that it acts directly to inhibit the growth or multiplication of these bacilli and that its mechanism of action on other bacilli is similar. He states that a prophylactic effect has been noted whenever it has been used therapeutically in experimentation. He suggests that prophylactic doses of 2-3 tablets every 4 hours with 10 grains of NaHCO3 be given in all severe or crushing injuries in which infection with streptococci or gas bacilli might subsequently occur. (7)

SUMMARY

1. The Ist case represents an amazing, not to say dramatic result in a desperate case of gas gangrene. Cases 2 and 3 are confirmatory.

2. Sensible, conservative surgical principles should be combined with the use of sulfanilamide.

3. No previous record has been found of its employment in this manner.

4. Sulfanilamide probably has a specific effect on gas bacilli;
but the results may in part be due to checking symbiotic growth with the streptococcus.
PROGNOSIS
In search of the literature which occurred before the World War, no figures on the mortality rate of this condition could be found. It was not until the Surgeon General’s Report (60), that one finds any mortality statistics. According to this report, the death rate for the American Expeditionary Forces in France was 48.52% in cases of gas bacillus infections.

In certain series of war injuries reported by Van Buren (69), of 1168 cases treated without serum the mortality was 26%; of 575 treated with it the mortality was only 6%.

Weinberg and Sequin (75), who did much toward perfecting this serum, reported in 1918 60 cases so treated, with only 6 deaths, 2 of which were from other causes.

In reviewing the literature on gas gangrene in civil practice, the available statistics, while small, tend to show a gradual decrease in the mortality rate.

Miller (54) has reviewed the greatest No. of cases (607) and has presented a comprehensive summary of them.

<table>
<thead>
<tr>
<th>End Result:</th>
<th>No. of Cases:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery----48.0%</td>
<td>291</td>
</tr>
<tr>
<td>Death-------47.2%</td>
<td>287</td>
</tr>
<tr>
<td>Known Outcome</td>
<td></td>
</tr>
<tr>
<td>Unknown Outcome-----4.8%</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>607</td>
</tr>
</tbody>
</table>

One can see from the above figures that the mortality rate in his series of cases reported in civil life was approximately equal to those reported in the Surgeon General’s Report. However, if one makes a more comprehensive study of these cases and their treatment,
you will soon see that different types of treatment gave better results than one would gather from reading the mortality rate as given for the whole group. This is shown in the chart below.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Recovered</th>
<th>Died</th>
<th>Cases %</th>
<th>Not Stated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputations</td>
<td>71</td>
<td>50</td>
<td>41.3</td>
<td>7</td>
</tr>
<tr>
<td>Incision and drainage</td>
<td>57</td>
<td>64</td>
<td>52.9</td>
<td>4</td>
</tr>
<tr>
<td>Amputations and serum</td>
<td>19</td>
<td>21</td>
<td>52.5</td>
<td>0</td>
</tr>
<tr>
<td>Amputations and incision</td>
<td>23</td>
<td>8</td>
<td>22.3</td>
<td>2</td>
</tr>
<tr>
<td>Serum</td>
<td>15</td>
<td>7</td>
<td>31.8</td>
<td>0</td>
</tr>
<tr>
<td>Serum plus incisions</td>
<td>17</td>
<td>4</td>
<td>19.0</td>
<td>1</td>
</tr>
<tr>
<td>Amputations plus</td>
<td>7</td>
<td>7</td>
<td>50.0</td>
<td>1</td>
</tr>
<tr>
<td>incision and serum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscel. (rib resection-charcoal, etc.)</td>
<td>4</td>
<td>5</td>
<td>55.5</td>
<td>0</td>
</tr>
<tr>
<td>No. not stated and not surgically treated</td>
<td>73</td>
<td>121</td>
<td>49.7</td>
<td>29</td>
</tr>
<tr>
<td>Totals</td>
<td>607</td>
<td>291</td>
<td>287</td>
<td>29</td>
</tr>
</tbody>
</table>

So although the mortality rate of 49.7 is given for the whole series, it can readily be seen from the above chart that the cases treated by amputations and incision, by serum and by serum plus incisions gave much better mortality figures than that of the whole series.

In the series of Boland (8) of 15 cases reported in 1929, of which all were complications of compound fractures; two fractures involved the upper extremity and thirteen the lower; six patients died giving a mortality rate of 40%. The shock of amputation apparently was the immediate cause of death of one or two of the patients, but since the
operations were done to cure gas gangrene, and the patients would have died without such treatment, gas gangrene must be assigned as the cause of death.

Larson and Pulford (49), in an excellent review of the subject, in 1930, reported a death rate of 13% in a series of seven cases.

Stone and Holsinger (65), in 1934, reported 67 cases from the University of Virginia Hospital in a 12 year period; the mortality in this series was 32.4%. However, in those cases in which an adequate dose of antitoxin was given as part of the treatment, a mortality of only 15.3% was noted.

Ghormley (32), in 1935, gives the results in his series of 33 cases reported from The Mayo Clinic in the table shown below:

<table>
<thead>
<tr>
<th>End Results</th>
<th>No. of Cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition recognized and antitoxin given</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovered --------------------- 13</td>
<td>76.4</td>
<td></td>
</tr>
<tr>
<td>Died----------------------------- 4</td>
<td>23.6</td>
<td></td>
</tr>
<tr>
<td>Condition recognized and antitoxin not given</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovered-------------------------- 6</td>
<td>54.5</td>
<td></td>
</tr>
<tr>
<td>Died----------------------------- 5</td>
<td>45.5</td>
<td></td>
</tr>
<tr>
<td>Condition not recognized and antitoxin not given</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovered-------------------------- 0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Died----------------------------- 5</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

The findings indicate a mortality of 42.5%. This is somewhat below the percentage of the World War. However, in the above table, the cases are presented in a manner to show the value of gas gangrene antitoxin. Excluding the group of patients with abdominal involvement, most of whom were hopelessly ill and in the four of whom the condition was not diagnosed as such but was recognized at necropsy, the percent of them who recovered following the use of the antitoxin is high. Others
have reported similar results with the use of antitoxins. In general it may be said that, with recognition of the condition and a judicious combination of the use of antitoxin and surgery, a mortality of approximately 15% may be expected. Thus, the cases of gas gangrene and infection with gas bacilli encountered in a five year period at The Mayo Clinic excluding abdominal cases give the following results:

End Results.

<table>
<thead>
<tr>
<th>Antitoxin given.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovered</td>
<td>86.6</td>
</tr>
<tr>
<td>Died</td>
<td>13.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antitoxin not given.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovered</td>
<td>55.5</td>
</tr>
<tr>
<td>Died</td>
<td>44.5</td>
</tr>
</tbody>
</table>

As for the prophylactic use of the antitoxin is concerned, there is little opportunity to give any significant figures as yet. In the present series, one patient had only prophylactic doses of antitoxin, and it was felt that the infection was much mitigated by use of the antitoxin. Ghormley feels that the only way in which we can arrive at any definite conclusions in this regard is to wait until a large enough series of patients who have had prophylactic doses of antitoxin has been studied to permit a satisfactory comparison with a large series of patients who have not been given prophylactic doses of antitoxin. The later writers all deal with the importance of the use of gas gangrene antitoxin in such cases. The consensus of opinion is that antitoxin is of value in the treatment of the infection if administered as soon as the infection is recognized, and the earlier it is used the better. As yet, the statistics are far from sufficient to permit us to base any great claims on them, but the remarkable similarity between the figures presented by the various writers and those obtained at The Mayo Clinic in-
dicates a step toward improvement in the treatment of this condition.

Warthen (72), in 1935, reported upon 24 typical cases of gas gangrene treated in the Medical College of Virginia Hospitals from Jan. 1, 1931 to 1935. The first nine cases, treated between Jan. 1, 1931, and Jan. 1, 1932, did not receive prophylactic or therapeutic injections of gas gangrene antitoxin. Surgical measures alone were used in these early infections. The involved extremity was amputated in eight cases and an extensive debridement was done in the remaining case. One patient died, a mortality for the non-antitoxin cases of 11%. The average hospital stay was thirty-five days.

All cases of gas gangrene treated since Jan. 1, 1932, have received gas gangrene antitoxin. The majority of accident cases presenting extensive and crushing injuries received a prophylactic injection and all cases which developed the infection were treated by large therapeutic doses of gas gangrene antitoxin. Fifteen cases have been treated since Jan. 1, 1932. The surgical procedures have been less radical than those followed in the earlier infections. An extensive debridement was done in 12 instances and only three amputations were necessary. One patient in this series died, a mortality for the cases receiving gas bacillus antitoxin of only 6.6%. The average hospital stay was more than 69 days or approximately twice that of the non-antitoxin cases. The combined mortality of all cases of gas gangrene reported in this series by Warthen was 8.3%.

The mortality rate in the series reported by Kelly (48) in 1936 was given under the section of treatment as to the effect of x-rays and serum upon this condition. Of his 56 patients treated, 51 lived; 5 died of gas bacillus infection giving a mortality of 8.9%. Although seven patients in his series did not receive the serum and lived, Kelly still
believes that the use of antitoxin, used both prophylactically and therapeutically is very important in the treatment of gas gangrene.

Bohlman (7), in his report of 3 cases in 1937 with regard to the use of sulfanilamide in the treatment of gas gangrene, gives a 100% recovery in his small series of three cases. However, he does advise the use of proper surgical measures and antitoxin therapy along with this drug since it has not been used in enough cases to see if its results will warrant it as an accepted form of treatment or at least as a help in the treatment for gas gangrene.

It appears that the polyvalent serum given early, in sufficient amounts and frequency, by the intra-venous route will save life, limb and even tissue. Failure to observe these important rules probably accounts for some of the unsuccessful results of which one hears. Although it does not replace surgery and possibly x-ray, it is a valuable adjunct and seems to decrease the amount of surgery necessary.
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