

REVIEW

How Radiotherapy Was Historically Used To Treat Pneumonia: Could It Be Useful Today?

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X-ray therapy was used to treat pneumonia during the first half of the 20th century. Fifteen studies report that approximately 700 cases of bacterial (lobar and bronchopneumonia), sulfanilamide non-responsive, interstitial, and atypical pneumonia were effectively treated by low doses of X-rays, leading to disease resolution, based on clinical symptoms, objective disease biomarkers, and mortality incidence. The capacity of the X-ray treatment to reduce mortality was similar to serum therapy and sulfonamide treatment during the same time period. Studies with four experimental animal models (i.e., mice, guinea pig, cat, and dog) with bacterial and viral pneumonia supported the clinical findings. The mechanism by which the X-ray treatment acts upon pneumonia involves the induction of an anti-inflammatory phenotype that leads to a rapid reversal of clinical symptoms, facilitating disease resolution. The capacity of low doses of X-rays to suppress inflammatory responses is a significant new concept with widespread biomedical and therapeutic applications.

INTRODUCTION

Pneumonia has long been a serious risk of mortality. In his famous 1892 text, Osler [1] said of lobar pneumonia, “It is a self-limited disease and runs its course uninfluenced in any way by medicine. It can be neither aborted, nor cut short by any known means at our disposal.” However, by 1913, leaders at the Rockefeller Institute

initiated equine serum therapy for the treatment of pneumonia, especially for lobar pneumonia [2]. Two decades later, the mortality from lobar pneumonia displayed an incidence of 25 percent to 40 percent in patients not receiving serum; while in those receiving such therapy, the risk was reduced by approximately half, to 10 percent to 20 percent [3,4]. While serum therapy

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represented a major advance in the treatment of lobar pneumonia, it was expensive, time consuming, and not useful to patients with allergic reactions to the horse (and later, guinea pig) sera and fatal in about 4/1000 patients due to severe anaphylactic responses. The use of serum therapy would soon be eliminated after the introduction of sulfonamides in 1939.

While the principal therapeutic option for the treatment of pneumonia prior to 1939 was serum therapy, a potential alternative to this therapeutic monopoly was emerging during the 1930s in the form of radiotherapy. Radiotherapy had been broadly accepted by the radiological community starting in the second decade of the 20th century, with notable successes in the treatment of a wide range of inflammatory and infectious diseases [5] such as gas gangrene [6], carbuncles [7], sinusitis [8], arthritis [9,10], and inner ear infections [11]. Based on clinical successes in these and other areas [12,13], it was not unexpected to see exploratory attempts to treat pneumonia patients with X-rays using similar protocols. This paper, therefore, assesses the historical use of X-rays in the treatment of various types of pneumonia in the United States during the first half of the 20th century, based on clinical findings, animal model investigations, and recent mechanistic insights that likely account for at least some of the reported therapeutic benefits.

INITIAL TREATMENTS OF PNEUMONIA PATIENTS WITH X-RAYS

The initial report using X-rays to treat patients with pneumonia was in 1905 by Musser and Edsall [14] at the University of Pennsylvania. They believed that X-rays may be useful in the treatment of unresolved pneumonia, that is, when the disease resolution process fails to proceed to a cure, with lung exudate material showing consolidation, enhanced bacterial infestation, and risk of prolonged serious illness. Since X-rays enhanced ferment (i.e., metabolic) processes in a range of tissues, they hypothesized that the X-ray treatment may accelerate autolytic

processes and enhance the metabolism of conditions that had been slowed down, including unresolved pneumonia. They hypothesized that X-ray treatment would increase the metabolic digestion of the exudative material, leading to a resolution of the pneumonia. If this hypothesis were valid, the authors argued that “rational” therapy would involve the induction of ferment activity to digest the exudate. Based on this premise, Musser and Edsall [14] selected five cases, all with pneumonia-related fever having disappeared but with clear signs of lung consolidation. Metabolism was estimated by measuring changes in urinary excretion of nitrogen, chloride, uric acid, and phosphorus after having been placed on a standard diet several days prior to the X-ray treatment.

Following X-ray treatment, a progressive and consistent disease resolution took place based on clinical observations and X-ray confirmation. Since only five cases were assessed, the authors were cautious in their conclusions, stating only that further research into this area was justified. Despite its potential clinical implications, their principal focus was on the validity of the X-ray metabolism hypothesis.

The observations by Edsall and co-authors would not be extended for a decade, until Quimby and Quimby [15] reported on the successful treatment of 12 cases of unresolved pneumonia. It is not clear why Quimby and Quimby [15] used X-rays to treat unresolved pneumonia as they did not cite the earlier research of Edsall and colleagues. However, they began their paper with the statement that “no pathological process in the body responds quicker to an X-ray exposure than the non-resolved following pneumonia,” suggesting a clinical basis for this statement. These researchers acted upon a different theoretical mechanism than Edsall and colleagues by which X-ray treatment reverses the unresolved pneumonia. They proposed that the “vibratory actions of the X-ray explains the beneficial ... result in raying the chest. One of the most characteristic properties of the X-ray is the power of ionization, that is, of

breaking up the molecular structure of the substance upon which it falls and liberating ions or electrons ... the rays ... penetrate the mass of leucocytes, ionized or disintegrated them into their constituent parts, enabling them to be carried away by the lymphatics.” Even though the paper was published in 1916, the cases were accumulated from 1910 onward. As was the case with the Edsall studies, the authors did not continue to publish findings on this topic.

MAJOR TRANSITION

In 1924, Heidenhain and Fried [16,17] stimulated research on the effects of X-rays on the clinical course of pneumonia. They reported on 243 cases of acute and subacute pyrogenic infections of numerous types treated with X-rays. This paper offered a new mechanistic insight founded on the dose response, proposing that low doses of X-rays would affect disease resolution [18].

Heidenhain and Fried [16,17] showed that not only did X-ray treatment block/reduce superficial inflammations such as those seen with carbuncles and furuncles, but inflammation of all types, regardless of location in the body and whatever the cause, was also reduced. Within this generalized framework, low doses of X-rays were seen as having clinical utility for the treatment of deeper penetrating infections, including pneumonia. Of particular significance were observations that not only did the X-ray treatment have lifesaving potential, but it was also effective when other treatments had reached their therapeutic limits as seen in cases of chronic bronchopneumonia, which could be resolved with a single administration of X-rays.

Fried [19] offered a brief clinical description of a common acute post-X-ray treatment patient, a response he had often observed: “A patient with a high fever, severe dyspnea, and cyanosis is irradiated. A few hours later, often within a period of six hours, he states that he can breathe more easily, and he takes some nourishment. After twelve to twenty-four hours the fever abates, in most cases by crisis, breathing is no

longer painful, and dyspnea decreases or disappears entirely. In most of the cases reacting favorably a normal condition is re-established in twenty-four to forty-eight hours. In some cases the fever does not resolve by crisis but falls in two long steps; in some there is a gradual decline to normal. In all these cases the decline of temperature, disappearance of dyspnea, general improvement, and indeed the whole course of the disease appear to have been definitely hastened by irradiation. And as this observation was made consistently, it would seem to be an established fact.”

The capacity of X-ray treatment to accelerate recovery of unresolved pneumonia in children was subsequently reported by Krost [20], based on five cases of lobar pneumonia, five cases of bronchopneumonia, and two combined cases. Eleven of 12 patients displayed notable improvement following the X-ray treatment. Krost’s [20] interest was initiated by an unpublished observation by a colleague that a diagnostic lung X-ray of a child with pneumonia seemed to have enhanced the recovery process of an unresolved pneumonia. That diagnostic X-rays could trigger the healing process had been suggested by Schillinger in 1924 with acute mastoiditis, although he did not report this in the literature until 1932 [21].

Following a positive but limited paper by Merritt and McPeak [22] concerning unresolved pneumonia in six cases, the notion that X-ray therapy could be more broadly effective in the treatment of pneumonia emerged with the research of Eugene Powell, who obtained visibility for his findings by making them the subject of his Chairman’s Address before the Section on Radiology and Physiotherapy at the Medical Association meeting in Houston, Texas, in May 1936 and later at the Fifth International Congress on Radiology in Chicago in September 1937, inspiring a spate of follow up studies, including McIntire and Smith [23], Scott [24], Solis-Cohen and Levine [25], Settle [26], Rousseau et al. [27], and others (Table 1).

Despite previous publications concerning X-rays as a treatment for pneumonia,

Table 1. X-ray therapy in the treatment of pneumonia.

Reference	Types of Pneumonia	Case Number	Cases Cured
Musser and Edsall [14]	Unresolved pneumonia	1	1
Edsall and Pemberton [37]	Unresolved pneumonia	2	2
Quimby and Quimby [15]	Unresolved pneumonia	12	11
Krost [20]	Unresolved pneumonia	12	11
Fried [72]	Post-operative pneumonia	40	32
Fried [73]	Post-operative pneumonia	57	N/A
Merritt and McPeak [22]	Unresolved pneumonia	7	6
Powell [3,28,33]	Lobar pneumonia and bronchopneumonia	231	215
Scott [24]	Lobar pneumonia	138	111
Solis-Cohen and Levine [25]	Lobar pneumonia	42	40
Settle [26]	Lobar pneumonia	34	32
Rousseau et al. [27]	Lobar pneumonia	104	98
Rousseau et al. [27]	Viral pneumonia	29	22
Correll and Cowan [34]	Acute atypical pneumonia (not pneumococcal)	23	22
Correll and Cowan, 1943	Unresolved pneumonia	9	7
Oppenheimer [32]	Interstitial pneumonia (children)	36	33
Oppenheimer [35]	Virus pneumonia	56	45
Torbett, 1936 (see Abstract of Discussion in Powell [3])	N/A	30	29
Total		863	717

Powell [3] was unaware of the earlier research. He was encouraged to explore this area based on comments by Dr. Samuel Stern, who informed Powell of clinical studies he witnessed during a trip to Europe. Stern noted that in many cases, the crisis occurred within 24 hours after X-ray treatment and often were followed by complete recoveries. This observation suggested that the recovery process was causally related to the

X-ray treatment. Even though Stern was inspired by such observations, he had not been successful in convincing his peers to adopt the X-ray treatment for pneumonia. Nonetheless, Powell was motivated, and in January 1933, he noted that his chance to test the Stern suggestion occurred when he got permission from the physician in charge to use radiotherapy on a patient with lobar pneumonia. Not knowing what dose to em-

ploy, he adopted a technique useful for the treatment of carbuncles, with several modifications. This first patient responded with rapid relief of his distress and a notable drop in temperature. The recovery was uncomplicated and complete. This first apparent success led to an extensive study with 231 patients, about 70 percent of whom had lobar pneumonia and the remainder with bronchopneumonia. The mortality rates were about 5 percent and 13 percent, respectively, rates that were considerably improved over his past mortality experience without the X-ray treatment.

It is important to establish that Powell [28] had intended to employ radiation therapy in alternative cases of pneumonia. This was a critical methodological approach, establishing an objective means to evaluate patient responses. This approach had been first adopted by Bullowa [29] in the assessment of the capacity of serum therapy to effectively treat pneumonia patients, establishing an early gold standard in the development of the clinical trial [30]. However, Powell [3] stated that his staff would not permit this alternating process to continue since patients receiving the X-ray treatment were relieved of the respiratory and circulatory distress within 0.5 to 3.0 hours after treatment. It was deemed as unethical to deny treatment that could benefit the patient. In fact, in Bullowa's [29] serum therapy-pneumonia controlled study, the same decision was made. The Bullowa [29] decision was based on satisfying an a priori statistical difference. In the case of Powell, the basis of the criteria was not provided beyond that noted above. The mortality incidence in Powell [3] was also markedly decreased from the historical experience of nearly 30 percent. The X-ray treatment appeared to be effective against a broad range of pneumococcal pneumonia strains/types, offering a distinct advantage over the use of serum therapy that was differentially selective among the various types of bacterial pneumonias. In addition, convalescence time for X-ray treated patients was reduced by about half of the untreated patient, with documented health care savings [24].

While the end of the 1930s witnessed a broadened recognition of the capacity for X-rays to effectively treat the range of bacterial causes of pneumonia, the arrival of sulfonamides early in 1939 quickly led to the demise of serum therapy and further exploration of the potential of X-rays to be a therapeutic option. The demise of serum therapy was largely a function of its cost, inefficiency, allergenic response risk, and failure to perform better than the sulfonamide treatment. With the arrival of penicillin, which outperformed the sulfanilamide, there was no continuing political, administration, or financial support to maintain ongoing serum therapy programs in state health departments and associated hospitals. In the case of X-ray therapy, it had never achieved broad administrative support in the medical community nor widespread scientific standing. As a consequence, it did not become a component of system wide public health measures to treat pneumonia as serum therapy had in a substantial number of states [30]. Interest was lost in this aspect of radiotherapy despite the fact that its reported mortality rates for pneumonia were comparable to those of serum therapy and sulfonamides [31].

As for X-ray therapy, it had two short-term reprieves. One occurred because sulfa drugs were ineffective in the treatment of interstitial pneumonia [32]. The administration of X-ray therapy to such patients was as successful as with patients with bacterial forms of pneumonia. Secondly, X-rays were used successfully with patients who were unable to be treated with sulfa drugs due to enhanced toxic susceptibilities and/or side effects [27]. Despite these two potential considerations, the therapeutic utility of X-rays for the treatment of pneumonia would quickly disappear.

METHODOLOGICAL AND RELATED CONSIDERATION

The following section identifies and assesses a series of issues critical to the evaluation of how radiotherapy was employed to treat pneumonia within an historical con-

text. These include the role of control groups in case studies, strategies for dose selection, the treatment of various types of pneumonia, and the capacity of X-rays to effectively treat pneumonia in experimental animal studies.

Control Groups

Some of the X-ray therapy studies made various attempts to utilize a control group. In the six human case study investigations, the types of control groups included:

- Comparison with the contemporary clinical experience of the researcher's hospital (N = 76 for the hospital control group) [3,28,33]. For part of his study, Powell used alternating subjects to serve as a control group. However, as noted elsewhere, this approach was abandoned once it was determined that the X-ray treatment was very beneficial, resulting in all subjects being treated with the radiation exposure. This necessitated the reliance on the hospital subjects as the control group.

- Compared treatment group mortality response to the pneumonia mortality experience of the community over the past 10 year period [27].

- Correl and Cowan [34] used a contemporary comparison control group of 72 patients in a quasi-experimental framework.

- Provided a limited case-control comparison for two of the treatment subjects that were matched very closely to treated patients. In addition, the authors provided a comparison to national data [35].

- A contemporary hospital patient control group (i.e., patients served as own control) was used with an N = 36 [32].

The attempts to use comparison control groups were unique to each investigation. The types of controls ranged from alternating subjects to historical hospital controls, historical community controls, and national controls, as well as contemporary subjects with pneumonia in the same hospital serving as controls. The control group values tended to yield mortality rates that were consistent with national norms, that is, about 30 percent for untreated groups. In no case was the control group selection strategy without

limitations. Nonetheless, the diverse strategies for control group selection and the general response that was consistent with the contemporary medical literature suggest that the mortality experience for untreated pneumonia subjects during the 1930s had a reasonable measure of stability.

Marked decreases in mortality as seen with the X-ray therapy supports the reliability of the conclusion about its protective effect. Nonetheless, the control group validity is an area of weakness in the X-ray therapy-pneumonia data that affects the degree of confidence in individual study conclusions. However, it is less of a concern when set within the contextual framework of all the published studies and recent mechanistic insights.

Other Issues

Pneumonia: Dosing Based on Carbuncle Publications

Selection of a dose to treat pneumonia patients was problematic for interested clinicians during the 1930s. However, they were guided in a significant manner by publications in the clinical literature concerning carbuncles. The carbuncle literature typically based the X-ray treatment on the framework of the skin erythema dose (SED†) concept as developed for occupational health during the late 1920s [36]. The treatment of carbuncles by X-rays was generally similar from about 1910-1950. The clinicians used the SED as an upper bound exposure. The published papers of this era did not clearly specify the SED, the precise definition of an SED or provide references upon which their professional judgments were based [7].

During the 1920s and 1930s, the SED varied in the carbuncle literature by author, typically being in the 350-500 R range. The SED was also affected by whether the X-rays were filtered and the filter material, factors that were not typically addressed. These conditions introduced more variability among studies than was actually reported. Furthermore, there was a trend toward the use of lower exposures over time. For example, in the 1920s, X-rays used in the treatment of carbuncles ranged from 0.5-0.75

SED, dropping to 0.1-0.2 SED during the 1930s. In a number of cases, the clinician had already been using X-rays to treat infectious diseases as in the case of carbuncles [7]. Powell [3] noted that this was the case with his practice. He merely carried over the same dose, applying it to pneumonia patients. In the case of McIntire and Smith [23], they reported using a treatment dose of 1/5 to 1/4 of the SED, a value similar to that used by Powell. Scott [24] reported similar X-ray dosing. In selecting the same dose as used for carbuncles or other infectious diseases, they were confident it would be tolerated well but uncertain if the treatment would be efficacious in the treatment of pneumonia.

Problem of Lack of Literature Awareness

A theme in the literature concerning the effects of X-rays on patients with pneumonia was that it was not uncommon for investigators to be unaware of past experience. For example, the paper of Quimby and Quimby [15] was undertaken without the apparent knowledge of the Edsall and Pemberton [37] report. The Krost [20] paper was undertaken without any prior knowledge of the Edsall [14,37], Quimby and Quimby [15], or Heidenhain and Fried [16,17] reports. Merritt and McPeak [22] were also not aware of the Krost [20] report. As noted earlier, Powell's [3] 1936 paper was based on the suggestion of a colleague without any reference to publications on the topic. Despite each of these rather independent clinical research initiatives, it is rather surprising that their findings were consistent with respect to the clinical and X-ray descriptions of patient responses.

Interstitial Pneumonia

In 1943, Oppenheimer [32,35] reported on his application of radiotherapy to treat interstitial pneumonia, a life-threatening and progressive condition. He claimed that inquiries to numerous institutions revealed that none had previously used X-rays for this condition. Oppenheimer [32] stated that he first started to use X-ray treatment for patients to help control cough in the recovery

from pneumonia. Since it seemed to work well, he extended its application to acute stages as well. He used a dose of approximately 1/3 to 1/5, "commonly advocated" in the treatment of inflammation. Such dosing was quite similar to that recommended by Chamberlain [38]. More specifically, Oppenheimer [32] employed an average dose of 50 r (in air) to the affected lung area. This dose was adopted following initial exploratory treatment equal to or greater than 100 r that induced several undesirable effects, including chills, convulsions, and cold sweats, in several patients. Children were administered the somewhat lower dose of 35 to 45 r. He treated 56 patients with X-ray therapy that failed to respond to various standard medical treatments, including sulfonamide therapy.

The X-ray treatment for interstitial pneumonia was very successful when the duration of illness prior to the therapy was 2 to 5 days and nearly as successful when duration of illness prior to the radiotherapy was 6 to 14 days. After 14 days, the successful response rate dropped by about 50 percent. The so-called failure in the cure rate meant that the symptoms did not completely disappear within a period of a few days. The author concluded that X-ray therapy offers excellent potential as a treatment for interstitial pneumonia, especially when used during the early stages of the disease.

Lack of Sulfonamide Treatment Efficacy

Rousseau et al. [27] noted that since 1939, their treatment of pneumonia switched to sulfonamides, dropping the use of X-rays. However, in 1942, they reported on a series of pneumonia patients who were not benefited by treatment with the sulfonamides. Each patient had a positive clinical diagnosis, as well as X-ray and bacterial culture confirmation. These patients were at serious risk, with rapidly deteriorating health status. Based on the clinical criteria, the physicians believed that death would occur in all 29 patients in this group. In light of the seriousness of the situation, each patient received radiotherapy. Of the 29 patients, 22 recovered and seven died. The authors reported

Table 2. Experiment description of the X-ray therapy experiment by Lieberman et al. (1941) with dogs.

Experiment	# of Dogs	Voltage	Average Time to Death (Control)*	Treatment*	Average Time to Death (Treatment)
#1	20	Voltage 80 kV	10 dogs (N=10) 3.5 days	10 dogs	4.5 days
#2	4	Voltage 135 kV	1 dog: insufficient data	3 dogs	Insufficient data
#3	21	Voltage 200 kV	8 dogs (N=8); 2.25 days (combined controls); Type 1: 4 dogs; Type 3: 4 dogs	Type 1: 9 dogs (5 died, 4 recovered); Type 3: 4 dogs (3 died, 1 recovered)	8.5 days (N=8 for combined Types 1 & 3 treatment groups); Type 1: 10.14 days (N=5); Type 3: 3.66 days (N=3)

*Gender of dogs was not specified

that those who died exhibited bacteremia and granulocytopenia. Likewise, all patients who died had a time interval between X-raying and death of < 15 hours. The authors felt that this temporal aspect confirmed their belief that these cases were close to helpless upon reaching the hospital and that the X-ray treatment may not exert its main effect on the disease for 15 to 24 hours.

Allergic Sensitization-Based Pneumonia

There are many cases in which the sputum shows no evidence of bacterial presence. While it is possible that the cause may be viral, others have argued that some patients display pneumonia that represents an allergic response due to a previous sensitization. In fact, Powell [33] argued that the capacity of X-rays to induce an anti-inflammatory response would account for its capacity to effectively treat this type of pneumonia.

Animal Studies: X-rays and Pneumonia

Several animal model studies were conducted to assess the capacity of ionizing radiation as a potential therapeutic modality for bacterial and viral pneumonia from 1941 to 1946. These studies utilized the guinea pig and dog in the assessment of bacterial pneu-

monia, whereas the cat and mouse were used to assess viral pneumonia. Studies with the guinea pig and dog were conducted by two different research groups. In contrast, experiments with cats and mice were performed by the same research group. In the cases of the guinea pig, dog, and mice, the severity of the infection was very high and potentially life threatening. The degree of infection and severity was much less in the cat.

The guinea pig study presented a histological comparison of the lung tissues between the control and treatment groups [19]. It revealed that the radiation treatment was effective in reducing the effects of the pneumonia inoculations. The radiation treatment was more effective the sooner it was administered after the pneumonia bacterial inoculation (6, 12, and 24 hours). The therapeutic findings were convincing to Fried [19], who had considerable human clinical experience.

In the case of the dog model, the experiments involved 45 young males and females. Twenty-six dogs received the radiation treatments, while 19 comprised the control groups [31]. The research involved two different pneumonia bacteria types (Types 1 and 3) and three voltage levels (80, 135 and 200 KV) of radiation exposure. In the Type 1 bacterial study, 37 dogs were tti-

lized, whereas only eight dogs were used in the Type 3 bacterial assessment. The 45 dogs, two bacterial Types, and three voltage levels were organized into three experiments as shown in Table 2.

While all 20 dogs (10 control and 10 radiation treatment dogs) in the first experiment died, the irradiated dogs died on average one day later than the control dogs (3.5 vs 4.5 days). The second experiment was too limited to draw conclusions, with only three treatment and one control group dog used. In the third experiment, which utilized 13 treated and eight control dogs, all controls died within a few days of the pneumonia inoculation (2.1 day average survival reported; 2.25 average survival days based on our calculation). The eight treated dogs that died during the third experiment lived an average of 8.5 days. Five of the 13 treatment dogs survived (four from the Type 1 and one from the Type 3 treatments) and were not counted in the 8.5 day average (mean). The 8.5 day mean represented the survival duration of the treated dogs comprising the combined Type 1 and Type 3 exposure groups. While there was no difference between the two control groups for Type 1 and Type 3, as the two groups were identical (2.25 days), the two treatment groups notably differed (10.14 day survival duration for Type 1 vs. 3.66 day survival duration for Type 3). Furthermore, the findings with the Type 1 treated animals were highly variable with two dogs surviving 17 and 28 days, respectively. These findings, and the fact that the five dogs survived the experiment, led to the conclusion that the radiation treatment reduced the harmful effects of the pneumonia inoculation.

In the case of viral pneumonia, two different viruses were tested. In the cat, a feline virus was selected that induced a condition similar to human atypical pneumonia: a relatively mild condition, yet prolonged and with a low incidence of mortality [39]. Despite the similarity to the human condition, this specific virus is not considered to be typical of the majority of human cases. The experiment involved a control and two radiation groups. The radiation (100 r/adminis-

tration) was administered either at 24 hours (group 1) or 48 hours (group 2) after the inoculation.

The key endpoint measured was the length in days of the acute phase of the induced pneumonia illness. The radiation treatment reduced the effects of the virus pneumonia by about 50 percent in group 1 (24-hour group) and by 25 percent in group 2 (48-hour group). The effect was statistically significant at the 24-hour time point. Clinical symptoms (e.g., photophobia, lacrimation, sneezing, sniffing, and coughing) were employed as principal criteria for the severity of the induced condition. The symptoms were graded from 1 to 6. There was no presentation of the quantifying criteria of these specific graded responses. The authors suggested that the mechanisms of the protection may involve an enhanced phagocytosis response based on the findings of Glenn [40].

Dubin et al. [41] assessed whether X-ray therapy could prevent a high risk of mortality from a severe case of viral pneumonia. They considered their earlier findings with cats as conclusive [39], showing that X-rays administered 24 hours after the onset of symptoms of pneumonia shortened the acute phase of the disease condition from 10 to 5 days. To test the generalizability of this protective effect, they administered swine influenza virus to white mice, as this exposure would kill the treated mice in a few days. This research was unique in that the X-ray exposure was administered either before inoculation (48 hours) or after (24 hours or 48 hours) exposure to the virus treatment. When the mice were exposed to a single dose of 5 r 24 hours after inoculation, there was a decrease in mortality when two replication studies were combined. Likewise, there was a similar decrease in mortality when 100 r was administered 48 hours prior to the inoculation. No effect was seen when 5 r was given 48 hours before the inoculation.

These studies constitute the entire set of animal model studies assessing the capacity of X-rays to affect pneumonia-induced clinical symptoms and mortality. Each study demonstrated some measure of support for the hypothesis that X-ray treatment could re-

Table 3. Quotes from researchers on the effects of X-ray therapy on the treatment of pneumonia.

Quimby & Quimby [15] (first paragraph p. 681) "No pathological process in the body responds quicker to an x ray exposure than the nonresolution following pneumonia. The action seems to be a specific one. These unfortunate terminations in the lung leave the patient in a debilitated state, and the older forms of treatment often fail to bring about the desired result."

Krost [20] (page 59) "Russ found that large doses of roentgen ray caused profound changes and reduced immunity by destroying lymphocytes. Large doses, then, would certainly not be logical. Small doses were found to increase immunity in mice by stimulating lymphocytosis." "It would seem more logical to assume that the small doses of roentgen ray penetrating the lung tissue acted as a stimulant to phagocytosis. It would also seem logical to use relatively small doses."

Merritt and McPeak [22] (last 2 paragraphs p. 48) "The results in these few cases have been prompt and gratifying with no untoward effects. The treatment is of brief duration, entailing no strain nor discomfort to the patient, and appears to be a distinct addition to the meager and unsatisfactory methods in common use." "We offer the suggestion that irradiation should be instituted in all cases showing definite roentgen signs of delayed resolution three weeks after the onset."

Powell [3] (p. 237) "I do not wish to leave the impression that we have relied on the radiation alone. We have used it in addition to whatever other treatment would have ordinarily been given, except that none was given serum. At first, so as to have the direct comparison, we intended to alternately irradiate, and not irradiate lobar pneumonia cases as admitted to the hospital, regardless of the stage of the disease at the time of admission. It was soon evident, however, that those patients receiving radiation became comfortable much more quickly than those who did not. So, after we had observed only a few cases, we decided to irradiate practically all of them."

Mcintire and Smith [23] (last paragraph p. 426) "From our observation we believe that x-ray therapy has advantage over other types of special therapy in that it is of value in all types of pneumonia exhibiting an adequate white blood count and in all stages except very early in bronchopneumonia with considerable congestion or a minimum consolidation. Although our series is not large enough to warrant final conclusions, we feel that x-ray therapy will possibly reduce the incidence of crippling complications, such as empyema and pulmonary abscess."

Powell [33] (p. 414) "In addition to the usual therapeutic routine, 105 cases of lobar pneumonia have been given roentgen treatment. Of these only five died. Thirty cases of bronchopneumonia have been given roentgen treatment and of these four died. Even if the mortality had not been reduced so very sharply, the use of roentgen therapy in these cases would be justified by the relief of anxiety and discomfort experienced by the patients. All Type II and III pneumonias treated with roentgen rays have recovered."

duce the effects of the pneumonia induced by bacteria or viruses. However, each of the studies, as reported, has important limitations. None of the studies were double- or single-blinded, possibly affecting judgments on symptoms. The guinea pig study failed to report the dosing and number of animals used per control/treatment group [19]. In the case of the dog studies, there was no designation which dogs were male or female [31]. There was also no indication of how long a dog was required to live for it to be designated as recovered. In the case of the mouse pneumonia study, the replication did not support the initial findings but still retained a treatment-related effect when both experiments were combined. In only one study was

hypothesis testing applied to the data [41]. The most significant finding was the observation that five of the 13 dogs in the third experiment in the radiation-treated group recovered and survived, while none of the control group animals recovered, with the average time to death being 2 to 3 days [31]. While each experiment had important limitations, they demonstrated a consistent trend indicating that X-ray exposure can reduce the effects of virus-induced pneumonia.

DISCUSSION

This paper provides the first detailed historical assessment of the use of radiotherapy for the treatment of pneumonia.

Table 3 provides a series of quotes from researchers capturing their view as to the therapeutic efficacy of X-ray treatments in patients with pneumonia. X-ray therapy was successful in decreasing the mortality rate in untreated patients from about 30 percent to 5 to 10 percent. These results were in the same range and perhaps somewhat better than reported for serum therapy [3] and sulfonamides [42]. Typically, a single X-ray treatment effectively reversed the course of the pneumonia, quickly relieving respiratory distress and other symptoms and markedly reducing the risk of mortality. These findings were consistently reported, with similar success noted by a wide range of clinicians in diverse medical settings, as well as patients across vast age differences and health status [23,24-27]. The X-ray therapy was also effective in the treatment of viral [34] and interstitial [32] pneumonia. Since pneumonia in the 1930s presented a very serious risk of death, some hospitals routinely treated such patients therapeutically with X-rays prior to assigning the patient to a room, that is, the policy was to apply X-ray therapy during the triage stage.

Are There Any Serious Objections to the Use of X-ray Therapy in the Treatment of Pneumonia?

A significant problem with the use of X-rays in the treatment of pneumonia is that no new research papers have been published since 1946. It is difficult to base health and medical decisions upon scientific knowledge on key endpoints that has not changed in nearly 7 decades. While this argument is a reasonable one, experienced clinical researchers published many studies in leading journals in this earlier era that encompassed more than 850 patients with impressive findings of highly protective effects along with a rapid resolution of the disease. The X-ray treatment prevented considerable human suffering, reduced the health care costs and the burden on the family, and accelerated a return to normal living, whether work, school, or other activities.

The question may be asked as to whether these findings have been estab-

lished with adequate scientific reliability. Essentially all the human studies were case reports, not reflecting modern randomization of subjects and blinded investigators. Bullowa [43] confronted this question over the efficacy and proof of serum therapy in the treatment of pneumonia.

“The evaluation of the effect of any therapeutic procedure in pneumonia is attended with certain inherent difficulties. Probably seven of every ten patients recover regardless of treatment, and therefore, if one chances on a succession of favorable cases, one is apt to attribute the benefit to the special treatment then in use. ... (Conversely,) a short series of fatalities, unless carefully controlled and analyzed, may lead to a condemnation of what is really a very useful procedure.”

While there are substantial and consistent findings supporting a therapeutic role for X-rays in the treatment of pneumonia, the question remains as to how to reactivate a well-established, yet 65-year-old hypothesis, with contemporary research questions, methods, and technologies that still may hold public health potential. This concept may not be as unusual as it seems. For example, the use of X-rays has continued for the treatment of arthritis in Germany with 50,000 people treated annually. During the past several decades, research has addressed the area of cancer risk from therapeutic X-rays [44,45]. Estimates of cancer risk using a linear dose response methodology is approximately 20/million, a value about four orders of magnitude below the background malignant tumor incidence. In addition, low dose mechanisms for such therapeutic effects have been clarified [9,46]. Such complementary and contemporary research developments have given support to the therapeutic use of X-rays for arthritic treatments in Germany.

Despite the series of case study publications in the treatment of pneumonia with

X-rays and supportive complementary findings, there are still significant research needs. These include a clarification of treatment efficacy, reproducibility, pneumonia-type specific responses, optimal dosing, and optimal patient targeting of treatments (i.e., area of body), as well as targeted health risk estimates for differing ages (and other characteristics) of patients, how optimal dosing may differ if a second or even third X-ray treatment were to be administered, and if X-rays could be given along with antibiotic treatments in a safe and efficacious manner, among other potential questions. Furthermore, since the X-ray treatment profoundly reduces the inflammatory response, it is possible that the X-ray treatment may yield a net reduction in mutations and therefore cancer risks than if the X-ray treatment were not administered. Thus, it is possible that the estimate of an enhanced cancer risk of 20/million by the X-ray treatment could represent an overestimate in cancer risk.

Mechanistic Considerations

A basic question that needs to be resolved is the mechanism by which X-rays affect the resolution of the pneumonia. The principal observation is that X-ray treatment in the low fractions of the SED reproducibly induces an anti-inflammatory state [9]. This capacity to induce the anti-inflammatory condition is dependent on the physiological state of the tissue. If the tissue is inflamed, then the X-ray treatment suppresses the immune response, inducing an anti-inflammatory phenotype via the integration of multiple mechanisms. This accounts for how X-rays are effective in the treatment of a very broad range of inflammatory conditions, ranging from the treatment of infectious conditions such as gas gangrene, skin infections such as carbuncles/furuncles, arthritis, sinusitis, Otitis media, and other conditions. A common feature of these conditions is massive inflammation. By reducing inflammation and creating an anti-inflammatory phenotype, the X-ray treatment facilitates the healing process. In fact, this suggests that the X-ray treatment would be insufficient to affect a complete remission in

the case of bacterial pneumonia but still enhancing the disease resolution process. While the X-ray treatment may not act by killing the causative agent as an antibiotic would, its induced anti-inflammatory function may enhance the efficacy of antibiotic treatment.

While the mechanism by which X-rays reduced symptoms of pneumonia and enhanced its resolution has not been explicitly evaluated within a contemporary molecular fashion, substantial research has revealed that low doses of ionizing radiation induce an anti-inflammatory phenotype in a wide range of *in vitro* (e.g., activated murine macrophages-RAW 264.7 cells, mouse resistant peritoneal macrophages, adult human peripheral blood mononuclear cells, primary cultures of human umbilical vein endothelial cells, HC 60 cells [i.e., leukocytes], the hybrid endothelial cell line EA-hy.926, and the murine endothelioma cell line mlEnd) and *in vivo* models (e.g., murine air pouch models with Tuck mice, NMRI mice, Lewis Rats, C57 BC/6 mice, DBA mice, BALB/C mice, human tumor necrosis factor 2 transgenic mice) [9]. The anti-inflammatory phenotype has been induced whether the ionizing radiation was localized to an inflamed area [47,48] or administered via a whole body treatment [49]. The mechanism(s) accounting for the anti-inflammatory phenotype(s) in the broad range of biological models also displays a common strategy with similar patterns and sequences of biochemical/molecular events, including NO/iNOS decrease [50-52], reduction in reactive oxygen species [53], enhancement of heme-oxygenase 1 (HO-1) [51,54,55], induction of apoptosis [56-62], suppression of TGF α , enhancement of TGF β 1 [54,55], activation of transcription factors NF κ B and activating protein 1 (AP-1) [63,64], decreased adhesion of leukocytes and PMN to endothelial cells (EC) [47,48,65-69], and enhancement of T regulatory cells [55,70,71].

This mechanistic research reveals that ionizing radiation 1) can affect the occurrence of localized, as well as systemic anti-inflammatory phenotypes; 2) that it is dose dependent, achieving this with the applica-

tion of relatively low doses (0.3-0.5 Gy) of ionizing radiation within the context of a hormetic-like biphasic dose response; 3) that the induced anti-inflammatory phenotype may be generalized across multiple types of biological models/cell types; and 4) that this response represents a highly coordinated and integrated adaptive process that reflects substantial biological redundancy, underscoring its significance. The biological/molecular plasticity of the anti-inflammatory phenotype response in different species and tissue/organs also reveals a refined and highly selected evolutionary strategy that drives the quantitative features of the X-ray-induced dose response relationship for the anti-inflammatory phenotype. Finally, the ionizing radiation-induced anti-inflammatory phenotype induction process also depends on the physiological state of the affected cells/tissue, requiring a prior activation process that is associated with an inflammatory process. While the highly generalized nature of the X-ray induced anti-inflammatory phenotype may provide a molecular framework that accounts, at least in part, for the historical clinical efficacy of X-ray treatment of pneumonia, it offers a valuable experimental framework upon which this mechanistic concept can be further studied.

FUTURE DIRECTIONS

The question may be raised as to how the medical community should address the issue of radiotherapy for the treatment of pneumonia as well as other conditions. Despite the fact that X-rays were used with considerable success in the treatment of pneumonia during the mid-1920s to the mid-1940s with adequate methodological procedures reported, we believe that a reasonable next step would involve the creation of a focused clinical research program that could assess the use of X-ray therapy for pneumonia as an adjunct treatment for high-risk patients. The initiation of this activity would require strong leadership as X-ray therapy for the treatment of pneumonia has not been employed since the early 1940s. Yet its renewed use would not be for a new applica-

tion but for an already well-documented, effective clinical treatment.

Within the context of the X-ray therapy pneumonia application, it would be of considerable value to initiate a parallel X-ray therapy evaluation of the detailed contemporary research on arthritis with its substantial clinical data and experimental studies that use advanced research designs, protocols, and appropriate statistical power, as well as modern clinical and molecular techniques. Research in this area and extensive clinical application are available within multiple medical research centers in Germany.

We suggest the creation of a prestigious expert advisory committee, under the administrative leadership of the U.S. Institute of Medicine, to assess the practice of radiotherapy for arthritis and shoulder bursitis/tendonitis in Germany. The German research program and its clinical practice was selected due to its long tradition of use, copious peer-review of research findings, and acceptance by governmental agencies, the medical community, and the patient community, as well as the legal system. This type of integrated acceptance and participation is essential, especially given the unique place that ionizing radiation occupies with its many opportunities and potential public health concerns. As part of this process, it would be important to recognize that a substantial proportion of research papers published on these topics are written in German. As such, their citation among non-German-speaking biomedical/clinical researchers is often quite limited, despite their notable clinical advances. These papers need to be translated into English and be readily accessible. A series of conferences and workshops should be held on the topic, thereby mainstreaming access to the information and enhancing dialog among scientists in this area, especially the German investigators.

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