

DISINFECTING WOUNDS WITH RADIATION

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ABSTRACT

Infection with clostridium bacteria, which live in the soil, is most often associated with war wounds, car accidents, complicated abortions, etc. The incidence is highest in areas with poor access to proper wound care. Such infections lead to gas gangrene, a deadly disease that spreads very quickly in the body and causes rapid death. Present-day treatment consists of administering antibiotics and surgical removal of dead, damaged and infected tissue. Amputation is usually necessary to control the spread of the infection, which can advance at the rate of six inches per hour. Before the 1940s, this disease was treated successfully with low doses (50 rad) of radiation (X-rays) in the area of infection. A review of 364 cases treated in this manner, from 1928 until 1940, indicated that patient mortality would be reduced from 50 percent (or higher) to ~5 percent if patients were treated reasonably early and with the correct technique. X-ray therapy stopped the infection without the need for amputation to control its spread. Low-dose irradiation (LDI) therapy, given immediately, acted as a prophylaxis to prevent the onset of gas gangrene. This is but one example of the extensive use of radiation treatment of many types of infections, before the advent of antibiotics. Low doses are inadequate to kill invading bacteria directly, however, they will stimulate our defences to destroy the infection. The observed beneficial effects are consistent with the large amount of scientific evidence of radiation hormesis - the stimulation of an organism's own defences by low doses of radiation (to destroy invaders and heal wounds). In view of the ineffectiveness of antibiotics in many cases and the evolution of antibiotic-resistant strains of bacteria, physicians should start to use LDI therapies again. Many patients would benefit greatly.

INTRODUCTION

In a paper presented at the 2001 Annual Conference of the Canadian Nuclear Society, I explained why the linear-no-threshold (LNT) model of radiation carcinogenesis is invalid and

be ignored and discarded after the mid-1940s - about the time that antibiotics started showing dramatic success in a variety of applications. While "miracle pills" made other medicines seem outmoded, the LNT theory was creating a negative image about all nuclear technologies. This theory, that no amount of radiation was safe, discouraged exposure to any amount of radiation by associating it with cancer.

A recent historical review by Berk and Hodes shows clearly that radiation was used extensively for the treatment of many types of infections before the advent of antibiotics.[2] Based on the widespread clinical evidence, radiation therapists of that era were firm believers in the ability of low-dose local radiation, in the range of 75 to 300 rad, to cure a wide variety of infections. The mechanism of action was unclear. One rationale held that the effect was due to radiation damage to the immune system, causing it to be stimulated. Another - that it was due to the increase in local inflammation with resultant increase of blood flow. (It was understood back then that these low doses did not significantly destroy the bacteria directly.)

Calabrese and Baldwin define *hormesis* as an adaptive response of biological organisms to low levels of stress or damage - a modest overcompensation to a disruption - resulting in improved fitness.[3] They point out that observation of this reproducible phenomenon has a long history (since the 1880s), and it has been widely reported in the scientific biomedical and toxicological literature. These scientists screened 20,285 articles suggesting a chemical hormesis effect and extracted hundreds of dose-response relationships that met their special *a priori* criteria - the requirements for rigorous evidence of hormesis. They also carried out a review of the history of radiation stimulation on plants, as well studies on insects, bird eggs, salamanders, etc.[4] This review includes a description of the clinical verification and application of the concept of "low-dose stimulation, high-dose inhibition" in the early decades of the 20th century, in the treatment of human diseases and other conditions. Within one year of Roentgen's discovery of X-rays, 1000 papers were published on their application. The first therapeutic application reported (in 1897) the disappearance of inflammatory symptoms following treatment. Radiotherapy was widely employed for the successful treatment of many inflammatory conditions and infections, including pneumonia. The magnitude of the clinical literature is substantial. It is interesting to note that the term *hormesis* was not coined until 1943.

GANGRENE

What is it? The current Britannica Concise Encyclopedia states that gangrene is: *Localized soft-tissue death (necrosis) from prolonged blood-supply blockage. It can occur in arteriosclerosis, diabetes, or decubitus ulcer, and after severe burns or frostbite. In dry gangrene, gradual blood-supply decrease turns the part discolored and cold, then dark and dry. Treatment requires improving bloodflow. Moist gangrene comes from a sudden blood-supply cutoff. Bacterial infection causes swelling, discoloration, and then a foul smell. Along with antibiotics, tissue removal may be needed to prevent spread, which can be fatal. A more virulent form, gas gangrene, is named for gas bubbles under the skin produced by a highly lethal toxin from clostridium bacteria. The wound oozes brownish, smelly pus. Infection spreads rapidly, causing death. All dead and diseased tissue must be removed and antibiotics given; an antitoxin can also be used.*[5]

In dry gangrene, healing usually takes place naturally at the junction between the living and dead tissue. In moist gangrene, some cells stay alive while surrounding cells begin to quickly die and leak fluid. Bacteria flourish in this environment. Gas gangrene, the most deadly form, occurs in wounds that are affected by bacteria that live in low oxygen environments and release gas and poisons into the body. It is most often associated with war wounds, car accidents, complicated abortions, etc. The incidence is highest in areas with poor access to proper wound care.

GAS GANGRENE AND CURRENT TREATMENT

A search of the Internet (Yahoo/Google) in March 2002 yielded ~9000 web-page matches for the words "gas gangrene". Since gas gangrene or *clostridial myonecrosis* is caused by a family of bacteria that live under low-oxygen (anaerobic) conditions in the soil, hyperbaric oxygen (HBO) treatment can be employed to kill the bacteria, "possibly avoiding amputation, previously the only treatment."

The US National Institute of Health states that clostridium bacteria produce many different toxins, four of which (alpha, beta, epsilon, iota) can cause potentially fatal syndromes.[6] In addition, they cause tissue death (necrosis), destruction of blood (hemolysis) local decrease in circulation (vasoconstriction) and leaking of the blood vessels (increased vascular permeability). These toxins are responsible for both the local symptoms - tissue destruction - and the systemic symptoms - those that occur throughout the body - sweating, fever and anxiety. If untreated, the person develops a shock-like syndrome with decreased blood pressure, renal failure, coma and finally death. To prevent the disease, one must clean any skin injury thoroughly and watch for signs of infection: redness, discoloration, and/or puffiness. If the symptoms occur, medical care must be obtained promptly. The treatment consists of prompt surgical removal of dead, damaged and infected tissue (debridement). Amputation may be indicated to control the spread of infection. Antibiotics, preferably of the penicillin type, should be given - initially intravenously. Analgesics may be required to control pain. Hyperbaric oxygen (HBO) treatment has been tried with varying degrees of success. The complications include: disfiguring or disabling permanent tissue damage, jaundice with liver damage, kidney failure, spread of infection systemically through the body, shock, stupor, delirium and coma.

An HBO caregiver provides additional information.[7] The infection is so progressive that the patient would die before any immunity could develop. The action of HBO is based on the formation of oxygen free radicals in the relative absence of free-radical degrading enzymes. An oxygen pressure of 250 mm Hg is necessary to stop alpha-toxin production and inhibit bacterial growth locally, thus enabling the body to utilize its own host defense mechanisms. The onset of gas gangrene may occur between 1 and 6 hours after injury and presents itself with severe and sudden pain in the infected area. The infection can advance at the rate of 6 inches per hour. A delay in recognition or treatment may be fatal. Since the acute problem is the rapidly advancing phlegmon caused by alpha toxin in infected but still viable tissue, it is essential to stop alpha toxin production as soon as possible and continue therapy until the advance of the disease process has been arrested. Major clinical studies indicate that the lowest morbidity and mortality are achieved with initial conservative surgery and rapid initiation of HBO therapy.

The University of Idaho points out that the infection can advance through healthy muscle and destroy it at the rate of several inches per hour in spite of antibiotic treatment.[8] Even with

modern medical advances and intensive care, amputation is often the only choice and even then 40 to 70 percent of victims will die. Research is underway in Idaho, using an enzyme, on "a new strategy to fight gangrene that would rely on the body's own immune system and reduce the need for amputation".

LOW-DOSE IRRADIATION THERAPY – 1931 REPORT^[9]

In a remarkable presentation before the Radiological Society of North America, Dr. James Kelly reported his experience, since 1928, in the treatment of a group of eight cases of gas gangrene using low doses of X-rays. The mortality rate for this disease up to that time had been 50 percent or higher, but in this group it was only 25 percent. No additional tissue was removed in any case, after radiation therapy was begun. In six cases involving the limbs, improvement followed immediately after the first X-ray treatment; amputations were unnecessary in three cases. But the two patients with involvement of the trunk died. For the treatment of such cases he advised that a higher X-ray voltage be used to increase the penetration. St. Catherine's Hospital (Omaha, Nebraska) started to use this method of treatment, in addition to other measures, on all gas gangrene cases.

Dr. Kelly urged other physicians to use this form of treatment for gas gangrene because everyone had access to X-ray apparatus and no special knowledge was required for applying the mild doses he employed. He pointed out that *"roentgen treatment of many localized infectious processes, due to other types of organisms, has been so definitely beneficial in the past that to neglect its use in gas bacilli infection may truly be considered poor judgment. In fact, x-ray treatment of these localized infections has been so successful and the results so widely published for the past twenty-five years or more that it seems unnecessary to make a plea for its use in such a fulminating and serious infection as gas gangrene usually proves to be. However, the use of the x-ray as an aid in the treatment of localized infections seems to have escaped the attention of many sincere practitioners."*

Although there had been no animal experimentation completed, he advised that, in the meantime, in the treatment of a serious infection, any simple measure which did not interfere with other indicated measures, was not inherently dangerous, and appeared to be beneficial on all occasions, should be employed regularly, regardless of possible lack of confirmation from the laboratory.

With a mobile 80 kV X-ray unit (and a filter to prevent skin burns), he applied a local dose of 50 rad (0.5 Gy) over a 3-minute period. Most patients received this dose twice on the first day, twice on the second day, once on the third day, and once again on the fourth day. All tissues suspected of involvement were irradiated by moving the X-ray tube as needed, with overlapping on the areas.

Dr. Kelly did not understand the action, but mentioned some useful characteristics of X-rays, among them, their ability to penetrate, cause chemical change, stimulate defensive powers of living cells or destroy them depending on the amount of radiation received. The power to penetrate is very important because he was attempting to reach an infection situated deeply in the muscles. He pointed out that a radiologist recommending the application of X-rays would often encounter objections from a surgeon who would state that X-rays have no action - they could not destroy any organisms. The same physician would then explain to patients that X-rays would

cause a burn. Dr. Kelly stated that the ability of radiation to exert a stimulating or destructive action on living cells, depending on the dose, was a scientific and clinical fact, beyond any possibility of question.

The discussion that followed this presentation mentioned other applications of X-ray therapy for inflammatory diseases - severe arthritis identified in 1906 and diphtheria in 1920. Progress in applying this treatment had been very, very slow due to the lack of scientific proof of the action of the X-rays in the inflammatory tissue. One success that survived criticism was the treatment of acne and boils.

TWELVE-YEAR REVIEW OF RADIATION THERAPY OF GAS GANGRENE.^[10]

The mortality rate for gas gangrene up to 1928 had been 50 percent or higher, and that figure was attained only by the sacrifice of many arms and legs. The reduced mortality of 25 percent in the first group of eight cases, reported in the 1931 meeting, led many radiologists, a number of surgeons, and a few practitioners in the other specialties to try this therapy. Kelly and Dowell presented the data from a total of 364 cases, during the period 1928 to 1940, before the Radiological Society.

Figure 1 shows the drop in the mortality rate. It indicated, *"gas gangrene need no longer be regarded as a serious disease. The x-ray has definitely removed gas gangrene from that group of disease in which experimental therapy is any longer justifiable."*

Kelly stated that chemotherapy failed in well-developed cases because there was definite interference in the circulation to the infected area and consequently the chemical did not reach the diseased tissue. The X-ray, however, had no difficulty in effectively reaching all cells and fluids in any infected area. Other ways of treating gas gangrene might be developed, but there could be no question as to the status of the X-ray in the prevention and treatment of this serious infection. Since the mortality rate in cases treated with radiation was so much lower (4.7 to 11.5 percent) than that obtained by any other methods employed up to that time, Kelly suggested that those who refused to use irradiation should feel called upon to offer some explanation.

All but one of the 21 published reports on the roentgen treatment of gas gangrene that had appeared in the literature up until 1941 were favourable to the use of radiation, both as a preventative and as a therapeutic measure. The unfavourable publication reported ten deaths in fourteen cases, but no details of the cases were given. Based on his assessment of the 364 cases, Kelly stated that the mortality rate in the post-traumatic cases should not be in excess of ten percent. *"Any patient, no matter how far his disease has advanced, is entitled to a trial of x-ray therapy. Patients treated reasonably early and with the correct technique will respond favorably in most instances."*

Prophylaxis

The incubation, after injury, of gas gangrene in 134 available cases occurred in 15 percent of the cases within 24 hours - the incidence peaking between the 48th and the 72nd hour. X-rays were used successfully by several workers to prevent the onset of gas gangrene and it was observed that the incidence of other infections also, osteomyelitis after compound fracture in particular,

seemed lessened by their use. Kelly did not suggest a reason for the action of radiation in preventing osteomyelitis, but if the rapidly growing organisms, such as the gas formers and the streptococci, can be kept from establishing an infection immediately after the injury, it was possible that the more stubborn slowly-growing secondary invaders would never have an opportunity to develop, as the wound might be well on the way to recovery before their usual period of incubation has been completed. The effect is prophylaxis in the same sense that cleansing the wound is prophylaxis. Figure 2 shows a severe hand injury case, with multiple fractures and some gas in tissues (left X-ray). The same hand a few days after prophylactic irradiation (right X-ray) shows no gas in the tissue - no infection - the hand on the way to complete recovery. The patient received anti-tetanus and anti-gas serum, but no sulphanilamide.

Dosage

For treatment, Dr. Kelly and his colleagues gave 150 rad per day in two doses of 75 rad or three doses of 50 rad to the area they believed to be infected. For prophylaxis, they gave 75 rad daily in one dose. The voltage varied from 90 to 130 kV, depending on the thickness of the part. Filtration increased with voltage.

Amputation

In Kelly's opinion, amputation during the acute toxic phase of gas bacillus infection that is receiving adequate and proper radiation therapy has never benefited any patient in the least. Whatever surgery is indicated because of the injury should be performed, but there should be no extensive removal of muscle groups or other major surgery for the infection itself during the acute toxic phase. With radiation therapy, the tissue that is destroyed during the invasive stage becomes demarcated as the disease regresses, and the dead tissue, if there be any, may be removed after the acute toxic stage has passed. In Kelly's judgment, there should not be more than one or two percent mortality because of deferred amputation and about the same mortality from the infection itself. In essence, he advocated a simple and effective measure to replace drastic measures that were ineffective. Previously there had been no treatment for the infected part in gas gangrene, since amputation, or elimination of the infective area by surgical measures, can hardly be considered treatment. The area was not treated; it was simply removed. With radiation therapy the infected part is actually treated and is removed only if it does not recover. X-ray therapy was far superior to any other method when it was available. Questionable and experimental measures of whatever character should not be substituted.

Use of sulphanilamide

The records of some deaths, particularly among diabetic patients, suggested that the use of "serum" (sulphanilamide, the early form of the "sulfa drugs" - the first use of the chemical antibiotics) might have been an important factor in the fatal outcome. The many instances in which *serum* had failed to prevent or cure the disease, while radiation therapy had been followed by prompt improvement, gave the impression that if radiation therapy was available *serum* was unnecessary. Large doses of *serum* after the toxin of a gas infection had damaged the kidneys appeared to be more than some patients could withstand, and urinary suppression and death ensued. The mortality rate in 65 cases without *serum* was lower than in 248 cases with *serum*.

Kelly (and others) determined that sulphanilamide and radiation therapy could not be used simultaneously with good effect. Little was known about the interaction of these two agents, but they should not be given at the same time. *Serum* was not effective in stopping the gas gangrene infection and, when used simultaneously with irradiation, completely degraded the effectiveness of the radiation therapy. In fact, it seemed that the destruction of tissue was accelerated.

Acute peritonitis

In applying the X-ray treatment to patients with acute spreading peritonitis (inflammation of the membrane lining the abdominal cavity), Kelly found that the response of patients was as prompt and convincing as it was in gas gangrene.

CONCLUSIONS

The experience of Dr. Kelly and others shows that ionizing radiation provides a certain and definite means of prevention and treatment of gas gangrene that should have removed it from the class of acute diseases having high mortality and morbidity. Sulphanilamide chemotherapy is unnecessary; irradiation was effective after this *serum* failed. *Serum* may even be harmful to the diabetic who develops a gas infection and raises the question of whether *serum* will injure aged patients. Radiation is successful for the prevention of other varieties of infection, following injuries. It seems to have completely eliminated the necessity of extensive surgery as a means of treating gas gangrene during its acute invasive stage. Kelly recommended that any surgery indicated by the initial injury or disease should be performed, but no surgery for treatment of the gas gangrene, except for occasional incisions to relieve local tensions. So amputation and extensive debridement should be obsolete procedures in the toxic stage of the disease. Kelly practically eliminated them after the disease had subsided, because they were seldom necessary. He said they should never be necessary if treatment is started early and is properly given.

This 12-year study should have been an important basis for the promotion of the general use of X-ray therapy for inflammatory disease at the bedside, with an apparatus of adequate voltage. The curative action of the X-ray in gas gangrene should have established beyond any doubt the fact that irradiation is of value in treating infections, because the gas infections are uniformly resistant to other treatments, but responded consistently to LDI therapy. The antitoxic effect of radiation in acute infections was amply demonstrated in treating gas gangrene, acute spreading peritonitis, surgical mumps, erysipelas (local febrile disease) and other toxic acute infections. This general reaction as well as the favourable local effect was evident to many clinicians, years before gas gangrene was treated with radiation. So why was LDI therapy ignored and discarded after the mid-1940s?

Calabrese and Baldwin addressed this question in a recent paper¹¹ The most critical factor was the lack of agreement over how to define the concept of hormesis and quantitatively describe its dose-response features. If radiation hormesis had been defined as a modest overcompensation to a disruption in homeostasis, as would have been consistent with the prevailing notion in the area of chemical hormesis, this would have provided the theoretical and practical means to blunt the criticism of this hypothesis. The second critical factor was the total lack of recognition by radiation scientists of the concept of chemical hormesis, which had been more advanced,

substantiated and generalized than in the radiation domain. The third factor was the major scientific criticism of low dose stimulatory response that occurred when the US was organizing a national research agenda on radiation. The hormetic hypothesis was generally excluded from the future planned research opportunities. On top of this came the criticisms of the leading scientists of the 1930s and the LNT hypothesis, which undermined the concept of radiation hormesis. These criticisms, limited in scope and highly flawed, were perpetuated over the decades by other "prestigious" experts, who appeared to simply accept the earlier reports. This setting was then linked to a growing fear of radiation as a cause of birth defects, mutations and cancer - factors all reinforced by later concerns over the atomic bomb. Findings on hormetic effects by Soviet scientists were either not available or disregarded. A massive, but poorly designed experiment on low-dose plant stimulation in the late 1940s failed to support the hormetic hypothesis.

Even in the 1940s, there were many physicians who had never heard of the X-ray as a means of prevention or treatment of gas gangrene, and others who insisted that there were not yet a sufficient number of cases in the literature to establish its true status. Today, with penicillin and more advanced antibiotics, it is easy to regard the 60-year old LDI technology as primitive. However, the current status of gas gangrene, as outlined at the beginning of this paper is not encouraging. Even advanced antibiotics will not reach areas where there is no circulation, and antibiotic-resistant bacteria continue to evolve and proliferate. HBO is useful, but it cannot reach deep-seated regions of infection. Radiation (which also creates oxygen free radicals) can reach these regions. The availability of HBO chambers is severely restricted compared to radiation treatment devices. But when we consider the enormous influence of the pharmaceutical industry and the pervasive preference for chemotherapy solutions, it is not surprising that there is still no mention at all of LDI therapy.

In trying to understand the action of the low doses (50 or 75 rad) to destroy invading bacteria in a living organism, we should be aware that a radiation exposure in the range 10 to 50 kGy (1000 to 5000 kilorad) is necessary for sterilization.^[2] Like HBO therapy, ionizing radiation creates oxygen free radicals. A more direct effect may be a delay in the cell cycle, allowing our immune kill rate to exceed the bacteria proliferation rate. But the large amount of evidence in support of the radiation hormesis hypothesis provides a very high degree of confidence that the principal action of LDI therapy is to stimulate our own defences to destroy infections and cure wounds. The likelihood of delayed cancers due to such small radiation doses is negligible compared with the likelihood of cancer due to normal metabolic processes.^[1]

The action of LDI therapy can be better understood by comparing it with local radiation treatment for cancer. Typically, a tumor is exposed to 200 rad (2 Gy) per day, 5 days per week, for several weeks, and this is a universally accepted treatment, i.e., the risk/benefit ratio is judged to be highly favourable. Like cancer, gas gangrene is life threatening, but the doses in LDI therapy are much lower. So the residual risk would be much lower, assuming the potential for cancer formation is proportional to dose (i.e., the LNT model). However, the real effect of radiation is to impair many cellular functions at high doses and stimulate them at low doses.^[13] So, in addition to treating the infection, LDI therapy reduces the risk of cancer from what it would be without the therapy.

The potential benefits of using low dose irradiation therapy on gas gangrene patients and other patients are enormous. By rejecting this form of treatment, it seems that physicians are denying its important benefits to many needy patients.

When will the medical profession start again to apply such treatments?

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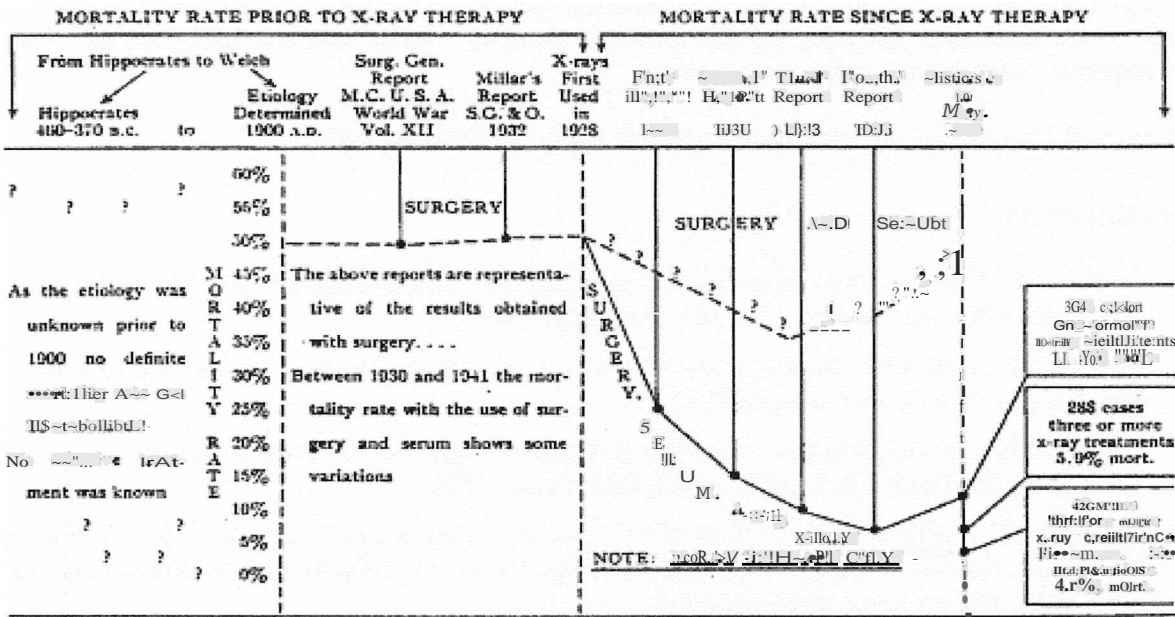


Figure 1. End of gas gangrene as a serious infection (if X-ray therapy is used) From Hippocrates' time (460-370 B.C.) to 1900 A.D. the etiology of gas bacillus infection was unknown and as a result the mortality rate during that period cannot be accurately determined. Between 1900 and 1928 the mortality rate was 50%. Since 1928, the mortality has been reduced to 5% by the use of X-ray therapy without serum or radical surgical measures. X-ray therapy will prevent or cure the disease. Kelly and Dowell[7]

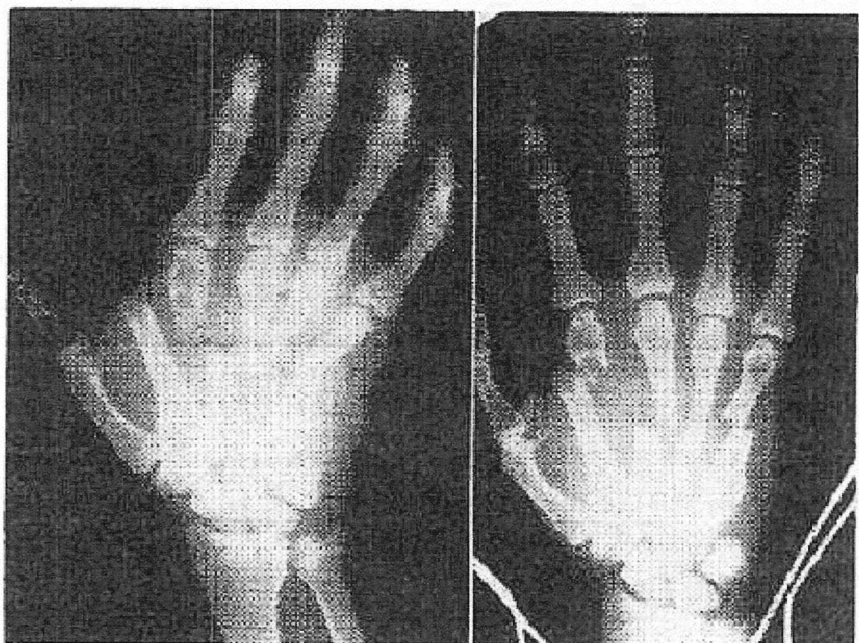


Figure 2. Severe hand injury with multiple compound fractures and some gas in tissues (left). Same hand a few days later after prophylactic X-ray irradiation: no gas in the tissue, no infection, hand on way to complete recovery, Kelly and Dowell[7]