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THE ROLE OF X-RAYS IN THE TREATMENT OF GAS GANGRENE: A HISTORICAL ASSESSMENT

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□ While the use of x-rays to treat patients with gas gangrene ended in the early 1940's with the advent of antibiotics, x-ray had been widely accepted as a useful and highly effective treatment for this condition. The present paper re-assesses the historical foundations of this belief, the quality of the data, use of confirmatory animal models, and underlying mechanisms that might account for the therapeutic role of x-rays in the treatment of gas gangrene.

Key Words: x-ray, gas gangrene, dose-response, history of medicine, hormesis

INTRODUCTION

Gas gangrene is a progressive and often fatal disease caused mainly by the bacterium *Clostridium welchii* (now known as *Clostridium perfringens*) and most commonly associated with car accidents, war wounds, necrotizing myositis, debridement and amputation. Currently employed treatments include surgery, antibiotics, and hyperbaric oxygen. The use of radiotherapy for the treatment of patients with gas gangrene ended nearly 70 years ago with the advent of antibiotics (Reed and Orr 1941; Gordon and McLeod 1941; Sadusk and Manahan 1939; Bohlman 1937) and the growing fear of enhanced cancer risks from x-rays (Cuttler 2007). While such radiotherapy practices have now become a nearly forgotten footnote in the history of radiology, it is important to note that for nearly two decades the use of radiotherapy emerged as an excitingly new and potentially valuable treatment for this potentially debilitating and rapidly fatal condition. The medical risks of gas gangrene were therefore extremely high, being linked to a disease time course that was also often rapid, placing considerable pressure on physicians managing patient treatment. During the early decades of the 20th century, the treatment options for gas gangrene were limited, with the administration of horse serum which had antibodies to one or more of the bacteria known to cause gas gangrene being prominent. However, due to the potential rapidity of the disease process, there was often a lack of time to identify the causative agents via microbiological assessment in order to match the serum to the dis-

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ease-causing microbes with certainty. Thus, given the limits of medical knowledge and treatment options during this time period and the rapid course of action of the disease, it is not surprising that mortality occurred in about 50% of the patients with surviving patients at risk for amputation. The present paper evaluates the historical use of x-ray therapy in the treatment of gas gangrene, including its origin, scientific and medical bases, efficacy, as well as the extent to which this treatment was adopted by the medical community.

HISTORICAL FOUNDATIONS

The first known case of x-rays to treat a patient with gas gangrene occurred on August 31, 1928. Dr. John R. Dwyer, Staff Surgeon at St. Catherine's Hospital, an affiliated hospital of Creighton University, School of Medicine, requested a consultation with Dr. James F. Kelly, a radiologist, in order to obtain an x-ray for diagnosis, rather than for treatment purposes. The 21 year old patient, who was diagnosed with gas gangrene, was in poor condition, being comatose and near death. His infection had rapidly spread from below his right knee to the hip area, with amputation no longer a possibility. Since there was little or no expectation of survival, Kelly administered an x-ray therapeutic treatment late in the afternoon of the second hospital day. Since Kelly had treated patients with erysipelas (i.e., an acute skin infection of the deep epidermis with lymphatic involvement due to streptococcus bacteria) and other acute infections with low doses of x-rays (i.e., typically twice per day) he decided to treat this patient in a similar fashion. Returning to the hospital that night to administer a second treatment, he was surprised to find the patient still alive. However, Kelly's greatest surprise occurred the following morning when the patient was discovered sitting up in bed. No longer in a coma, his general condition was dramatically improved. Following similar treatments the next few days, all symptoms of the disease disappeared, with amputation(s) no longer needed. This experience inspired Kelly (1933) to look for opportunities to use radiotherapy in the treatment of gas gangrene.

The first formal report that x-rays could be employed therapeutically in the treatment of gas gangrene was during a presentation by Kelly at the annual conference of Radiological Society of North America on December 1, 1931. The findings of this presentation were subsequently published in the journal *Radiology* in 1933. In this paper Kelly (1933) reported on the results of x-ray treatment of gas gangrene in patients ranging in age from 8-82 (Table 1). Each of the individuals had open wounds, with active gas formation, all with microbiological confirming cultures. In six extremity related gas gangrene cases treated with x-rays all patients recovered without amputations. Of the three remaining cases, x-rays were not used, with two dying while the third lived but lost an arm at

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TABLE 1. Summary of initial case histories by Kelly concerning x-ray treatment of patients with gas gangrene (Kelly 1933)

Kelly, 1933					Treatments				Treatment		
Case #	Age	Gender	Occupation	Nature of Injury	Location of Disease	Lab Micro. Validation	Other	Serum	X-ray	Amputation	Hospital Release
1	21	M	Farmer	Auto accident	Laceration below right knee	B. welchii positive		Yes	Yes	No	7 weeks
2	10	M	School-age	Stepped on nail	Leg	B. welchii positive	Anti-tetanus	No	Yes	No	3 weeks
3	23	M	Laborer	Dynamite blast	Left leg	B. welchii positive		No	Yes	No	5 weeks
4	42	M	Merchant	Bullet wound	Below left knee	B. welchii positive		Yes	Yes	No	8 weeks
6	61	M	Farmer	Tractor (fell from)	Left ankle	B. welchii positive		Yes	Yes, only after 2 amputations	Yes	6 weeks
7	82	M	—	Strangulated hernia	—	B. welchii positive		Yes	No	No	Died
8	8	M	Fell under plow		Left forearm, compound fracture	B. welchii positive		Yes	No	No	No information provided

the shoulder. Kelly (1933) used a dosage of 150 rads/day in two doses of 75 rads each or three doses of 50 rads each for a three minute period and a voltage range of 90-100 kV on an extremity and 130-160 kv on the trunk depending upon the affected tissue's thickness. Kelly increased the thickness of the filter (range was 0.5-1.0 mm aluminum filter) as the voltage increased to avoid skin burns in the patient. Unlike dose range, the duration of treatment and total dose were not standardized and were defined by physical condition of the patient, nature of the affected part (trunk or extremity) and severity of the disease.

Kelly (1933) also reported that lower doses of x-rays (75 rads/day in a single dose) were used by several workers as a prophylactic measure for gas gangrene. According to Kelly, amputations and devitalizing surgeries were not effective for patients during the acute toxic phase of the disease and thus should be done after the acute phase is over only to remove the dead tissue.

Popularity and acceptance of low dose x-rays as a standard form of treatment in that era was evident from the fact that the U.S Army's World War II vintage picker

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portable field radiographic unit was specially created to give prophylactic radiation to open war wounds to prevent gas gangrene (Bowen 1940). Similarly, Cantril and Buschke (1944) reported nine cases of gas bacillus infection (no mortality) successfully treated with the use of low dose x-rays in 1944 at the 29th Annual Meeting of Radiological Society of North America. Patients in this case series were treated for 3-13 days with 50-150 rads/day depending upon the site and severity of the disease. These authors stated that use of serum did not affect recovery in any of their patients; they believed that cases who received serum recovered as well as the ones who did not. They supported Kelly's conclusion that diligent use of low dose x-rays with surgery could produce results which had never been obtained for this disease before.

ANIMAL STUDIES

Kelly (1933) indicated that no animal model research had yet been published on the effects of x-rays on the therapeutic treatment of gas gangrene. Despite this lack of a confirmatory experimental model, Kelly argued that clinical application of the x-ray treatment should not be delayed pending confirmation of results by animal studies since this treatment offered strong promise of an improved clinical outcome, that is, life and limb saving outcomes. Three years later Kelly and Dowell (1939) briefly summarized their further clinical studies and attempts at animal model investigation. With respect to animal model experiments, Kelly indicated studies using guinea pigs were not successful, claiming that the guinea pig was too diminutive in that an injection of a highly virulent bacterial culture would result in such a rapid spreading of the disease that the x-ray treatment would have to be a whole body exposure, something far different than used in humans. Dowdy and Sewell (1941) were also dismissive of the use of experimental research with mice, guinea pigs, and rabbits since the findings with these animals models had been too unpredictable. Research by Erb and Hodes (1942) using pigeons also did not reveal an x-ray induced therapeutic effect although the experimentation conditions may have been too limited to adequately assess this hypothesis. Later work by Merritt *et al.* (1944) also led to a conclusion that the guinea pig was an unacceptable animal model for humans because of its unique susceptibility to x-rays. For example, a normally therapeutic dose of 200-250 rads in humans induced lethality in the guinea pig model. Guinea pigs also displayed a strong tendency to chew at their wounds, which would lead to enhanced drainage, and that this could have therapeutic value. Despite these noted limitations of the guinea pig model, Caldwell and Cox (1941) conducted an extensive investigation with guinea pigs in assessing the effects of x-rays on the course of gas gangrene infectivity. The investigation revealed that a single x-ray treatment of 25 rads administered one hour after the inoculation of the *Clostridium welchii*

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only modestly enhanced survival (i.e., ~21%) as measured in hours following exposure to the disease causing agent. More specifically, they reported 39.0 hours survival in the x-ray treated animals after inoculation as compared to controls (i.e., 32.9 hours survival after inoculation) that were similarly treated (i.e., incision and inoculation). Two other comparisons using x-rays (i.e., with debridement and in the absence of an incision) did not result in any improvement. Whether the failure to achieve a more consistent and greater beneficial response was due to the above concerns or due to other methodological limitations such as a non-optimized x-ray dose or time for treatment or other reasons was unknown.

In contrast to the research with guinea pigs follow up experiments concerning gas gangrene with dogs and sheep provided limited, but consistent suggestive evidence that x-rays could enhance survival. In the dog study it was shown that an x-ray dose of 100 rads administered about 4 hours after the inoculation of the clostridium into muscle with the needle reaching to the femur prolonged survival (Dowdy and Sewell 1941). Such survival was further enhanced by the administration of a second x-ray 24 hours later. Taken together, proportion of dogs surviving increased from 20% in the controls to 36% in the treated group. Likewise, the average survival period in terms of hours increased from 24.5 hours in the controls to 45.4 hours or nearly double that in the treatment dogs. The findings were probably somewhat understated. Whenever there was a recognized variation amongst the dogs, the investigator matched the dogs such that in the control versus treatment dog pairs that were studied, the x-ray treated dogs were older, smaller as well as less vigorous. Thus, there was a deliberate bias against observing a treatment related effect. No follow up research was published that extended the report of Dowdy and Sewell (1941).

In 1944 Merritt *et al.* reported on what they described as a “long delayed decision to demonstrate, if possible, the effects of radiation therapy on gas gangrene by animal experimentation...” This study utilized sheep since the authors believed that guinea pigs were not an appropriate model for humans. Secondly, they chose not to utilize the dog model since dogs were known to develop strong immunity against clostridial infections. In contrast to the dog experiment the sheep right hindquarter had a 7 cm skin incision followed by the macerating of muscle *in situ* in the wound area, and by suturing. After macerating of the muscle tissue the inoculation was administered. In the sheep study it was reported that the x-ray therapy (600-1600 rads) was associated with a markedly lower mortality with the controls showing 75% whereas the x-ray treated animals had only 29%. Furthermore, there was no case in which the x-ray treated sheep displayed evidence of the spread of the infection across the perineum or along the flank of the treated leg whereas this was quite common in the controls. The authors noted that the key to a successful

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recovery was the application of x-ray treatment as early as possible, an observation consistent with that reported in the clinical literature.

These findings generally supported a conclusion that x-rays can enhance survival, and reduce gas gangrene disease progression and severity in dogs and sheep under differing experimental conditions. Despite the consistent findings, neither of the two key supportive studies provided a statistical analysis with hypothesis testing, nor were the studies replicated. The sample sizes were also modest with 25 control and 25 animals tested in the dog study whereas only 15 sheep (12 of one breed, 3 of a different breed) were used in the Merritt *et al.* (1944) study. Thus, these findings were too limited to provide an adequate experimental foundation to support human clinical studies, especially in relationship to experimental design optimization. Despite their obvious limitations, the generally strong pilot nature of the findings provided an excellent foundation for follow up experimental research which was never undertaken.

ARE X-RAYS AN EFFECTIVE TREATMENT OF GAS GANGRENE?

The belief that x-rays could be effectively used to treat gas gangrene originated with James F. Kelly in the late 1920's, as noted earlier. Kelly resorted to the use of x-rays based on the limited effectiveness of available methods as well as the effectiveness of x-rays to treat other bacterial infections and the apparent hopeless outlook for many patients. During the time leading up to Kelly's observations that x-rays may be useful in treating patients with gas gangrene, it was generally observed that mortality from gas gangrene was typically quite high. Based on Miller's (Miller 1932) report of 607 cases of gas gangrene in civilian life (1910-1930), the mortality was 49.7%, while it was reported as 48.5% amongst the American Expeditionary Force (AEF) (Charbonnet and Cooper 1939). Prior to WWI reported fatalities from gas gangrene were also approximately 50%. For example, Welch (1900) reported 59%, whereas Cramp reported 48% in 1912, while Chalier (1914) noted a death rate of 67.4%, a value that is probably high since some of the cases were military (see Charbonnet and Cooper 1939). Following WWI, improved surgical techniques emerged along with the use of anti-toxic serum, combined to reduce mortality to about 25% (Boland 1929; Stone and Holsinger 1934; Ghormley 1935; Veal 1937).

The above cited studies were generally modest in size (e.g., 50-70 patients), having limited potential statistical power. Nonetheless, the consistency of the findings suggested a reduction in the mortality rate. It was during this period that Kelly superimposed his recommendations for the use of x-rays, eventually claiming to further decrease the occurrence of gas gangrene related mortality and amputations.

Proving the cause and effect relationship for x-rays in the reduction in mortality from gas gangrene however was not easy. The cases of gas

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gangrene were generally infrequent, highly individualistic, viewed as potentially high risk of rapid mortality while having an inconsistent diagnostic criteria, in part, because of the seriousness of the disease and the need to act quickly. The treatments were also not standardized for surgical strategy, x-ray equipment and technique as well as the possibility that the type of anti-toxic serum may not have been appropriate for the specific types of causative bacteria. These factors led to the use of x-rays in the treatment of gas gangrene, resulting in a sizeable number of case histories by generally well experienced clinicians, who provided clinical data to Kelly for subsequent analysis. These case histories were also influenced by “impressions” from apparently unexpected successes in which a patient who was thought to be near a sure death rapidly recovered. For example, Charbonnet and Cooper (1939) stated that “a critic may think those interested in this work are too enthusiastic over a mortality rate based on so few cases. But when one witnesses the spectacular effect of therapeutic x-rays in gas infection he will realize that this value is not overestimated....” Such situations can also lead to clinical decisions being more subjective rather than objectively based. Furthermore, it is not known to what extent x-ray induced treatments of gas gangrene may have failed to cure and were not reported. It would not be unexpected that a positive publication bias existed. Only two negative papers (Caldwell and Cox 1941; Cubbins *et al.* 1941) were published against nearly 30 papers which found a possible beneficial x-ray treatment, a ratio of about 10-15 favorable to one against. We also do not know the acceptance or rejection rate based on the medical subfields (e.g., radiology vs surgery) and the journal. For example, most of the papers on x-ray induced treatment were published in x-ray related journals such as Radiology. Perhaps there may have been a bias in favor of their publishing in such journals while there may have been a bias against such papers in general medical/surgery oriented journals. Regardless of the papers and when they were published none incorporated statistical analyses, including hypothesis testing.

The goal of most, if not all, participating clinicians was not primarily to prove that x-rays should be used but to save the life and limbs of their patients. Over time this desire also affected the capacity to effectively evaluate the efficacy of the x-ray treatment. For example, there was a strong tendency for physicians to use the x-ray treatment prophylactically in addition to a therapeutic manner (Bowen 1940). That is, physicians starting to treat patients with “possible” gas gangrene, with x-ray treatment before the diagnosis was made. This decision was also made based on the belief that x-rays were more effective when used early in the disease process rather than later. However, this could also drive up the appearance of successful outcomes even when the disease condition could not be verified. Despite this set of challenges that affected an objective

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appraisal of x-ray efficacy, efforts were made to be fair minded and objective in the assessment of data.

KELLY'S DATA ASSESSMENT

Kelly advocated the use of x-rays as a prophylactic and therapeutic treatment for gas gangrene. This position emerged from his initial noted successful treatment of six subjects with gas gangrene in an extremity. These cases were observed over a period from 1928 to about 1932-mid 1933, about 4-4.5 years, with only about 1-2 cases/year. After reporting on these cases Kelly observed four more patients over the next two years and obtained case history information from other colleagues via personal communication and case reports for 32 more cases, bringing the total to 40 (Kelly 1936). For each of the 40 cases Kelly (1936) reported x-ray treatment parameters, serum treatment, location of the gas gangrene (i.e., extremity, trunk and extremity), occurrence of amputation, if the patient died, and, if so, whether the death was due to gas gangrene or its complications. Of the 40 cases, most had serum treatment (38/40) and probably all (40/40) had x-ray treatment(s). Of the 40 patients, 33 survived, with four dying as a result of the gas gangrene. Thirteen cases had amputations. The adjusted mortality rate of 10% was impressive to Kelly who noted a far higher rate of mortality with other treatments (e.g., ~40%).

As a result of these 40 cases (including 10 of his own) Kelly (1936) recommended that (1) x-ray treatments were needed in all cases of gas gangrene; (2) x-ray treatments should be initiated no matter how apparently dismal the chances of survival; (3) treatments should be given twice/day at 100 rads/dose for at least three days; (4) that amputation should be discontinued except in cases where the damage is extensive and not related to gas gangrene. He noted that the appearance of dark tissue discoloration may not reflect actual gas gangrene. In fact, such discolored tissue typically cleared up after successful x-ray treatment, suggesting that the darker skin may reflect local cyanosis.

The results of the first publication were understandably limited and Kelly (1933) was cautious in his comments. For example, Kelly (1933) stated that "one naturally hesitates about reporting any results on such a small series. However, the condition is not met with frequently enough in time of peace to warrant a large delay in order to accumulate a larger number of cases. If the method has any merit, it is offered here so that many others may have an opportunity to use it and so that its value, if it has any, will be more quickly established..." (page 296). "In every case it was employed in conjunction with the other usual therapeutic measures; this fact renders any claim, at this time, for its specific action out the question..." (page 296-297). In this preliminary report, roentgen therapy was recommended as an aid in the treatment of gas gangrene infection. With the accumulation of 32 more cases Kelly (1936) offered the set of rec-

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ommendations noted above. In a third series of cases (e.g., 16 more cases) no deaths occurred, but there were two amputations. In contrast to the earlier research, five of the 16 cases did not receive serum treatment (Kelly 1939). This led the authors to conclude “the questions of serum are still undetermined...” (page 1116) but they did not recommend that it should not be employed.

Two years later Kelly *et al.* (1938) reported a cumulative total of 18 x-ray treated cases without serum treatment (prophylactically or therapeutically) in which 17 survived (5.5% mortality rate), leading the authors to suggest that serum treatment may not be needed to achieve recovery. This mortality rate was similar to those reported when x-rays and serum were used together, indicating that x-rays were the more significant therapeutic option of the two. Furthermore, the death of some diabetics with gas gangrene appeared to be associated with the serum treatment itself. In this paper which now had a cumulative total of 132 cases, none of the cases were reported in specific detail as Kelly did for the previous 46 additional contributed cases by medical colleagues.

In 1941 Kelly and Dowell published a 12-year review of the x-ray-gas gangrene treatment literature. By this point 143 cases had been reported in the medical literature. This included gas gangrene cases related to trauma, diabetics and arteriosclerosis. Kelly also summarized the total experience of x-ray treatment for that reported for post-traumatic cases. Of a total of 364 cases, Kelly worked directly with 52 cases, 21 as a clinical investigator and 31 as a consultant. Only 12 of Kelly's patients were reported as “cases” in the medical literature, with the remaining being reported only in summary statistics. Of the remaining 312 ($364-52=312$) cases 37 were reported in detail in the literature, 35 were reported in the literature but not in detail. Two hundred forty cases were sent to Kelly but not reported in detail by anyone. Kelly reported a mortality rate of 11.5% for the 364 cases. The likelihood of survival was more than doubled if three or more x-ray treatments were administered as compared to one, although there were only 42 patients in the >3 category.

Did Kelly and colleagues prove their case? Could they do so, with the methods available during the 1930s and 1940s? Kelly amassed 364 case studies of x-ray treatment of gas gangrene. He was personally involved with 52 or 14.2%. Forty-nine (37 from other clinicians plus 12 from Kelly) case studies were reported in detail in the medical literature (13.4%) (Kelly and Dowell 1942). Three references have been published that were not supportive of the case of x-rays as an effective treatment (Caldwell and Cox 1941; Cubbins *et al.* 1941; Warthen 1942). These non-supportive papers suffer from a lack of specificity in the reported cases; it was also clear in the cases of Caldwell and Cox (1941) and Cubbins *et al.* (1941) that the x-ray treatment was generally reserved for a stage when the disease progression was far advanced and most patients were moribund. In

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such a situation, the x-ray treatment was a type of final hope after other procedures had failed.

The Kelly analyses relied heavily on comparisons with mortality statistics for soldiers in WWI and after the war with civilian cases. The mortality rate, as summarized above, was approximately 50% for both groups during the WWI time period. Why the mortality rate was about 50% and why it was much lower in the data reported by Kelly is hard to resolve. First, Kelly seemed to focus on the older data with the high mortality rate, rather than the lower rates after the war. This may have been done to emphasize his apparent successes. There are other factors that could affect the mortality rate (e.g., access to hospitals, use of ambulances, training of physicians and other services, health status of the patients, including nutritional state and quality/availability of serum). Over time there may have been cultural changes in the acceptance of amputations, rather than risking death without surgery with both patients and physicians. Furthermore, in the experience of Kelly and others, during the late 1920's to 1940, they saw relatively few cases of gas gangrene. The extremely low frequency of gas gangrene cases, the nature of the disease, including its potential for rapid progression, made it difficult to assess for treatment efficacy as the goal was to ensure survival and avoid amputation. This meant using any available treatment possible. The use of multiple treatments with most patients would make it difficult, if not impossible, to discern the effects of any single treatment such as x-rays. Such a situation forced Kelly to acknowledge that case studies have limited scientific application. In fact, this was why he initiated studies with guinea pigs in order to have an experimental model. Yet, the guinea pig, mouse, rat and rabbit models were tried and abandoned, without adequate data and explanation. Only research with the dog and sheep models seemed favorable for an experimental model, but only one paper was published with each model. While both showed a value for x-rays in the treatment of gas gangrene, both studies were very limited in the strength of their conclusions. Thus, overtime there was no substantial experimental model research that paralleled the clinical findings of Kelly and his collaborators. This was also a time before the advent of clinical trials with random allocation of patients to treatment. Yet, gas gangrene was not very amendable to this type of evaluation due to the high risk of death and amputation.

MECHANISM

Assuming that case study and supportive animal studies provide a reliable basis to conclude that x-ray treatment(s) reduce the severity of gas gangrene via prophylactic and/or therapeutic means, what could be the mechanistic basis? The occurrence of gas gangrene cases in the x-ray treatment literature has generally occurred following profound biological trauma, typically involving a compound fracture, along with substan-

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tial soft tissue damage often following an automobile/tractor accident. While it has generally been assumed that soft tissue damage provides an ideal environment for clostridium growth, major trauma has long been known to suppress immune function; T-lymphocyte function and splenic lymphocyte activities (e.g., cell proliferation and cytokine release) are especially known to be depressed (Miller *et al.* 1973; Esrig *et al.* 1976; Stahel *et al.* 2007; Ayala *et al.* 1996; Napolitano *et al.* 1996; McCarter *et al.* 1997; Hauser 1997). Several papers with rodent models have shown that trauma induced limb damage mimicking a compound fracture in humans results in a similarly profound depressive effect on immune responsiveness (Napolitano *et al.* 1996; Buzdon *et al.* 1999). It is hypothesized that such significant major decreased immune function may be a factor in affecting the rapidity and severity of gas gangrene disease progress. Considerable research exists demonstrating that low doses of ionizing radiation, including x-rays, enhance a broad spectrum of immune responsiveness (Calabrese 2005). Liu *et al.* (Liu *et al.* 1987; Liu *et al.* 1992; Liu *et al.* 1996) provide possible cellular and molecular mechanisms (i.e., increased product of oxygen free radicals) by which low doses of radiation enhance immune function while inhibiting it at higher doses. Despite a large number of studies showing the hormetic effect of low doses of ionizing radiation on immune function, none of these studies have been published in animal models following a trauma such as femur bone fracture. An alternative mechanistic hypothesis is the suggestion of Desjardins (1931) that low dose x-rays (75-200 rads) cause destruction of infiltrated lymphocytes, polymorphonuclear (PMN) cells and other immune cells (eosinophils) in the affected area. Desjardins hypothesized that this destruction released bacteriolytic compounds into the area which helped kill the *Clostridium bacilli*. This hypothesis also suffers from the fact that such responses were not reported within the context of the trauma of a compound fracture.

As discussed previously, gas gangrene cases have partially or completely occluded blood supply to the affected area creating an anaerobic environment to foster the growth of clostridium bacteria. The reduced blood supply may increase toxin concentration and decrease dead tissue removal from the affected area, thus further creating an environment that enhances the bacterial growth. Pendergrass *et al.* (1944) held that small doses of radiation were not able to induce significant damage to cellular components and affect the inflammatory process; however, low doses of radiation produce a local dilation of blood vessels, thereby increasing the rate and quantity of blood flow through the x-ray exposed area. Furthermore, passive hyperemia is converted to active hyperemia in the surrounding area by low dose x-rays. This enhanced blood flow leads to increased flow of electrolytes, increased temperature and increased

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lymphatic flow from the affected area, leading to increased efficiency of anti-infective and anti-inflammatory responses.

Within the past decade there has been considerable research directed toward the effects of low dose of x-rays in the treatment of various inflammatory conditions. While this research has not been directed to the issue of gas gangrene, the findings may have relevance to why x-ray treatments were successful in the treatment of gas gangrene during the 1930s and 1940s. In general, low doses of x-rays have been consistently shown to affect the development of an anti-inflammatory phenotype that is mediated by: decreases in nitric oxide/inducible nitric oxide synthetase, decreases in reactive oxygen species, increases in heme oxygenase, suppression of TNF α , increases in TNF β , activation of several transcription factors such as NF κ B and API as well as decreased adhesion of leukocytes and PMNs to endothelial cells (Rödel *et al.* 2007; Rödel *et al.* 2002). The low dose-induced anti-inflammatory phenotype is also biological context-dependent, occurring within an inflammatory setting when immune cells (e.g., lymphocytes) are activated, with these cells being radioresistant. This is in marked contrast to resting-immune cells which are susceptible to x-ray induced cell death (Trott and Kamprad 1999). Further research will be necessary to clarify whether the x-ray induced anti-inflammatory phenotype would be induced within the biological context of a traumatic injury such as a compound fracture and how this may affect the course of a gas gangrene infection.

DISCUSSION

This historical evaluation has revealed that x-ray treatment of gas gangrene was widely accepted in the U.S. during the 1930's to the early 1940's. The data were based on a substantial number of case studies that were widely reported in the medical literature and summarized in broadly integrated papers by Kelly and colleagues (Figure 1). The reports were made by experienced clinicians with findings at regional and national meetings and published in mainstream medical journals. Despite such acceptance in the field, x-ray treatments of gas gangrene therapeutically and later prophylactically unequivocal cause-effect relationships were never established due to the limits of case-control methodology, the presence of other co-treatments and the limits of animal model findings. Nonetheless, despite the presence of potentially confounding factors there was a strong belief by practitioners that x-ray treatment was predictably effective in the treatment of gas gangrene, being the treatment of choice. Table 2 provides a listing of quotes of researchers of the 1930's-1940's that strongly supported the effectiveness of x-rays in the treatment of gas gangrene. These observations and the accompanying data of the published literature reveals a strong association between x-ray treatment and the successful treatment of patients with gas gangrene. It is interest-

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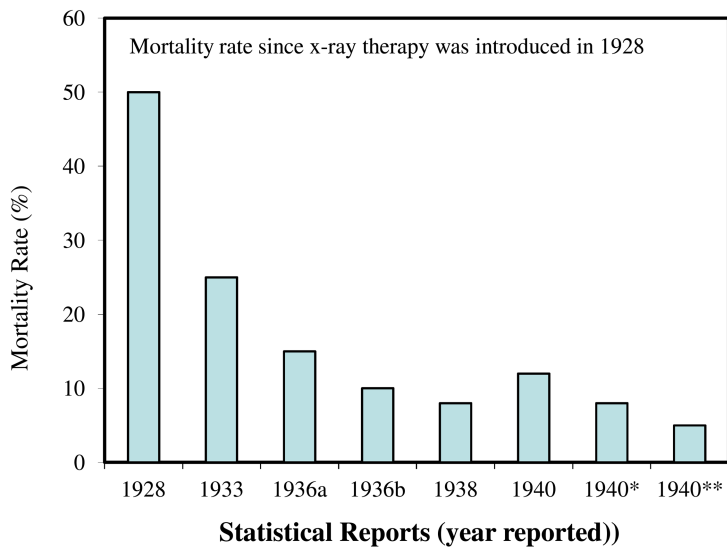


FIGURE 1. Mortality rate since x-ray therapy was introduced in 1928. Note: mortality associated with patients receiving surgery, serum, and one or more x-ray treatments unless indicated otherwise; (*) indicates mortality associated with patients receiving surgery, serum, and three or more x-ray treatments; and (**) indicates mortality associated with patients receiving three or more x-ray treatments with no surgery or serum treatments. [Data based on Calabrese and Baldwin 2000]

ing to note that in 1940 U.S. Army medical staff at Fort Sam Houston strongly supported the use of x-ray for prophylactic and therapeutic approaches in the treatment of patients with gas gangrene (see quote of reference 7-Table 2). Bowen (1940) states that the “successful use of x-ray therapy in gas gangrene suggests to the military surgeon that possibility of such therapy in war casualties... Mobile x-ray therapy should be part of the Medical Department’s armamentarium in any fatal campaign.” Yet, with the military of the U.S. entering WWII just one year later, we find no evidence that x-ray’s were used prophylactically or therapeutically in the treatment of gas gangrene (Jeffrey and Thomson 1944; Langley and Winkelstein 1945 nor was it used by the British (MacLennan and MacFarlane 1944). These studies date from 1943 to the end of the war. The treatments of choice during World War II included both serum anti-toxin therapy and chemotherapy, which included sulphonamides and then later penicillin or proflavine-sulphathiazole mixtures (MacLennan and MacFarlane 1944). Even with the use of penicillin in Italy military trenches, the over-all gas gangrene related mortality was in the mid 30% range (Jeffrey and Thomson 1944; MacLennan and MacFarlane 1944). The articles did not cite any literature on the use of x-rays in the treatment of gas gangrene.

It is now some 70 years since anyone has witnessed the striking treatment successes reported in the papers of the 1930’s and early 1940’s. From the perspective of today we have only two successful pilot animal

*X-Ray Treatment of Gas Gangrene***TABLE 2.** Perspective offered on the clinical efficacy of x-ray treatment of gas gangrene by practitioners of the 1930's and early 1940's

Reference	Quote
Ham, 1940	"It is not too much to say that those of my colleagues on the staff of the Prince Henry Hospital who were associated with these cases and who carried out the medical and surgical care in such an expert manner have been profoundly impressed by the results and are convinced of the great value of x-ray therapy. It should be especially noted, first, that all patients have recovered from the infection, and secondly, that in no case has amputation been necessary." Page 288
Bowen, 1940	"A case of gas gangrene involving the trunk died at Fort Sam Houston just prior to the receipt of Dr. Kelley's first report. After reading that startling presentation it was reasoned that if x-ray would stop gas gangrene after it had developed, it should abort it while in the incubation period, so since early in 1937 every lacerated wound and compound fracture has received prophylactic x-ray therapy. To date 40 cases have been so treated. Usually one dose of 120-150 r units has been given as soon after admission as possible. In a few badly contaminated cases the treatment has been repeated the following day. There has been no adverse effect of the x-rays in any case and it has been the impression of the surgical service that the cases receiving prophylaxis have shown less mixed infection and have healed more rapidly than the average case." Pages 109-110.
Cantril and Buschke, 1944	"The civilian surgeon, faced with a single case of traumatic gas bacillus infection, or the military surgeon with a ward full of its victims, is confronted by a menace to the life and future welfare of his patients. Well directed roentgen therapy has proved its efficacy in saving both lives and limbs. The thoughtful and diligent combination of surgery and x-ray therapy can produce results not heretofore obtained by any approach to this most severe complication of traumatic wounds." Page 345
Eliason <i>et al.</i> , 1937	"Although good results are reported from x-ray therapy, one is not justified at present in omitting serum therapy." Page 1014
Faust, 1933	"The writer has had the opportunity to observe and treat five gas gangrene cases [using x-ray therapy], with satisfactory results in each instance." Page 105 "The number of cases reported is not large, but the importance of the condition and the splendid results so far obtained make one feel that the information should be passed on..." Page 105 "Should new cases be found, we may attempt early treatment with x-ray alone and use the serum only if results are not favorable in a reasonable time." Page 106
Faust, 1934	"The x-ray treatment are a definite aid to recovery from gas gangrene infections." Page 550
Hubeny and McNattin, 1938	"Two more formidable complications can scarcely be asked for, and yet, withal their devastating aggressiveness, they can be throttled very effectively with irradiation therapy. The only cases we have lost, especially in the series of patients suffering from gas infection, have been those who have been sent to us in a semi-moribund state, post-operative, with crepitus involving half of their body and temperatures of 104-105 degrees F. We urge all those who read this article <i>never</i> to hesitate to recommend x-ray therapy for any patient whom you suspect of having gas infection or erysipelas. If there is ever an emergency x-ray treatment needed, regardless of the time of day or night, it is for the treatment of either of these diseases." Pages 438-439

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TABLE 2. Continued

Kelly, 1933	"Roentgen rays are established aids in diagnosis and in teaching (including research), but it is in connection with their status as an aid in therapy, especially in connection with the treatment of gas gangrene in conjunction with other measures, that this article has been written. Furthermore it is sincerely hoped that the widespread use of them in many cases will be as generally successful as it has been in the few cases reported here. If so, there will be fewer amputations and transfusions, a lower mortality, and, probably, the use of less serum, which sometimes leads to severe reactions and much discomfort." Page 301
Kelly, 1936	"If one may be permitted to draw conclusions from such a small series of cases, it seems to be definitely certain that x-ray treatment is indicated in gas gangrene, both in extremity and in trunk cases; that the treatment should be started as soon as the disease is suspected and be given throughout its course, twice each day for at least three days." Page 43
Kelly <i>et al.</i> , 1938	"The x-ray has also been of benefit in treating the arteriosclerotic, diabetic cases developed the complication of gas gangrene." "The analysis of the data so far available in connection with the x-ray treatment of gas gangrene seems to prove that x-ray treatment, properly given, is the answer to the question of what to do in treating a gas-forming infection." Page 619
Kelly and Dowell, 1941	"The x-ray provides a certain and definite means of prevention and treatment of gas gangrene." "The x-ray has been used successfully for the prevention of other varieties of infection after recent injuries as well as gas gangrene." "The x-ray has removed gas gangrene from the class of acute diseases having a high mortality and morbidity, in which experimental therapeutic measures are justifiable." Page 437
Von Briesen, 1940	"Many, many cases of proved gas gangrene have been cured with radiation alone." "As far as infections are concerned the use of radiation is empirical, but it does work. In the case of gas gangrene it works when nothing else will." Page 161
Williams and Hartzell, 1939	"That roentgen therapy is of value as a therapeutic agent has been established beyond a reasonable doubt." "The mortality rate was 58 per cent in the traumatic group <i>not</i> having roentgen ray therapy and eight per cent in the traumatic group which <i>did</i> have roentgen ray therapy – a difference of 50 per cent, or six living patients." Page 565

experiments, and about 364 cases reported in the literature but with only about 1/6 of these given in some degree of detail. Could the generally consistent findings of the dozen or so research groups have made an error on causality of the treatment effect? Despite the heterogeneity of the patients (age, gender, extremity affected, cause of condition, different causative agents, time to treatment, other types of treatments) none of these treatment variables accounts for the reported success of the x-ray treatments. In the absence of a good alternative, x-ray treatment became the treatment of choice and was associated with notable success. However, it is important that no substantial animal model research developed to confirm the efficacy of the x-ray treatment. Today we are left with an his-

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torical recognition of the efforts of James Kelly to create this area of research, to encourage others to collect and share data and to present their findings at conferences and to publish findings in leading journals. To the treating practitioner of the 1930's the x-ray treatment was a practical and potentially hopeful means to treat gas gangrene even if data were empirical.

The question that emerges today is whether the efforts of the 1930's and 1940's should remain only an historical footnote or should they inspire new research initiatives to determine whether x-ray administration could be a useful and available complementary treatment, under what clinical conditions, and with clarification of its underlying mechanisms. This could be of particular value for poor countries that bear the greatest burden of this disease and where cost drives the treatment. Low cost and easy availability of x-rays may be a useful option in countries treating many patients who are unable to afford surgeries, antibiotics, and hyperbaric oxygen.

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