

Part III

CLINICAL—GAS BACILLUS INFECTION

Chapter IX

HISTORY AND CLASSIFICATION

Gas gangrene has been selected for first consideration of the use of x-rays in the treatment of infections for two main reasons: (1) All the favorable changes in clinical signs, symptoms and results can be demonstrated in the study of a series of gas gangrene cases treated with x-ray. (2) The effects of x-rays in infections can be proved beyond question in the treatment of a series of gas gangrene cases, since no other therapeutic measure has ever been able (to this date) to bring about these same favorable changes in the clinical symptoms and signs or the same result.

Before proceeding to a consideration of the x-ray treatment of gas gangrene, a thorough review of every aspect of this disease seems essential. There seems to be no agreement among various writers as to what gas gangrene infection really is, and to make it clear what we consider gas gangrene to be, this detailed discussion including the early history of the disease is necessary. In this way it is hoped that some common ground for discussion of the disease can be established.

No consideration of gas gangrene or gas bacillus infection is complete without a brief preliminary discussion of the general term gangrene, which may be defined as necrosis due to the absence of blood supply, the result of infection with certain organisms or the local action of various drugs or toxins. There are a great many varieties; in fact, some classifications are so broad that they create a separate type for every possible factor which can cause a complete obstruction in the circulation or the local death of tissue. Obviously such a classification offers too many types for consideration. A few varieties need discussion because of the confusion in their pathogenesis, prognosis, and treatment, a fact only too evident to one who has attempted to analyze the data on several hundred questionnaires concerning the treatment of gas bacillus infection.

Any area of gangrenous tissue which is primarily dependent on some constitutional or local disease other than an infection may become secondarily infected with gas-forming organisms.

These organisms may be the immediate cause of death from toxemia. However, the underlying disease which caused the original area of gangrene in which these organisms developed is always an added, and often the deciding, factor in the patient's inability to repair the local gangrenous process or to withstand even a relatively mild toxemia resulting from infection.

A few of the commonest types of localized gangrene which often become secondarily infected with gas-forming organisms, either before or after some surgical procedure, require some consideration. They are: arteriosclerotic gangrene, diabetic gangrene, decubital gangrene, and post-traumatic gangrene.

Arteriosclerotic Gangrene.—An area of gangrene in an aged individual, usually on the lower extremity, caused by closure of the peripheral vessels incident to hardening and narrowing of these structures, is known as arteriosclerotic gangrene.

Diabetic Gangrene.—A diabetic patient may develop a true gangrenous area in a lower extremity or elsewhere in the body because of an association of factors incident to the underlying constitutional changes often present in diabetes; such an area is known as diabetic gangrene.

Decubital Gangrene.—A form of true gangrene commonly seen in debilitated patients, caused by a combination of pressure and trophic changes, is known as a bed sore or decubital gangrene.

These forms are true primary gangrene localized in the area of tissue deprived of its blood supply. They usually occur in patients in advanced years.

These areas of primary gangrene in elderly patients may become infected with gas-forming organisms, but these invaders seldom show an appreciable tendency to invade or produce toxins, or else their toxins are not absorbed. However, in the same individual, if the organisms reach an area with good blood supply, as is often the case after débridement or amputation, they immediately exhibit their tendencies to invade, to form gas, to produce toxins and to cause extensive gangrene.

In the first phase, before any surgery is performed, the patient is not considered clinically to have gas bacillus infection. But after surgery the most acute and serious form of gas bacillus infection develops, and its treatment eclipses all other clinical aspects of the case. The underlying constitutional dis-

ease, however, can never be entirely neglected, and hyperglycemia, if present, must be controlled.

X-ray therapy is used for these primary gangrenous areas infected with gas-forming organisms solely to influence the course of the infection; no change in the dead tissues caused by diabetes or arteriosclerosis can possibly be expected from x-ray therapy. In practically every case, early and adequate x-ray therapy will cause the gas infection to subside and prevent gangrene as a result of infection. But, after tissue is dead, regardless of the cause, no one ever thought or claimed that x-ray treatment would restore it to life.

The fourth type of gangrene is usually due to acute interference with the circulation. Location permitting, they constitute surgical emergencies.

Post-Traumatic Gangrene.—The traumatic form of gangrene which occasionally follows the accidental destruction of the circulation to an area but is not associated with any infection or constitutional disease may be seen in patients of any age. This form calls for prompt and adequate surgical measures and is only mentioned here to distinguish it from the gangrene which follows a gas bacillus infection. The latter, which also follows trauma of variable severity, does not necessarily destroy the vessels of the area involved but does have the essential factors of the presence of the toxin-producing, mixed infection. Briefly, post-traumatic gangrene is an area of gangrene due to the traumatic interruption of the circulation to a part. Infection plays no part in this type of gangrene.

Gas gangrene is gangrene found in the advanced stage of gas bacillus infection. This infection may occur in the tissues deprived of their blood supply by an injury, as described in post-traumatic gangrene, or it may develop in a less severely injured area even when the circulation is only slightly damaged.

In gas gangrene developing after a hypodermic injection, there is relatively little local damage to the tissues at the beginning, but the course of the gas bacillus infection is more fulminating and is associated with a higher mortality than other types of gas gangrene.

Of 10 or more other varieties of noninfectious gangrene, none is encountered with sufficient frequency to merit discussion here. None of these less common types should be confused with

gas gangrene; it must be remembered, however, that any of them may be complicated by a gas bacillus infection.

NOMENCLATURE AND HISTORY OF GAS GANGRENE

In addition to confusion arising from the varieties of gangrene, there is lack of agreement about the nomenclature applied to gas bacillus infection. This disagreement is easily understood because in earlier days little or nothing was known about the etiology of the disease or its mode of dissemination. A brief history, which is difficult to trace back in the literature with any certainty, follows.

Before 1900, all the different forms of gangrene had names more or less descriptive of the clinical stage in which they were seen by each observer; seldom did the name have any relation to the cause. Only in the occasional classic description of an advanced case of gas gangrene was the disease definitely recognized in the early literature. By this means alone, it is certain, however, that the disease was known at least as early as Hippocrates' time. His description of the disease was presented by Millar.¹

From then on, it can be followed down through the centuries as an acute, generally fatal toxemia which developed rapidly following various types of injuries associated with gas formation in the tissues and later gangrene. The helplessness of early surgeons in treating the condition is well shown by the following excerpts from Warren, whose comments about the disease in the last 50 years of the nineteenth century are interesting.

In the Crimea, during the summer of 1855, after the taking of the quarries and the assault in June on the Great Redan, not a few cases of amputation of the thigh were lost from "moist gangrene" of a most rapid and fatal form. In the case of a few, who lived long enough for the full development of the disease, gangrene in its most marked features became established, but most of the men expired previous to any sphacelus of the part, overwhelmed by the violent poison which seemed to pervade and destroy the whole economy.

Two cases under Macleod's own care, in men who had a limb utterly destroyed by round shot or by grape, are thus described: "During the night previous to death the patient was restless, but did not complain of any particular uneasiness. At the morning visit, the expression appeared unaccountably anxious and the pulse was slightly raised. The skin was moist and the tongue clean. By this time the stump felt, as

the patient expressed it, heavy like lead, and the burning stinging pain had begun to shoot through it. On removing the dressings the stump was found slightly swollen, and the discharge had become thin, gleet, colored with blood and having masses of matter like gruel occasionally mixed with it. A few hours afterward the limb became greatly swollen, the skin tense and white, and marked along its surface by prominent blue veins. The cut edges of the stump looked like pork. Acute pain was felt. The constitution had by this time begun to sympathize. A cold sweat covered the body, the stomach was irritable, and the pulse was weak and frequent. The respiration became short and hurried, giving evidence of the great oppression of which the patient so much complained. The heart's action gradually and surely got weaker till, from fourteen to sixteen hours from the first bad symptom, death relieved his sufferings."²

Macleod apparently was able to do little or nothing for these wounded and infected men; at any rate, he mentioned no attempt at treatment.

During our own Civil War, according to Warren, the disease was recognized under the general term of "hospital gangrene." The two principal types were the "ulcerating form," not related to gas gangrene, which ran a rather slow clinical course, and the "acute pulpy form" which, from the description, was undoubtedly what we call gas bacillus (gas gangrene) infection.

The lack of knowledge concerning the etiology and manner of dissemination of the disease during the period between the Civil War and the end of the century is well covered in the following passage from Warren.

Rosenbach reports in his earlier monograph two cases of traumatic gangrene in which the disease originated in a slight injury to the finger. Rapidly-spreading gangrene of the arm followed, and cultures taken from incisions made into the gangrenous portions showed the presence of the streptococci. In two cases of traumatic gangrene, with emphysema, of a most malignant type he was able to find, microscopically, a bacillus, but no streptococci. The cultures failed.

The writer mentions the following cases of traumatic gangrene—although clinically the disease is widely different from hospital gangrene—because they have a bearing upon a personal experience.

"In 1883 the writer was summoned into the country to a case of traumatic gangrene following a gunshot injury of the leg. The disease had in 48 hours spread from the foot to the middle of the thigh, and the odor showed that putrefactive changes were well advanced. The operation of amputation in the upper third was performed at midnight. Proceeding on his journey the next morning, the writer met a physician in consultation in the afternoon, and explored a sinus communicating

with a carious rib. A few days later a well-defined type of hospital gangrene was developed in the wound, which was not larger than would admit a good-sized drainage tube, and before the disease could be checked an ulcer the size of a dessert plate had formed. The only instrument employed in both operations was a pair of scissors, as, with this exception, the instruments of his colleague were used in the second operation. The scissors were employed to lay open the sinus where gangrene subsequently supervened. That they were the vehicle by which bacteria were transferred from one case to the other seems highly probable."

So far as the evidence goes, it would seem to favor strongly the assumption of a streptococcus bearing the same relations to gangrene that the streptococcus erysipelatis does to erysipelas. But the bacteriology of gangrene, after all has been said, from a modern point of view may be still regarded as almost a terra incognita.²

From this it is evident that toward the end of the nineteenth century surgeons recognized the fact that some types of bacteria were factors in the etiology and that surgery under antiseptic conditions gave the best prospect for avoiding the disease. But they were not certain as to the organism, and evidently even its mode of dissemination was still questioned by some, as the following quotation from Warren shows: "Much has been said about the contagiousness of gangrene. Medical literature contains too many examples of successful inoculation from man to animals and from man to man for the question to admit of any doubt."

From the time the disease was first described by Hippocrates to the present, it has been designated by many terms—gaseous phlegmon, moist gangrene, fulminating gangrene, hospital gangrene, acute pulpy form, emphysematous gangrene, traumatic spreading gangrene, acute microbic gangrene, gas gangrene and gas bacillus infection.

Of all the terms used, gas bacillus infection seems the most appropriate because the disease is an infection; it always included one or more forms of bacilli, but various other organisms may also be present, especially some anaerobic streptococci; gas is produced in the tissues, but only if allowed to progress does gangrene occur. In fact, many undergraduates and interns in our area have seen what the clinician terms gas gangrene but have never seen a case in a gangrenous stage; inclusion of the term gangrene in relation to the disease only confuses them. Others have the idea that the gas-forming organisms develop

only in tissue which is already dead or gangrenous. This, too, is an erroneous impression and is easily disproved by the occurrence of the disease following hypodermic injections into normal tissues. From every viewpoint the term *gangrene* gives rise to one misconception or another.

The term gas bacillus infection, with the understanding that numerous organisms may be involved and that gangrene may occur if the process is not arrested, is probably less open to criticism than any of the terms, and at the same time it is sufficiently expressive.

This discussion of terminology is in no sense an evasion of the contention some have made that the patients treated with x-rays did not have true cases of gas gangrene. In this text, every case history included, or in any way discussed, which has been designated as gas gangrene may also properly be described by any one or all of the foregoing synonymous terms; but we prefer the term gas bacillus infection.

PRESENT STATUS OF THE DISEASE

Definition.—Gas bacillus infection usually begins in an open contaminated wound, where there has been considerable destruction of tissue, or in a deep penetrating injury. Either permits the growth of one or more anaerobes in association with various other organisms to cause a rapidly spreading, toxin-producing, gas-forming infection. This condition, if not successfully treated, invariably results in a true local gangrene of the infected part in two to five days unless terminated prior to this stage by the patient's death from toxemia. It may, of course, be promptly and favorably influenced by properly administered x-ray treatment.

Etiology.—Welch first isolated *Bacillus aerogenes capsulatus* in 1892 and reported further observations on the organism, now known as *Clostridium welchii*, in 1900.³ In his later report he associated the organism with the cause of gas gangrene, and since then it has been correctly recognized as such.

Authorities now agree that the infection is mixed, due to a combination of numerous bacteria, aerobic and anaerobic, growing in symbiosis. Certain anaerobic gas-forming organisms are essential, but owing to the various types of injuries and the variations in the sources of contamination, one should not be

surprised to find any organism in addition to the essential anaerobic group. The etiology has been definitely known since 1900, and as a result the disease is more easily traced in the literature since that time.

Distribution of Gas Bacillus Group.—Their main habitat is the soil, and they are especially numerous around barn yards and in highly fertilized areas. In general, they may be considered a widely distributed type of organism and some contend that they are normally in the human intestinal tract. It is certain that they may cause a serious infection when hypodermic medication is given through carelessly prepared skin of the buttocks. They may be found in catgut, on the skin and in milk. Although they are anaerobic organisms, the spores tolerate oxygen.

Organisms.—All authorities include several organisms in the list of causative agents. Graham stated:

While the number of species and sub-species is legion, those which are commonly pathogenic fall into three groups with approximately the frequency indicated: *B. aërogenes capsulatus* (Welch bacillus, Welch-Fraenkel bacillus, *Bacillus perfringens*, *Clostridium welchii*, etc.) 60 to 80 per cent; *B. oedematiens* (*Bacillus novyi*, *Clostridium novyi*) 30 to 35 per cent; *Vibrion septique* (*Clostridium oedematis maligni*—bacillus of malignant edema) 10 to 15 per cent. Usually these infections are mixed with the streptococcus or with two or more members of this group itself, so that the disease may not be by any means identical in detail in any two individuals.⁴

Pathology.—Any consideration of the pathology of gas bacillus infection must necessarily result in the discussion of a twofold or possibly threefold type of disease. It is always a complication of some other pathologic condition, and, in turn, it may occasionally be followed by a severe if not fatal secondary infection due to other types of organisms, such as *Streptococcus haemolyticus* or tetanus.

The following outline indicates briefly the complicated problem which must be considered:

1. Disease or injury with gas bacillus infection as a complication.
 - a) Any contaminated penetrating or lacerated wound.
 - b) Any area of primary gangrene.
 - c) After amputation for primary gangrene.
 - d) Occasionally after certain diseases and operations.
2. Pathology resulting directly from gas bacillus infection.
 - a) Local changes: distention, discoloration, gangrene.

- b) Distant changes and effects: the toxins affect organs distant from the local infection.
- 3. Pathology from secondary infection or secondary invaders.
 - a) Streptococcus haemolyticus.
 - b) Tetanus.
 - c) Other organisms.

No attempt will be made to discuss in detail the pathology of any of these conditions or of gas gangrene since they are adequately presented elsewhere. They are mentioned to emphasize the rôle the various factors play in the clinical problem which one may face. Some of the conditions or types of conditions with which gas bacillus infection is most commonly associated will be mentioned.

I. DISEASE OR INJURY WITH GAS BACILLUS INFECTION AS A COMPLICATION

Any Contaminated Penetrating or Lacerated Wound.—This type of injury leads to temporary disorganization of the tissue, a condition which is ideal for the growth of these organisms; the infection may be of any variety and of almost any severity.

There may or may not be broken bones, severed blood vessels, severe hemorrhage and other factors giving rise to considerable shock which may cause death. Undoubtedly the deaths of many who die of their primary injuries are listed as from gas gangrene. It is often difficult to state whether the injury or the infection was the cause of death when death occurs a few hours after the injury but not before a fulminating gas bacillus infection is in progress. On the other hand, some patients are certainly said to have died of their injuries when they might easily have recovered had not the gas toxin been so potent. The combination of shock and gas infection is unfortunate. Occasionally one is forced to think that the severity of the shock is a factor in the rapidity with which the infection advances and overwhelms the patient, sometimes causing death in a few hours.

Formerly, shock was thought to be an essential factor in toxemia from gas-forming organisms if the patient died in less than 24 hours, as occasionally happened. There can be no question that shock from any source is an added burden to anyone having a gas bacillus infection. The high mortality in the

group undergoing amputation during the acute toxic phase of the infection seems to support that opinion, because the mortality in the group having therapeutic amputation is twice the mortality of those having no amputation (Fig. 18, page 165).

That a patient with an apparently trivial injury may be overwhelmed in a few hours is evident when one considers the gas bacillus infection which occasionally follows a hypodermic injection. In our Case 11 (p. 180 and Fig. 24) there was only a small area of damaged tissue and little or no shock in a fairly normal individual. Despite all these favorable factors, an uncontrollable infection with severe toxemia was followed by early death. There is yet much to be learned about the gas bacillus infections. One problem in the case of early death following hypodermic injection is important: Besides the organisms introduced at the time the patient receives the hypodermic injection, is it not possible, at least in some cases, that preformed toxins are also introduced? These preformed toxins might easily be contained in the supposedly sterile milk given by hypodermic injection. If the organisms are alive in the milk, it is only logical to assume that the milk contains the toxins. If toxins are present, they might account for the rapidity of the toxin effect and the early death of the patient.

The possibility of introducing preformed toxins when attempting animal experimentation must also be kept in mind. This may account for the general failure of many experienced workers to confirm the clinical results obtained with x-ray therapy in man.

Some authorities state that the toxin of *Bacillus welchii* is weakened by filtration, slowly deteriorates by exposure to air and light and is totally destroyed by heating to 70 C. for 30 minutes. The spores are also destroyed by heating to 100 C. for 5 to 15 minutes. Thus it is quite likely that the organisms and toxins are not part of the contents of the hypodermic medication but are a contamination introduced from the skin. One must remember that tetanus organisms are much more resistant to heat than *B. welchii*; for this reason one should not take chances of administering hypodermically material which one has prepared to produce a foreign protein reaction.

This entire group of organisms has not been thoroughly studied relative to their toxin and spore resistance to heat.

When one uses any material for hypodermic purposes which may be contaminated by these organisms, the possibility of a subsequent gas bacillus infection must be kept in mind. Another fact to remember is that hypodermic injections should not be given in the gluteal regions or thighs without proper preparation of the skin. They should be given elsewhere if there is any question as to the cleanliness of the skin.

Any Area of Primary Gangrene.—This condition provides a means through which the gas-forming organisms may gain entrance to the tissues in an arteriosclerotic, diabetic or senile patient. Such patients are poorly equipped to resist any serious complication. The pathologic processes of diabetes and arteriosclerosis are much too extensive for consideration here, but they are nevertheless a great factor in the death of these patients.

Amputation for Primary Gangrene.—The organisms are often present but quiescent preoperatively in primarily gangrenous areas in the arteriosclerotic and diabetic, but they may become active after amputation or any surgical attempt to remove a gangrenous area. In this event, many factors are involved, especially the shock of amputation and the toxin of the gas organisms, which are too much for the patient. After a brief period, the patient dies despite the attempts of surgeon, internist and radiotherapist to prolong his life. The prognosis for the arteriosclerotic patient is not quite as good as for the diabetic.

After Injuries and Operations.—In this group are included all rare injuries or diseases which may occasionally be complicated by a gas bacillus infection. The pathology depends on the condition, but it must be ascertained, if possible, as soon as the gas bacillus infection becomes evident. In this group are post-operative trunk infection following appendectomy, cholecystectomy or gangrenous infections after repair of a strangulated hernia.

II. PATHOLOGY RESULTING DIRECTLY FROM GAS BACILLUS INFECTION

As stated previously, the pathology of gas gangrene must be considered from two angles, locally, through the direct action of the organisms on the tissues, and generally, through the effects of toxins on the principal organs of the body.

Local Changes.—A mixed group of organisms, aerobes and

mainly anaerobes, gain entrance through damaged tissues and, growing in symbiosis, invade, destroy and produce toxins which give rise to systemic effects. If allowed to progress, they turn the local tissue into a truly gangrenous mass.

Before reaching the gangrenous stage locally, there is considerable swelling from the gas produced in the tissues. This swelling is accompanied by a bluish color or sometimes a brownish tint of the skin, which is not gangrenous at first and may recover its normal tone and function if it responds to x-ray treatment.

In addition to the swelling and gas formation by the saccharolytic organisms, there is a characteristic odor due to the putrefactive action of the proteolytic organisms. These organisms attack and some thrombose the arteries and veins, even those of large size, if the disease is not halted in its early stages.

Distant Changes and Effects.—The action of the toxin on the distant viscera is the most important feature of the disease. It is this which kills the patient if he dies during the first three to five days of the disease.

Toxin damage to heart, kidney, adrenals, liver and practically all the major viscera is not fully appreciated even by surgeons who are greatly afraid of the disease or its local consequences. The local gangrene is not as disastrous as the damage to the heart and other viscera.

The following comments on the pathologic findings in man by Williams⁵ and Kettle⁶ and in animals by Pasternack and Bengtson⁷ and others suggest that there is, in the main, an agreement as to the essential facts of the pathology of gas bacillus infections and the action of the toxin. The findings of the experimental investigators have considerable clinical significance and in a general way may be applied to man. In our experimental attempts to establish the therapeutic value of the x-ray in gas gangrene, we were unable to find a suitable animal which would consistently show signs of the acute disease and then live long enough for a satisfactory therapeutic test.

The following discussion of the relation of the amount of toxin administered to the length of survival of the animals may throw some light on the problem. The answer seems to revolve about the "all or none law," with the time factor of major importance. According to Pasternack and Bengtson:

A study of methods suitable for the standardization of Vibriion septique antitoxin in which extensive use was made of rabbits and mice afforded an opportunity for study of the action of the toxin and also of the pathology produced. Of interest was the determination of the relation of the effects produced to the survival time and to the size of the dose of toxin used.

As recorded in the literature, some variance of opinion in regard to the rapidity of the action of the toxin on rabbits may be noted. According to several workers, the length of time of survival of rabbits inoculated intravenously is dependent to a certain extent on the size of the dose of toxin administered. Thus, Robertson states that

but when smaller doses are injected, death occurs in 1 to 10 or 12 hours. Weinberg and Seguin produced toxins which killed rabbits in doses ranging from 1 to one-fourth cubic centimeter in 4 to 22 minutes. Lautenschlager, however, as the result of his experiments, reached the conclusion that the toxic dose for rabbits followed the "all or none" law; i. e., the smallest amount of toxin which was fatal reacted as quickly and potently as a considerably larger fatal dose. An amount slightly smaller than the minimal lethal dose had no effect.

The results of the tests bring out the fact that it is only when the minimal lethal dose is approached rather closely that the incubation period is increased to a considerable extent. If the toxin is a potent one and the doses are far apart, the minimal lethal dose may be missed and the results show either prompt death or survival without symptoms.

The distinction between a dose which is fatal and one which is not is very clear cut; i. e., all animals which show symptoms succumb sooner or later while those which survive never show symptoms or any late effects.

The peculiarity of variation in the length of survival of animals inoculated with the same dose of toxin is difficult to explain. One animal inoculated with a certain dose may die within two or three minutes, while another receiving the same dose may survive for a considerable number of hours. It appears that if the animal can withstand the first shock of the toxin it may live for a considerable length of time. The possibility was considered that the rapidity with which the toxin is injected might be a factor. In order to determine whether this was the case, tests were made on rabbits using doses of toxin of 1, 2, and 5 minimal lethal doses per kilogram of weight of rabbit and injecting as one ordinarily does, and more slowly and more rapidly.

Within the limits of the test, the time of death apparently was not related to the rapidity with which the injection was made. Straub and Lautenschläger, however, found that if the toxin were injected over a much more extended period of time, the results were quite different. A quick injection of 0.03 cubic centimeter of toxin was fatal to a rabbit in 30 seconds, while six times that amount given slowly in the course of 100 minutes, was borne without any reaction according to

the blood-pressure tracings, and was not fatal to the animal. They, therefore, concluded that a peculiar "time law" dominated the whole process of intoxication. In other words, the toxin can be introduced into the animal very gradually without untoward results, while the fatal reaction on the heart is dependent on a certain concentration of the toxin in the circulating blood. Obviously, greatly prolonging the interval over which the toxin is administered gives the animal mechanism an opportunity to destroy or inactivate the toxin, or to cause its rapid excretion. Straub felt that the toxin was probably largely destroyed because it is very sensitive to oxidation.⁷

Further discussion of Straub's⁸ and Lautenschläger's⁹ observations regarding this problem may not be amiss.

The "time law" in relation to the concentration of the toxin and its excretion is important in the problem of prophylaxis

tration, and frequent use of x-rays (the short space factor—twice or more each day) after the toxin has accumulated tends to retard its action and rapidly dissipates all clinical evidences of toxemia.

Thus it appears that the clinical response of the patients with post-traumatic gas bacillus infection who were treated with small doses of x-ray at frequent intervals¹⁰ fits in well with the observations of those experimental workers. As the small doses of x-ray appear to interrupt the action of the toxins temporarily, the patients soon recover their balance, or x-ray therapy “gives the animal mechanism an opportunity to destroy or inactivate the toxin, or to cause its rapid excretion.”¹¹ It appears to us that the “all or none law” and the time factor are also part of the disease in man as one observes its clinical course and its response to radiation therapy.

The value of disturbing the rate of growth of the organisms or of possibly interrupting the action of the toxin was obvious early in our clinical experiences and was so reported without knowledge of any previous research on the subject. The first report on x-ray treatment of gas gangrene contained the following statement:

The fourth characteristic is the power of x-rays to cause a biologic action when they are directed on living cells. One may think of several ways in which this action may be of value in the problem we are considering, but much work must be done before the correct solution is obtained. The ray, acting in a destructive capacity, may kill the organisms themselves, or it may act as a bacteriostatic, and, by preventing

their propagation bring their biologic course to an end. On the other hand, when it is acting in a stimulating capacity, the beneficial action of the roentgen ray may be on the cells of the host stimulating them to superior defensive powers, which, in the end, eliminate the invading organism. Many variations or combinations of the above-mentioned possibilities may be present.

The fifth characteristic is the power of the roentgen ray to ionize or split gases. Possibly, the gas formed in the tissues in this disease may be highly toxic in its original state, and the rays may, *through some oxidizing effect*, render the gas *less toxic* to the host or even destructive to the organisms which produced it.¹⁰

In the fourth report, the following statement was made:

Many of the patients who received one or two doses of x-ray and recovered were in the earlier stages; the disease seemed to regress immediately, the *patient's own resistance apparently coming in to control the situation from that time. The ability of the individual to respond and apparently assist himself in the battle following a dose or two of irradiation is a rather impressive clinical fact, and, once he gets control of the situation, he does not seem to lose it.*¹¹

Straub's impression that the toxin was probably largely destroyed because it is exceedingly sensitive to oxidation may hold the answer to the question why certain patients who have received sulfanilamide in large doses just prior to or simultaneously with the administration of x-rays fail to respond to the action of the x-rays. Many of these patients receiving sulfanilamide have some cyanosis when x-ray therapy is started, and if free oxygen in the tissues is prerequisite to any beneficial action from the ionizing effects of the x-rays, the presumption seems logical that this lack of available oxygen in the cyanosed patient receiving sulfanilamide may explain the failure of the x-rays to produce their usual favorable effects.^{12, 13}

At any rate, experimentally and clinically, many facts concerning the action of the toxin in animals and in man appear to coincide; and *the antitoxic action of the x-rays*, which may be administered easily every few hours, is extremely effective in the treatment of gas gangrene. Whether or not the action of the x-rays is fully understood does not seem as important as the fact that it apparently never fails. Its efficiency—and its dangers—should be the only elements in its use to be seriously questioned. Since the mortality rate in post-traumatic gas bacillus infection cases receiving one x-ray treatment is about 48 per cent, two treatments 27 per cent and three or more treat-

ments less than 6 per cent, the efficiency of x-ray therapy does not seem open to question, especially if it is given as the experimental investigators suggest and as we have recommended for the past 10 years—at frequent intervals in order to minimize the effect of the concentrated toxin on the important viscera. This method has been recommended from the beginning of the x-ray treatment of gas bacillus infection in man.

That the action of the toxin of *Vibrio septique* on the heart is an important factor in the fatal outcome is indicated by the following quotation from Pasternack and Bengtson: “From these studies it seems apparent that the (*Vibrio septique*) toxin acts directly upon the heart muscle. Our histologic studies bear this out.”

Lautenschläger also proved experimentally that impairment of respiration occurred much later than heart injury; from this fact he concluded that death of the animal is caused by the action of the toxin on the heart alone and that the respiratory symptoms are only secondary. Williams also showed evidence of toxic action (of *B. welchii*) on the human heart.

Since it is so important to prevent early concentration of the toxin in the circulatory system in order to protect the heart muscle of the experimental animal, it is evident that early and frequent x-ray treatment answers the question “what to do in the treatment of gas gangrene.” It is definitely indicated both by the experimental work and by the mortality figures for cases receiving one, two and three or more treatments.

Pasternack and Bengtson had this to say about Kettle’s observations:

Kettle has briefly discussed the histopathology of gas gangrene, using human postmortem material and animals inoculated with cultures. His investigations were undertaken in connection with war time studies of gas gangrene. He reports his observations of the effect produced by the organisms of gas gangrene in general, and states that he was unable to arrive at definite conclusions as to possible differences in the lesions produced by *Cl. perfringens* (*B. welchii*), *Vibrio septique*, and *Cl. oedematiens*. His results are not, therefore, easily compared with ours which are concerned with the effect of the specific toxins of these organisms, considering each one separately.

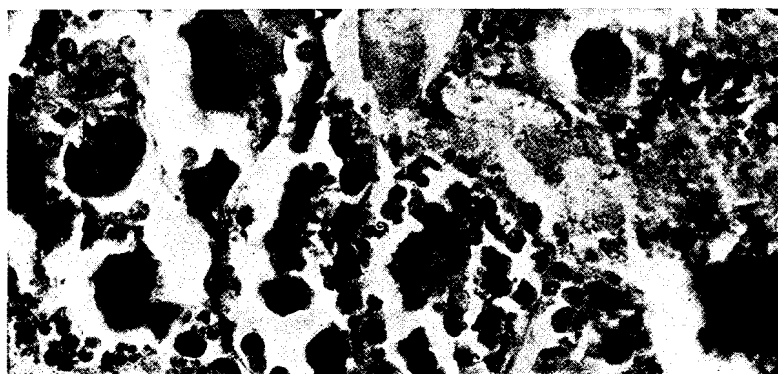
The local lesions produced experimentally in animals have been described by various workers. The muscles of guinea pigs inoculated with cultures show a characteristic intense deep red coloration at the site of inoculation and a softening of the tissue. *Vibrio septique* is,



FIG. 12.—Rabbit 83 hours after injection of *Vibrio septique* toxin. Zenker's "waxy" degeneration of the heart; $\times 540$. (Courtesy of Pasternack and Bengtson, National Institute of Health. Army Medical Museum Accession 63649.)



FIG. 13.—Rabbit 77 hours after injection of *Vibrio septique* toxin. Hemorrhagic necrosis in adrenal gland; $\times 12$. (Courtesy of Pasternack and Bengtson, National Institute of Health. Army Medical Museum Accession 63662.)



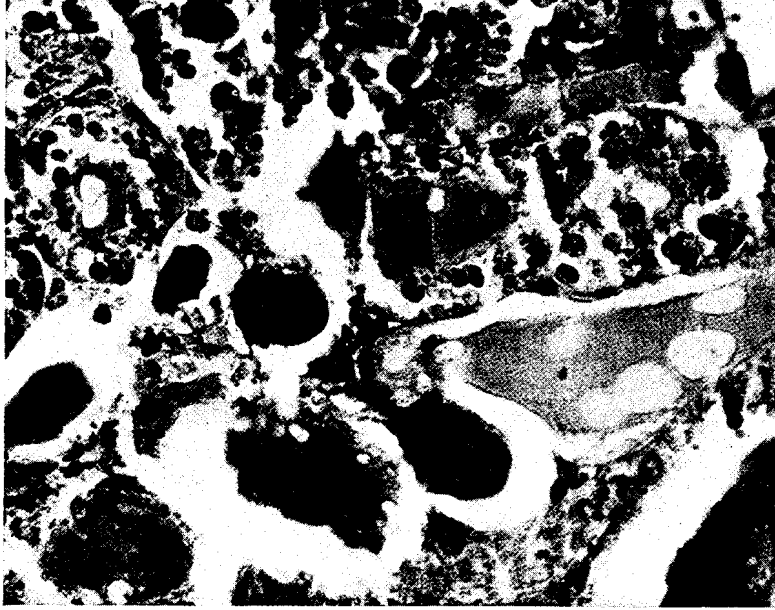


FIG. 14.—Mouse 44 hours after injection of *Vibrio septique* toxin. Colloid droplet degeneration and hyaline cast formation in the kidney; $\times 540$. (Pasternack and Bengtson, National Institute of Health. Army Medical Museum Accession 63650.)

however, an invasive organism and does not remain localized at the site of inoculation. It may be found in the various organs and tissues of the body, where it produces characteristic lesions.⁷

Pasternack and Bengtson described the changes found in many of the important viscera after the intravenous injection of *Vibrio septique* toxin. Figures 12 to 14, from their work, show the microscopic changes which are apparently serious. Figure 12 shows the shattered condition of the heart muscle of a rabbit.

Figure 13 shows hemorrhagic necroses of the adrenal of the experimental animal due to the action of the toxin. The destruction in these organs indicates what takes place in many important structures and should serve as a warning to any physician who has under his care a patient with gas bacillus infec-

not wait until gangrene develops to make one's diagnosis but should immediately take measures through early administration of x-rays to prevent the disease from reaching either the toxic or the gangrenous phase.

Figure 14 shows the destructive action of the toxin on the kidney of a mouse.

The work of Williams⁵ of London concerning importance of toxemia due to anaerobic organisms in intestinal obstruction and peritonitis combines a clinical and experimental investigation. It shows through illustration of pathologic specimens the changes in cardiac muscle and the liver resulting from the absorption of *B. welchii* toxin in the human.

Those interested in more scientific work than is afforded by this clinical presentation are advised to consult the original articles by these investigators: Pasternack and Bengtson,⁷ Kettle,⁶ Williams,⁵ Lautenschläger,⁹ Straub⁸ and Robertson.¹⁴

Thus we have evidence of the similarity of the action of the toxins of these several anaerobic organisms in animals and in man and some experimental data supporting the necessity for early and frequent doses of x-ray in treatment. The "none" law prevails if treatment is started early, in that practically no evidence of toxemia develops and the case tends to clear up promptly. The "all" law is well illustrated by the patient in whom gas bacillus infection developed following a hypodermic injection and who died in less than 24 hours. (Case 11, Fig. 24, p. 180.)

III. PATHOLOGY FROM SECONDARY INFECTIONS OR SECONDARY
INVADERS

This group includes infection with pathogenic organisms giving rise to a distinct disease other than the two already discussed. These organisms gain entrance at the same time the gas organisms make their invasion, but their presence is not evident until after the gas bacillus infection has subsided.

Streptococcus Haemolyticus.—Several patients have died in the fourth or fifth week of generalized invasion of *Str. haemolyticus*. At autopsy there was no evidence of gas bacillus infection, but the hemolytic streptococcus was demonstrated in all the lesions.

Tetanus.—Another patient died in the third month of a tetanus infection after surviving gas bacillus infection and amputation of a leg. Another patient developed tetanus but recovered after heroic treatment with antitetanus serum.

Other Organisms.—Certain cases may not be correctly placed under a classification of gas bacillus infection, but the infection of which the patients died was undoubtedly contracted at the time they were infected with the gas-forming organisms. They are mentioned here to show that other organisms causing less stormy clinical evidence of their presence may survive throughout the clinical course of the gas bacillus infection despite radiation therapy, only to give serious trouble later. Since early treatment with x-rays tends to prevent the development of some infections, its use as a preventive measure against these subacute or chronic infections seems indicated.

In many cases in which x-ray therapy is started late, other organisms are found in the wound after the gas bacillus infection has completely subsided.

All residual infections of this nature should be studied by culture methods and observed carefully to determine the pathogenic organism so that effective measures may be used in their treatment. For instance, x-rays might well be used during the first five or six days of the gas bacillus infection; then, after the acute toxic phase has passed, a change to some other measure effective against the particular type of secondary organism involved, such as *Str. haemolyticus*, is indicated.