

Radiotherapy for Pertussis: An Historical Assessment

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Abstract

X-ray therapy was used to treat pertussis/whooping cough during a 13-year period from 1923 to 1936 in North America and Europe. Twenty studies from clinicians in the United States reported that approximately 1500 cases of pertussis were treated by X-ray therapy usually with less than 0.5 erythema dose. Young children (<3 years) comprised about 70% to 80% of the cases, with the age of cases ranging from as young as 1 month to 50 years. In general, symptoms of severe coughing, vomiting episodes, and spasms were significantly relieved in about 85% of cases following up to 3 treatments, while about 15% of the cases showed nearly full relief after only 1 treatment. The X-ray therapy was also associated with a marked reduction in mortality of young (<3 years) children by over 90%. Despite such reported clinical success from a wide range of experienced researchers, the use of X-rays for the treatment of pertussis in young children was controversial, principally due to concerns of exposure to the thymus and thyroid even with the availability of lead shielding. By the mid-1930s, the treatment of pertussis cases via vaccine therapy came to dominate the therapeutic arena, and the brief era of a radiotherapy option for the treatment of pertussis ended.

Keywords

pertussis, whooping cough, X-rays, radiotherapy, history of science, hormesis

Introduction

Pertussis was a dreaded disease, especially for the very young, having a high risk of death for infants under the age of less than a year. It is characterized by paroxysms of cough, inspiratory whoop, and posttussive vomiting, with more severe forms leading to apnea in infants. The mortality rate for children less than 1 year was about 40% in the early 1900s in the state of Massachusetts.¹ Besides this mortality risk, the nature of the disease was extremely challenging to the affected individual as well as to parents, trying to care for the child, with substantial episodes of extreme coughing and projectile vomiting. Furthermore, the disease was highly contagious, leading to strict quarantining of the affected child. Lack of availability of treatment for pertussis resulted in clinical and psychosocial burden for both patient and the community. Numerous drug experiments were tried to accelerate recovery and enhance survival; however, none of the experiments achieved a significant therapeutic utility. In 1906, hope for a potential treatment arose when the bacterial cause of pertussis was identified. In fact, numerous groups competed to create an effective vaccine, with the next 3 decades witnessing a type of biomedical/clinical roller coaster of expectation and vaccine inadequacy being the norm. By the mid-1930s, an accepted vaccine emerged using a whole cell preparation. This

preparation, while broadly effective, would itself pose an array of potential health concerns, giving way to a cell-free preparation by 2000.² However, during the earlier decades of the 20th century, between the frantic use of a plethora of failed drug remedies and the adoption of an acceptable vaccine, there emerged a new hope of radiotherapy that resulted in a range of therapeutic possibilities. This article provides a historical assessment of therapeutic use of X-rays in the treatment of pertussis, including the origin of this proposed therapy and a review of the studies assessing its efficacy and associated health concerns. Based on the available data, we also assessed the consistency and robustness of the reported results and

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various proposed mechanisms that account for reported beneficial effects.

Origin of X-Ray Treatment of Pertussis

The first reported case of pertussis treated by X-rays in the United States occurred as a last resort rather than by design. The case involved the treatment of a young child who exhibited an extremely severe form of pertussis. During the course of disease, the child had been treated with some of the commonly employed drug treatments, without apparent success. In fact, the child had lost much weight, became acutely ill, and there was considerable concern about the development of pneumonia. Given this situation, the mother desperately pleaded with the treating physician for some other treatment. At this point, the physician indicated that he had tried everything except the use of X-rays. Since X-rays had recently received publicity in the apparent successful treatment of several other diseases, the mother pleaded for its use for her child. Despite the presence of considerable skepticism of its therapeutic efficacy, Drs Henry I. Bowditch and Ralph D. Leonard, on the medical staff of the Floating Hospital in Boston, Massachusetts, decided to treat the child with a "low" dose of X-rays, which they estimated to about 1/10 of the erythema dose (ED; note 1). Although the occurrence of paroxysms was markedly reduced that evening, the symptoms recurred the next day with the same severity. A second identical X-ray treatment 48 hours after the first dose yielded a similar transitory improvement. Following a third identical dose at 48 hours after the second treatment, the paroxysms ceased, with no recurrence. As recounted in their 1925 reflection of that event, Bowditch³ and his team began a major assessment of the effects of X-rays on children and adults with pertussis, with their first paper being first presented to the staff of the Floating Hospital on February 23, 1923, and then published in the *Boston Medical and Surgical Journal* on March 8, 1923⁴ (to be renamed the *New England Journal of Medicine* on February 23, 1928).

Clinical Investigations of X-Ray Treatment of Pertussis

The publication of Bowditch and Leonard⁴ was groundbreaking as it reported 21 (80%) of 26 individuals with marked clinical improvement, including significant reduction in severe bouts of cough and vomiting episodes, after 3 X-ray treatments given on alternative days. In a small proportion of cases, the improvement was more striking with a near complete elimination of symptoms following a single treatment. The cases ranged in age from 3 months to 43 years, with the dose being less than half of an ED. The authors expressed hope that these preliminary findings would encourage other investigators to evaluate the use of X-rays in the treatment of pertussis. In fact, a 1921 report of pertussis mortality in Massachusetts indicated a mortality rate of 6.4% for children under 3 years, with total annual deaths due to this disease approximating 3000.¹ Of particular significance is that for a sample of 850 cases in Massachusetts treated with the standard Bowditch protocol

published by Smith⁵ revealed mortality rate of only 0.4%, a more than 90% decrease.

By the end of 1923, there were several other reports on the effects of X-rays on cases with pertussis⁶⁻⁹ and other research in progress.¹⁰⁻¹⁴ Thus, the report of Bowditch had its intended effect. These follow-up investigations yielded results very much in line with the initial piloted findings of Bowditch and Leonard.¹¹ Smith and Kirby¹² reported 20 cases, exclusively including children of age ranging 1 month to 7 years, whereas Struthers¹³ reported on 45 cases with an age ranging 3 months to 30 years. Both studies closely followed the protocol of Bowditch and Leonard⁴ and Bowditch et al.¹¹ However, in the report of Bowditch¹⁰ the number of cases was 300, with about 80% showing significant clinical benefit. The number of patients treated via X-rays at the Boston Floating Hospital would increase to 850, with consistent clinical success still approximating 80%.⁵

Despite these striking findings, the use of the X-ray treatment of young children caused considerable concern for some treating physicians about potential adverse effects on the thymus and thyroid glands. Such concerns were raised by Cook⁸ and Percy¹⁵ who cautioned against giving multiple X-ray treatments to infants. Bowditch¹⁰ defended these treatments by stating that the doses were well under those known to produce skin burns or thymic or thyroid atrophy. Moreover, he stated that when desired, a lead shield was provided to cover the glandular areas. The position of Bowditch was supported in summary remarks of McKibben⁷ who cited the views of experienced roentgenologists who worked at the Boston Floating Hospital.

Interest in the therapeutic use of X-rays for pertussis continued until a final paper was published by Liebman¹⁶ in 1936 concerning his 13 years' experience in Montreal with approximately 170 patients with pertussis that started soon after learning of the original Bowditch report. It was during this time that sufficient progress had been made in the development and testing of a more reliable pertussis vaccine, leading to its widespread adoption and abandoning the use of X-rays for the treatment of pertussis.² Approximately 20 papers were published in 13 years, elaborating the therapeutic use of X-ray for pertussis. Table 1 summarizes key findings of these papers, while Table 2 provides a brief set of quotations from a sampling of these papers, permitting the authors to offer their perspectives on how effective they believed these treatments were. Over this time nearly 1500 patients were treated with X-rays, with over 75% being children. With 1 exception, the papers were uniformly consistent in concluding that the X-ray treatments were highly successful in the treatment of those of all ages. In the only study not showing a "successful" treatment, it was not possible to conclude that the X-ray treatment actually was not effective²¹ due to limitations of study design. This is because during the experiment the 22 X-ray treated patients was compared to a group receiving the drug antipyrine, with both showing a comparable improvement, no unexposed control group was employed.

Treatment efficacy via the use of x-ray therapy was higher with younger age-groups. In the experience of Bowditch and

Table 1. Summary of Studies Relating to the Effects of X-Ray Treatment of Pertussis.

Citation	Date	Cases	Gender	Age	Stage of Disease	Doses	Exposure	Results
Bowditch and Leonard ⁴	1923	26	NA	3 months to 40 years	Probably all stages, 1 to 10 weeks	3 to 4 doses at intervals of 2 to 3 days	Dosage regulated by age of patient, total dose under an erythema dose (ED)	Quick cure 15% to 20%; gradual improvement 70%; no recovery 10% to 15%
Kingston and Faber ⁶	1923	24	NA	7 months to 13 years	All stages of the disease, 3 to 30 days duration when treatments were given	1 to 3 doses at weekly intervals	1/4 ED	4/24: immediate remarkable improvement; 2/24: not helped after 3 treatments; 10/24: markedly better after 2 treatments; 8/24: gradual improvement but not cured after 3 treatments Considered a practical success; recommended further testing
Cook ⁸ (given in McKibben, 1927)	1923	6	NA	2 to 5 years and 1 adult	NA	1 to 3 treatments	1/9 ED	
Struthers ¹³	1924	48	NA	3 months to 30 years	Day 2 to week 8 (based on spasmodic episodes)	Two modes of treatment: (1) short exposures on alternate days 2 to 3 treatments; (2) with a single large dose 3 treatments: given on alternate days, possible second set of treatments, after a 10-day interval	Not given	7/48 (15%): prompt cure (within 24 to 48 hours); 20/48 (45%): relieved 4 to 5 days; 18/48 (40%): no appreciable improvement, believed the duration shortened More than 80% benefited from the treatment
Bowditch ¹⁰	1924	300	NA	Early weeks of age to 50 years; 30% <2 years, 70% <6 years	All stages of the disease present, 2 to 10 weeks			
Bowditch et al ¹¹	1924	20	NA	<1 year (6); 1 to 2 years (4); 2 to 3 years (8); >3 years (2)	All stages of the disease	NA	Not given	20 patients had 288 severe paroxysms; By day 5 after treatment – 157 paroxysms and much less in severity. After 2 weeks, only 43 were noted X-rays relieved symptoms in $\geq 75\%$ treated. Children treated had nearly 100% success. Average duration of disease in treated group was 5.5 weeks, whereas it was 8.7 weeks in the controls
Leonard ⁹	1924	400 plus 200 unexposed controls	NA	NA	NA	4 treatments every other day unless showing rapid response	1/3 ED	NA
Rhinehart ¹⁴	1924	40	NA	NA	NA	NA	NA	NA
Smith and Kirby ¹²	1924	20	NA	4 weeks to 7 years	3 treatments on alternating day anterior and posterior	Several doses administered	1/2 ED	Specific data not averaged, however, selected patients showed considerable benefit
Black ¹⁷ (cited in Hess ¹⁸ summary section)	1925	100	NA	NA	NA	NA	NA	2/100 have excellent improvements; 40% distinctly benefited; 24/100 displayed little/no improvement

(continued)

Citation	Date	Cases	Gender	Age	Stage of Disease	Doses	Exposure	Results
Freidman ¹⁹	1925	2	1 infant; 1 female	14 months; 6 years	Chronic (2 years) and (6 months duration)	Up to 3 treatments	NA	Both cases improved substantially during treatment, success after 2 series, probably due to total exposures
Leonard ²⁰	1925	20	NA	18 patients were <3 years old	17 in first 3 weeks of disease, average 2.5 weeks at admission	Same dose as Leonard ⁹ ; 3 treatments at 48 hour intervals; some patients were administered 2 or 3 sets of 3 treatments	Approximately 2/3 ED per set of 3	There was a significant decrease in disease incidence and severity. These findings had the same values (and most the same patients) as reported in Bowditch et al
Faber and Struble ²¹	1925	22 cases and 22 controls	NA	2.9 years of age for cases	9.4 days of paroxysms prior to treatment	Dose varied by age of patient	≤1 ED	There was no treatment-related effect as compared to the control group
Bowditch and Smith ³	1925	NA	NA	NA	NA	NA	NA	Review of post-Bowditch findings
Smith ⁵	1925	850	NA/	750 children < 7 years; 260 children < 2 years	Multiple stages of disease (most in paraoxymal stage)	3 to 4 doses at intervals of 2 to 3 days	Dosage based on age of patient, with total dose less than 1 ED	Approximately 80% of the cases displayed a lessening of the number and severity of the paroxysms in a time interval ranging from a few hours to 7 to 10 days
Hess ²²	1926	102	NA	<1 to 10 years	Multiple stages treated	Doses 1 to 4 each separated by 5 to 9 days	NA	Recommended treatment to start at paroxysmal stage
Alexander ²³	1927	NA	NA	NA	NA	NA	NA	Review of literature
De Puelles ²⁴	1924	This study was not translated into English	NA	NA	NA	NA	NA	Reports successful treatments
Boner ²⁵	1924	6	NA	8 months to 7 years	This study was not translated into English	NA	NA	Reports successful treatments
Sheriden ²⁶	1927	22	NA	NA	NA	NA	NA	50% showed marked improvement within a few days. The rest showed moderate improvement in 2 weeks. Nearly all 22 cases were very severe and most had been whooping 2 to 8 weeks
Samuel ²⁷	1929	NA	NA	NA	NA	NA	NA	Review paper
Von Meysenburgh ²⁸	1933	21	NA	>6 weeks	Multiple stages of disease	1 to 4 exposures	NA	15 of 21 required only 1 of 2 treatments; treatments were generally very effective
Liebman ¹⁶	1936	>300	NA	NA	NA	1 to 4 exposures	1/4 to 1/5 ED	80% of children were relieved and benefited; less than half of the remaining 20% failed to respond

Abbreviation: NA, not applicable.

Table 2. Quotations by Leading Researchers on the Effectiveness of X-Ray Treatments for Pertussis.

Reference	Quotes
Bowditch and Leonard ^{4(p313)}	While our evidence so far is not sufficient to warrant any definite conclusions, we have the feeling that the X-ray at the present time may be of more value in the treatment of pertussis than any other form of treatment, including serum. We are certainly convinced of this fact—that it will not do to let this method of treatment drop, but that further careful scientific study should be made.
Kingston and Faber ^{6(p429)}	While the exact value, and limitations of the method demand further study, we feel that the definite improvement secured in many patients and the prompt and almost complete relief obtained in a few, constitute a positive gain in the treatment of a disease which is very rarely susceptible by other methods of more than temporary symptomatic relief. The fact that complete failure is met with in a certain proportion of cases should be explained in advance to the parents, but does not alter our belief that the X-ray treatment is at present the most promising therapeutic measure which we possess for pertussis. No ill effects from radiation have been encountered.
Bowditch ^{10(p1424)}	In 300 cases of whooping cough treated by the roentgen ray, there is strong evidence that more than 80 per cent were benefited by the treatment.
Bowditch et al ^{11(p322)}	We have attempted to prove in two previous communications that in the roentgen ray we have a therapeutic agent for the treatment of whooping cough which is of definite value, and in our opinion, gives better results than any other single method of treatment. The object of this present paper is to present further evidence, which has been accumulating during the last year, of the beneficial action of this form of therapy.
Leonard ^{9(p266)}	First, that the roentgen ray relieves symptoms in at least 75 per cent of the cases, when used in the paroxysmal stage. In special groups, for instance in children under one year of age, nearly 100 per cent were definitely relieved. This may indicate that we are not giving just the proper dosage in older patients. I think it is fair to say that up to the present time, in the opinion of the Staff of the Floating Hospital, we have in the roentgen ray one of the best means for at least controlling the severe symptoms of whooping-cough.
Smith and Kirby ^{12(p145)}	No conclusions can be justifiably drawn from the small number of cases treated by us, but from published reports (3), it would appear that the roentgen ray offers a new hope in the treatment of whooping cough. In view of the rather wide prevalence of pertussis, it is earnestly suggested that where X-ray laboratories are available, physicians should employ the treatment. It is advised to begin treatment early, alternate radiation over chest and back at three and five-day intervals for three treatments and reradiate later if necessary.
Struthers ^{13(p142)}	From our results, however, we do feel that x-ray radiation in full doses has a definite place in the therapeutics of this most distressing disease of childhood. I know of no other method of treatment which gives equally good results.
Bowditch and Smith ^{3(p63)}	In summarizing, the work of the past two years of the Boston Floating Hospital in the treatment of whooping cough by X-ray seems to have proved that there is a very distinct benefit to be derived by this method; that the paroxysms are definitely reduced in frequency and severity; that the enlargement of the hilus lymph nodes and the peribronchial thickening are definitely reduced; that the lymphocyte count, both relatively and absolutely, is similarly reduced, and that this method offers more constant results than any of the usual means of medication.
Smith ^{5(p177)}	An analysis of 850 cases of pertussis treated by the roentgen ray proves that: This means of therapy is of value in reducing the number and severity of the paroxysms and in shortening the course of the disease. The majority of the cases (750) occur under 7 years of age. Most of the patients (499) present themselves in the paroxysmal stage. The greatest benefit occurs in the paroxysmal stage, and especially in the younger patients.
Sheridan ^{26(p5)}	In conclusion, let me say that x-rays help to stop the cough and vomiting, shortens the course of the disease, and lowers the mortality. In fact, many pediatricians state that x-ray therapy has proven to be the most valuable agent in the treatment of whooping cough.
Samuel ^{27(p550)}	The benefits to be derived from roentgen therapy of pertussis are primarily a very prompt relief of the paroxysms of coughing with the attendant vomiting. This usually occurs shortly after the first exposure and it is the outstanding feature, because with the paroxysmal coughing eliminated, the remaining cough which may still occur is of no great importance. In the majority of cases there is a distinct shortening of the usual long-drawn out course of the disease and the associated complications are, as a rule, absent, owing to the relief of the cough.
Von Meysenbug ^{28(p567)}	In conclusion, I wish to state that in x-ray treatment of pertussis we have available the most effective agent for relieving the distressing symptoms of the disease, shortening its course and preventing the dangerous complications which are often encountered.
Liebman ^{16(p646)}	Seven hundred children with persistent cough were treated with roentgen radiation. This form of treatment was found to be of distinct value when the cough was either an aftermath of pertussis or subsequent to an acute upper respiratory tract infection.

others, those children under 1 year of age were almost always reported to have significant reduction in symptoms after X-ray treatment. The marked success of the very young led to the suggestion that the dosing had been optimized for the young child but perhaps not so for the adult,⁹ even though it was very successful with this age-group as well.

Dose of X-Ray Treatment of Pertussis

The dose of radiation employed in all reviewed studies was noted to be less than 1 ED. Only the Liebman¹⁶ study provided a specific conversion into rad units, with his dose range being from 1/4 to 1/5 ED (135-225 rad). Using information provided in 7 papers,^{6,10,12,16,21,22} a dose reconstruction was made using the RadPro software and making several reasonable assumptions depending on the study. These reconstructions confirmed that all doses were below the ED as indicated by the authors. The doses ranged across these 7 studies from a low of 52²⁷ to a high of 430 to 450 rad.^{21,22} Doses were typically reduced by 50% to 70% in infants/very young children to the 50- to 60-rad dose range.^{10,27} It is of interest that Faber and Struble²¹ noted that “our single and total dosages appear to have been considerably larger than those of Bowditch and Leonard” (p. 816). This was the case for both dose rate and total dose. This conclusion would be consistent with the dose reconstruction presented here. It is unknown what the dose response may be for patients of different ages and gender as this was also confounded in the present series of papers by the existence of different disease stages and severity, all of which might affect treatment efficacy.

Discussion

Strengths and Limitations of Available Evidence

The clinical investigations revealed a range of strengths and limitations. On the strength side was the fact that most of the investigators were highly experienced clinicians with considerable knowledge of pertussis. They also worked closely with radiology experts. The patients do not appear to have been selected with any biased criteria. Usually, the cases were consecutively obtained and enrolled in the study. The studies, therefore, broadly included those of differing ages, gender, ethnicity, health status, and stage of disease. The most significant methodological limitation that was recognized was the lack of a concurrent control group in these studies. There were only 2 studies which reported the presence of concurrent control groups. One study was relatively small with only 22 treatment and 22 control individuals.²¹ The other study reported some 400 treatment cases and 200 control group individuals.⁹ Leonard⁹ did not report details on characteristics and the basis of selection of the control group. However, Leonard⁹ did report that the treated cases had an average disease duration of 5.5 weeks as compared to 8.7 weeks for the control. These findings indicate shortening of the illness by 3.2 weeks or nearly 40%. In the smaller study by Faber and Struble,²¹ the control was

generally selected by alternating patient's enrollment into the study. However, the investigators failed to follow their limited protocol on 5 different occasions that intentionally directed more severe cases into the X-ray group. None of these studies were blinded.

Thus, the lack of control groups in the overall database, and even the 2 studies reporting such controls, did not assist in a significant manner in the assessment of the findings. There was also a type of quasi control reported in the 1936 study of Liebman.¹⁶ He noted that at the start of the study cases treated with either UV or X-ray radiation were directly compared. After the first 10 patients for both groups were compared, the X-ray-treated patients fared so much better than the UV patients (data not shown in the Liebman study for the 20 patients) that they switched the treatment of all cases entirely to X-rays. Lacking the general presence of a concurrent control group, the researchers in this area of X-ray treatment effects on pertussis were left to infer the occurrence of a treatment-related effect when the cases displayed noticeable and quick relief from the various symptoms in a manner that substantially exceeded their professional experience.

A second issue of some importance that could affect judgment on the success of the treatment was the fact that a definite diagnosis of pertussis was difficult. This was due to reduced sensitivities of the diagnostic tests in the later stages of the illness. Since patients were treated at different stages, some patients would be negative for the presence of the causative agent. Thus, the diagnosis was often made based on the patient history, physical symptoms, diagnostic X-rays, and the experience of the treating physician.

Treatment Protocol Variation

The treatment technique, which originated with the initial publication of Bowditch and Leonard,⁴ included the radiation of the anterior chest for the first session, followed by the second session on the posterior chest on alternative days. In a third and usually final session, it was applied on the anterior chest. Other investigators would subsequently modify this protocol such that both anterior and posterior X-rays were administered during the same session. Others also reduced the multiple exposure sessions to only 1 session with a single larger dose. Finally, in the case of multiple treatments, the duration between treatments could be varied from alternate days, up to 1 treatment per week. Despite such differences in exposure protocols over time, the clinical responses were generally similar across studies, suggesting that the effects were independent of exposure interval duration.

Optimizing Dose

The concept of radiation-induced mutation was not discovered until the findings of Muller,²⁹ with fruit flies. Linkage of X-ray exposure to enhancement of childhood associated tumors would not emerge until after X-ray treatments for pertussis had ended. However, the issue of whether children who were

exposed to X-rays for the treatment of pertussis might experience an enhanced cancer risk was raised approximately 5 decades later by Webber³⁰ who wrote that “it is generally unappreciated by physicians that during the two decades from 1920-1940, hundreds of children received potentially carcinogenic doses of radiation therapy to the thorax for whooping cough” (p. 449). Webber³⁰ stated that the estimated dose was approximately 100 rad in air per exposure with a total X-ray dose in the range of 300 to 600 rad. In the mid-1930s, even after the introduction of the Sauer pertussis vaccine in 1934, it was likely that X-ray therapy for whooping cough continued for some time thereafter, noting a patient treated in 1937 in Michigan. Webber³⁰ concluded by raising the issue that as of the 1970s hundreds of adults may have potentially enhanced risk of thyroid cancer due to the radiation treatment during infancy for pertussis.

These speculative comments of Webber³⁰ are interesting but impossible to assess for multiple reasons. First, there is no record of which patients were lead shielded and the nature of the shielding protocol, if any. It is also unlikely that adult patients may even know that they were irradiated as an infant. Furthermore, the nature of the exposures were limited to generally 1 to 3 treatments, making any possible risks difficult to detect, especially with a very small sample size.

Mechanisms

The theoretical foundation for the use of X-ray treatment for pertussis, according to Bowditch,¹⁰ was based upon the same reasons for its use in bronchitis, that is, the proposed involvement of the hilum lymph nodes in an acute inflammatory hyperplasia. In theory, the X-ray treatment reduced the inflammation, reducing the size of these glands. Although focused mechanistic research of this issue was not undertaken during this era, considerable recent research has indicated that X-ray treatment in the general range of that used to treat pertussis induces an anti-inflammatory phenotype in multiple animal models.^{31,32} The radiation-induced anti-inflammatory phenotype has been extensively documented, being reported in a broad range of biological models. These findings suggest that this result may be broadly generalizable. These studies typically explored the underlying molecular mechanisms. Despite the broad range of biological models, consistent molecular patterns (Table 3) were reported that lead to the anti-inflammatory phenotype. Of particular significance is that the radiation-induced impact of disease end points was typically biphasic, showing decreases in disease-related responses at low doses, whereas at higher exposure levels adverse/undesirable health effects were typically noted. These findings have been hypothesized to provide a possible basis for the capacity of X-rays to affect therapeutic benefits on multiple diseases such as gas gangrene,⁵⁷ inner ear infections/deafness,⁵⁸ sinusitis,⁵⁹ shoulder tendonitis/bursitis,⁶⁰ arthritis,^{31,32} pneumonia,⁶¹ bronchial asthma,⁶² and carbuncles and furuncles.⁶³ Whether such X-ray-induced biphasic dose responses mediated the therapeutic effects seen with pertussis is unknown, but a reasonable

Table 3. Radiation-Induced Changes Leading to the Development of an Anti-Inflammatory Phenotype in Multiple Biological Models.

End Point	Radiation Treatment Effect	References
NO/iNOS	Decrease	Hildebrandt et al ^{33,34} ; Ding et al ³⁵
ROS	Reduction	Schaue et al ³⁶
HO-1	Enhancement	Hildebrandt et al ³⁴ ; Schaue et al ³⁷ ; Nakatsukasa et al ³⁸
Apoptosis	Induction	Kern et al ³⁹ ; Huynh et al ⁴⁰ ; Ren et al ⁴¹ ; DosReis and Lopes ⁴² ; Ferri et al ⁴³ ; Perruche et al ⁴⁴ ; Esmann et al ⁴⁵
TGF- α	Suppression	Schaue et al ³⁷ ; Nakatsukasa et al ³⁸
TGF- β 1	Enhancement	Schaue et al ³⁷ ; Nakatsukasa et al ³⁸
NF- κ B and AP-1	Activation of transcription factors	Martin et al ⁴⁶ ; Rödel et al ⁴⁷
Leukocytes and PMNs	Decreased adhesion to endothelial cells	Arenas et al ^{48,49} ; Trott and Kamprad ⁵⁰ ; Kern et al ^{51,52} ; Rödel et al ^{53,54}
T-regulatory cells	Enhancement	Nakatsukasa et al ^{38,55} ; Weng et al ⁵⁶

Abbreviations: AP-1, activating protein 1; HO-1, heme oxygenase 1; iNOS, inducible nitric oxide synthase; NF- κ B, nuclear factor kappa B; NO, nitric oxide; PMNs, polymorphonuclear neutrophils; ROS, reactive oxygen factor; TGF, tumor growth factor.

potential hypothesis, especially for those radiotherapeutic interventions which involved relatively low-level irradiations applied in fractions with sufficiently long intervals permitting the repair of inflammation-induced tissue injury.

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Note

1. The first apparent reported case of X-ray treatment of pertussis was mentioned by multiple authors in the X-ray pertussis literature of 1923 to 1936 cited in this article. However, none of these authors provided the specific reference(s) which was said to be in the

Russian scientific literature. They did provide a range of differing dates from 1907 to 1911.

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