**Radiation hormesis: its historical foundations as a biological hypothesis**

E J Calabrese and L A Baldwin

*Hum Exp Toxicol* 2000 19: 41
DOI: 10.1191/096032700678815602

**Human & Experimental Toxicology (2000) 19,** 41–75

0960–3271/00 $15.00
www.nature.com/het

# Radiation hormesis: its historical foundations as a biological hypothesis

EJ Calabrese*,[1] and LA Baldwin[1]

[1]*Department of Environmental Health Sciences, School of Public Health, N 344 Morrill Science Center, University of Massachusetts, Amherst, MA 01003, USA*

**This paper represents the first systematic effort to describe the historical foundations of radiation hormesis. Spanning the years from 1898 to the early 1940's the paper constructs and assesses the early history of such research and evaluates how advances in related scientific fields affected the course of hormetic related research. The present effort was designed to not only address this gap in current knowledge, but to offer a toxicological basis for how the concept of hormetic dose-response relationships may affect the nature of the bioassay and its role in the risk assessment process.**
*Human & Experimental Toxicology* (2000) **19,** 41–75

**Keywords:** hormesis; low dose; stimulation; $\beta$-curve; radiation

## Introduction

Since 1980 there have been two books concerning radiation hormesis,[1,2] various international symposia directly related to this topic,[3–7] and a substantial number of articles. However, none of these attempts to describe and assess the concept of radiation hormesis has addressed, except in a very limited fashion, the historical foundations of this concept. In fact, we have been unable to uncover any attempt to assess this topic, even in the earlier decades of the 20th century, despite a substantial effort to uncover such possible efforts. This paper therefore is designed to provide a comprehensive and critical review of the historical foundations of radiation hormesis, with particular emphasis on ionizing radiation. The timeframe of the paper encompasses the late 1890's to approximately 1940. A parallel type of evaluation was recently published concerning the historical foundations of chemical hormesis[8] and how it became marginalized within the toxicological community.[9]

At the onset of this paper it is important to define the term hormesis. Hormesis is a concept that describes the nature of dose-response relationships in biological systems as displaying a stimulatory response at low doses and an inhibitory response at higher doses. Recently Calabrese and Baldwin[10,11] have attempted to quantitatively define this relationship with respect to the dose range of the stimulatory response, the maximum stimulatory response and the relationship of the maximum stimulatory response to the traditional toxicological No Observed Adverse Effect Level (NOAEL). Although this proposed scheme is consistent with the vast majority of data currently assessed on this topic, notable and reliable exceptions do exist to this framework and have recently required a broader delineation of the above defined nature of the hormetic dose-response relationship and its mechanistic underpinnings.[12] The present paper has been guided in this evaluation of hormesis by the above quantitative criteria without regard for whether the low dose stimulatory response is deemed beneficial, harmful or of unknown biological significance.

This paper has opted for a broad search of the biological/radiobiological/toxicological literature including responses to plants, bacteria, fungi, other micro-organisms, invertebrates and vertebrates including human epidemiological/clinical data. This broadly based biologically oriented approach was principally designed to assess to what extent the concept of hormesis may be generalizable. This approach also sought to provide an evaluation of radiation hormesis as a biological hypothesis rather than as an explanatory feature of selected medical practices, such as in low dose radiological practices in traditional medicine or as a possible theoretical framework of the practice of homeopathy. It should also be noted that the term hormesis was not coined until 1943 by Southam and Erhlich[13] who were assessing chemical extracts from cedar wood on fungi. However, the concept of hormesis was

*Correspondence: EJ Calabrese
Received 15 October 1999; accepted 15 October 1999

embodied in terms such as the Arndt-Schulz Law and Hueppe's Rule, which came into widespread, but not universal, use in the early 1900's based initially on the independent work of Schulz[14,15] with yeast and Hueppe[16] with bacteria.

This review of the historical foundations of radiation hormesis will ironically conclude at about the same time the term hormesis was coined. Thus, the concept of low dose stimulation, high dose inhibition has had three specific designations over the century (i.e., Arndt-Schulz Law, Hueppe's Rule, hormesis), yet one underlying concept and these terms have typically been used interchangeably.

The information contained here will provide an assessment of the status of the hormesis hypothesis in the radiation and toxicological communities up to the 1940's. This paper will then serve as a basis (see companion paper[8]) to evaluate how this concept became abandoned by the mainstream leaders of both radiation and toxicology during the middle and later decades of the 20th century. Finally, a third paper[9] will offer a comparative assessment of both chemical and radiation hormesis with respect to differential development of an hormetic hypothesis, the relative strengths and weaknesses of their underlying data, and the differential factors affecting the acceptance of both hypotheses.

## Plants

### *Introduction*

The evaluation of the potential for radiation to stimulate plant growth has a long and complex history. Such an evaluation of plant responses to radiation is seen within the context of the type/source of irradiation including X-rays and naturally occurring sources such as radium, cobalt and other elements that emit various types of radiation including gamma, beta and alpha rays. Each type of radiation has a unique history and will be assessed separately.

The present review is designed to assess the historical foundations of the response of plants to radiation especially as it pertains to the nature of low dose responses. In the case of X-rays this historical review encompasses nearly 40 years, spanning the years from 1898 when the first claims of a low dose stimulatory response were reported to the 1940's when the plant research of the former eastern-block countries and Soviet Union became more readily available to western scholarly analysis and evaluation.

The first part of this review evaluates the effects of X-rays on plant growth and in certain instances on seed germination. While 70 different species of plants were evaluated in over 60 published papers for the effects of X-rays during these early decades of the 20th century, several species (i.e., wheat, sunflower, broad bean and rice) have been the object of more intense investigation. Consequently, the following section on X-rays will provide a more detailed evaluation of the response of these four species, since they provide the most comprehensive information on the nature of the dose-response, especially in the low dose range, as well as to the critical issue of reproducibility of findings. The findings of all 64 separate publications reviewed (Table 1) often included multiple experiments with multiple endpoints measured. Consequently, there is substantial information available to provide a general assessment of the effects of X-ray treatments on plant growth. The summarized data provide information on a number of relevant parameters, especially with respect to study design features (e.g., number of doses, dose range, and spacing of doses). For example, of the 63 publications, 18 papers reported experiments with greater than or equal to six doses (i.e., X-ray treatments). Experiments with such a large number of treatment groups offer an excellent opportunity to assess the hormetic hypothesis, especially if optimal dose selection was employed. The table also reveals that the investigators generally used seeds, as the principal object of exposure (i.e., more than two-thirds of the studies), followed by the use of sprouts. Common experimental considerations involved the use of either dry or soaked seeds, with the length of time that the seeds were soaked in water prior to irradiation differing according to the specific experiment. In general, the findings revealed that approximately two-thirds of the publications reported X-ray induced stimulation of plant growth, seed germination or other parameters. As expected, those studies using large numbers of doses, especially in the low dose range, provided the most useful information to assess the hormetic hypothesis and in general were supportive of this hypothesis.

The time span over which the evaluation of X-rays on plant growth is conducted is the period from the late 1890's to the early 1940's. As will be seen, during this period research methods underwent rapid developmental refinement not only with respect to X-ray technology and dosimetry, but also with complementary aspects relating to study design, statistical analysis procedures, and reporting of data. For example, statistical methods such as the chi-square test, the *t*-test of Student and analysis of variance were not developed until 1900, 1908, and 1918, respectively.[76] It was during this period that considerable data emerged to affect judgments on

**Table 1** A history and summarization of the effects of X-rays on plant growth from 1896–1941.

| *Author* | *Year* | *Type of radiation* | *No. of doses* | *Dose range* | *Specific doses* | *Plant name* | *Plant part exposed* | *If seed, D S G UK* | *Endpoint* | *Results* | *Conclusion* | *Comments* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Schober[17] | 1896 | X-ray | NA | NA | NA | Oat | Seedling | NA | Growth | Stimulation | Stimulatory | |
| Maldiney and Thouvenin[18] | 1898 | X-ray | NA | NA | NA | *C. alvensis* *L. sativum* *P. millaceum* | Seeds | UK | Germination | Acceleration of seed germination | Stimulatory | Low no. of seeds; low confidence |
| Perthes[19] | 1904 | X-rays | NA | NA | NA | *V. faba* | Seeds | UK | Root growth | Retardation | Inhibitory | |
| Euler[20] | 1906 | X-rays | NA | NA | NA | Beans, radishes | Seeds | UK | Sprouting, growth, time to blooming | Acceleration of blooming | Stimulatory | |
| Koernicke[21,22] | 1904, 1905 | X-rays | 3 | 16–26 H | 11, 20, 36 H | *V. faba* *V. sativa* *B. napus* | Seeds | D, S, G | Growth, germination | 20 H small acceleration for *V. faba* and large acceleration for *B. napus;* germination stimulated | Stimulatory | Study included methodology advances |
| Guillemi-not[23] | 1907 | X-rays radium | 16 | 10–20,000 R | NA | Gilly flower (methiola) | Seeds | D | Growth | Accelerated growth at 5000 & 7500 R; higher doses inhibitory | Stimulatory | Stimulatory responses thought to be too small to be significant |
| Schmidt[24] | 1910 | X-rays | 5 | 0.05–1 HED | 1/20, 1/10,¼, ½, 1 HED | Peas | Seeds | S | Height, leaf size, pod size | Considerable stimulation at low doses; bottom four doses stimulated | Stimulatory | Stimulation so great as to have commercial importance |
| Wetterer[25] | 1912, 1913 | X-rays | 4 | 5–40 H | 5, 10, 20, 40 H | Sunflower | Seeds | S | Growth | Retardation proportional to dose | Inhibitory | |
| Promsy and Drevon[26] | 1912 | X-rays | NA | NA | NA | Lentils, rye, beans, white lupine, kidney beans | Seeds | G | Growth | At 15°C strong retardation; at 30-40 °C mostly stimulation | Stimulatory | Temperature dependent response |
| Schwarz[27] | 1913 | X-rays | 4 | 30–120 s | 30, 60, 90 and 120 sec; 5 min | *V. faba* | Seeds Seedlings | D | Growth–height | 120 s produced most favorable results; 5 min retardation | Stimulatory | Small no. of experiments; lack of controlled conditions |
| Miege and Coupe[28] | 1914 | X-rays | NA | NA | NA | *R. lepidium* | Seeds | Growth–weight & height | 45% increase leaf weight; 59% increase | | Stimulatory | |

(*Continued*)

**Table 1** *(Continued)*

| *Author* | *Year* | *Type of radiation* | *No. of doses* | *Dose range* | *Specific doses* | *Plant name* | *Plant part exposed* | *If seed, D S G UK* | *Endpoint* | *Results* | *Conclusion* | *Comments* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Koer-nicke[29,30] | 1915-1920 | X-rays | 10 | 1/100–5 H | 1/100, 1/60, 1/40, 1/20, 1/10, ½,1.5,2.5, 3.5,5 H | *V. faba* *P. multiforma* *P. vulgaris* *L. albus* *S. arrensis* *P.somniferum* *T. vulgare* *B. napus* *Z. mays* *A. sativa* | Seeds | D, S | Growth | Growth at 1/60–1/30 H was accelerated for air dried seeds; seeds soaked 1-2 days were stimulated; seedlings stimulated | Stimulatory | 220-3000 seeds per experiment; acceleration only when air dried and germinated seeds irradiated |
| Yamada[31] | 1917 | X-rays | 4 | 3–11 H | 3,5,7,11 H | *O. sativa* | Seeds | S (168 hr) | Germination and growth | Growth stimulated (8.3%) at 3H | Stimulatory at lowest doses | Higher two doses showed a modest decrease |
| Nakamura[32] | 1919 | X-rays | 3 | 5–15 min | 5, 10, 15 min | *O. sativa* | Seeds | D | Crop yield | Plants in 5 min group were stimulated | Stimulatory at the lowest dose | |
| Sierp and Robbers[33] | 1923 | X-rays | NA | NA | NA | *A. sativa* | Sprouts | | Separate plant organs | Early stimula-tion, later retardation | Stimulatory/ inhibitory | |
| Lallemand[34] | 1922 | X-rays | 7 | 1/12–20 H | 1/12, ¼,1/3, 1/2,5,10 20 H | *P. miliaceum* *L. sativum* *B. napus* *T. sativum* *L. asulenta* *P. velgavis* Onion bulbs | Seeds | D, S | Growth after 14th day | Weakest doses did not sitmulate lentil, wheat and kidney beans; modest, high doses did not stimulate lentil & kidney bean | Inhibitory | |
| Weber[35] | 1922 | X-rays | NA | NA | NA | Lilac | Buds | | Sprouting | Stimulation | Stimulatory | |
| Altmann *et al.* [36] | 1923 | X-rays | > 4 | 1–12 H | 1,3,6,12 H | *P. vulgaris* | Seeds | D, S, G | Multiple growth endpoints | Transient stimulation; stimulation depends on stage of develop-ment | Stimulatory | Triplicated experiment |
| Komuro[37] | 1923 | X-rays | 7 | 40–150 H | 40, 50, 60, 80, 100, 120,150 H | *V. faba* | Seeds | S | Growth | Germination reduced | Inhibitory | Exp. 1 and 2 replicates |
| Komuro[37] | 1923 | X-rays | 8 | 20–155 H | 20, 30, 50, 60, 80, 100, 120, 155 H | *V. faba* | Seeds | S | Growth | Growth accelerated | Stimulatory at 20 H | Exp. 3 |
| Komuro[38] | 1924 | X-rays | 3 | 5–15 H | 5,10,15 H | *O. sativa* | Seeds | S | Germination and growth | Germination and growth accelerated | Stimulatory at 10 and 15 H | Exp. 1 |

*(Continued)*

**Table 1** *(Continued)*

| *Author* | *Year* | *Type of radiation* | *No. of doses* | *Dose range* | *Specific doses* | *Plant name* | *Plant part exposed* | *If seed, D S G UK* | *Endpoint* | *Results* | *Conclusion* | *Comments* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Komuro[38] | 1924 | X-rays | 3 | 5–15 H | 5,10,15 H | *O. sativa* | Seeds | D | Germination and growth | Germination stimulated early | Stimulatory at both doses | Exp. 2 |
| Komuro[38] | 1924 | X-rays | 3 | 7–15 H | 7,10,15 H | *O. sativa* | Seeds | D | Germination and growth | Germination and growth accelerated | Stimulatory at 7 and 10 H | Exp. 4 |
| Komuro[38] | 1924 | X-rays | 3 | 5–15 H | 5,10,15 H | *O. sativa* | Seeds | D | Germination | Germination stimulated | Stimulatory at all doses | Exp. 6 |
| Czepa[39] | 1924 | X-rays | NA | 0.5–25 and 150 H, 300 H | H NA | *V. faba* *V. sativa* *P. vulgaris* Lettuce | Seeds | | Rate of germination; growth | One experiment showed stimulation at 25-50 H | Stimulatory /inhibitory | Authors concluded no stimulation occurred |
| Martius[40] | 1924 | X-rays | NA | NA | NA | NA | NA | | NA | Failed to show stimulation | No stimulation | |
| Geller[41] | 1924 | X-rays | NA | NA | NA | NA | NA | | NA | Stimulation at some doses | Stimulatory | Experiments covered 1920-1923 |
| Gambarov[42] | 1924 | X-rays | 6 | 1–10 HED | 1,2,3,4,5, 10 HED | *V. faba* | Seeds | S | Root length; time of lateral root develop-ment | No stimulation | Inhibitory | Measured daily for 12 days |
| Ancel[43] | 1924 | X-rays | NA | NA | NA | | Seeds | | Germination rate | Large differences across treatments | No stimulation | Author did not relate to treatment |
| Tushanakova (as reported in Breslavets[44]) | 1924 | X-rays | 4 | 5–20 min | 5,10,15,20 min | Sedge, soya, blue lupine, tomato, melon | | | Fruit maturation | Soya & lupine: matured earlier; melons: fruited earlier; Tomato: increased no. of fruit | Stimulatory | Showed compensation stimulation; sedge stimulation too small to be useful |

*(Continued)*

**Table 1** *(Continued)*

| *Author* | *Year* | *Type of radiation* | *No. of doses* | *Dose range* | *Specific doses* | *Plant name* | *Plant part exposed* | *If seed, D S G UK* | *Endpoint* | *Results* | *Conclusion* | *Comments* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Iven[45] | 1925 | X-rays | 9 | 1/250–22 HED | 1/250, 1/100, 1/10,1/2, 1,5,10,18, 22 HED | *V. faba* | Seeds | D | Germination and leaf development | Stimulation noted | Stimulatory | Stimulation followed Arndt-Schulz Law |
| Ancel[46,47] | 1925 1925 | X-rays | NA | | | | Seeds | | | Negative | No stimulation | |
| Kol'tsov and Kol'tsov[48] | 1925 | X-rays | NA | NA | NA | Peas Wheat | Seeds | D, G | Height Flowering | Experiment with peas give more definite evidence of stimulation | Stimulatory | |
| Ancel[49] | 1926 | X-rays | 4 | 40-150 H | 40,70,100, 150 H | Lentils Beans | Seeds | D | Individual plant parts | No stimulation | Inhibitory | |
| Ancel[50] | 1926a | X-rays | 1 | | 8 H | Lentils | Buds | | Bud sprouts | Enhanced growth | Stimulatory | Seen as compensation to injury |
| Bersa[51] | 1926 | X-rays | NA | | 0.5 H | *V. faba* S. alba | | | Stem and root lengths | *V. faba*: 26% increase in root length; *S. alba*: rootlets & hypocotyls showed stimulation | Stimulatory | Limited power due to small n ($n$ = 10) |
| Johnson[52,53] | 1926 1928 | X-rays | 2 | 5–10 H | 5, 10 H | Sunflower | Seeds | D, S | Growth, germination, sprouting | No stimulation; plants from soaked seeds bloomed earlier | Inhibitory | |
| Doroshenko[54] | 1929 | X-rays | 3 | 5–20 min 50–80 min | 5,10,20 min; 20, 30, 40, 60, 75, 80 min | *A. bizantine* Millet Winter rye | | | Growth yield | *Avena bizantine*: stimulated at low doses; winter rye: stimulated; millet: inhibited | Stimulatory /inhibitory depending on species and dose | Higher doses cause inhibition; low doses cause stimulation |
| Sprague and Lenz[55] | 1929 | X-rays | NA | | 2H (exp1) 1H (exp2) | Irish cobbler Green mt. | Tubers | | Yield | Treatment effect; increased | Stimulatory | |
| Patten and Wigoder[56] | 1929 | X-rays | NA | 1/20 HED 3 HED | | Beans Mustard Barley | Seeds | | Growth | Mustard most rapid growth at 1/20 HED; barley inhibited; beans not clear | Stimulatory | Data not presented |

*(Continued)*

**Table 1** *(Continued)*

| *Author* | *Year* | *Type of radiation* | *No. of doses* | *Dose range* | *Specific doses* | *Plant name* | *Plant part exposed* | *If seed, D S G UK* | *Endpoint* | *Results* | *Conclusion* | *Comments* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cattell[57] | 1931 | X-rays | NA | 150–1100 r | 100, 250, 400, 700, 1100 r | Wheat | Sprouts | | Growth of roots, leaves, coleoptiles | Coleoptiles and leaves slightly enhanced at low doses | Stimulatory /inhibitory outcomes | 200,000 measurements |
| Johnson[58-60] | 1931, 1933 | X-rays | NA | NA | NA | Two thistles, several *Solenaceae*, *V. faba* | Seeds | S (40 hr) | Fresh and dry weights | Only sunberry plant showed stimulation with weak rays | Stimulatory /inhibitory | Grew plants for 25 days |
| Chekhov[61] | 1932 | X-rays | NA | NA | NA | Barley, rye, lentils, oats | Seeds | D, G | Germination and growth | Weak doses had stimulatory effect on development | Stimulatory | Like Arndt-Schulz Law |
| Shull and Mitchell[62] | 1933 | X-rays | 5 | 38–190 r | 38,76,118, 152,190 r | Corn, oats, sunflower, wheat (3 varieties) | Seeds | D, S | Growth | Coleoptiles enhanced 5–26% | Stimulatory | Optimum response determined |
| Benedict and Kersten[63] | 1934 | X-rays | NA | NA | NA | Wheat | Seeds | | Enzyme activity | Increased enzyme activities | Stimulatory | |
| Francis[64] | 1934 | X-rays | 6 | 565–13,560 r | 565,1130, 1695, 3390, 6780, 13,560 r | Wheat | Seedlings | | Growth | No stimulation | Inhibitory | |
| Breslavets and Afanas'eva[65] | 1935 | X-rays | 7 | 250–8000 r | 250, 500, 750, 1000, 2000, 4000, 8000 r | Rye | Sprouts | Sprouted seeds S | Height, number of stems/plant, number of ears | Height retarded; increased no. of stems/plant at low doses; ears stimulated at low doses | Stimulatory | Used hard and soft X-rays; Arndt-Schulz Law |
| Breslavets and Afanas'eva[66] | 1935 | X-rays | 7 | 250–8000 r | 250, 500, 750, 1000, 2000, 4000, 8000 r | Rye | Seeds | S | Height, number of stems/plant, ear size | Stimulated at low doses | Stimulatory | Growth at day 27 |

*(Continued)*

**Table 1** *(Continued)*

| *Author* | *Year* | *Type of radiation* | *No. of doses* | *Dose range* | *Specific doses* | *Plant name* | *Plant part exposed* | *If seed, D S G UK* | *Endpoint* | *Results* | *Conclusion* | *Comments* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tsuryipa (as reported in Breslavets[44]) | 1935 | X-rays | NA | NA | NA | Wheat, oats, cotton | Seeds | | Vegetative and reproductive endpoints | Wheat; greater impact on reproductive than vegetative; oats: increased sprouting, 60% increased yield, ripening shortened by 10 days | Stimulatory | |
| Long and Kersten[67] | 1936 | X-rays | 5 | 1–5 s | 1,2,3,4,5 s | Soya | Seeds | UK | Weight | Marked increase | Stimulatory | Field conditions 12,751 plants |
| Frolov[68] | 1936 | X-rays | NA | NA | NA | Soya, wheat, flax | | | Yield | Wheat: accelerated at 60% in yield; soya: not stimulated; flax: stimulated only early growth | Stimulatory | Results with soya contrast with Long & Kesten |
| Johnson[69] | 1936, 1936a | X-rays | NA | NA | NA | Tulip | Bulbs | | Leaves Blooms | Leaves lengthened flowers not affected | Stimulatory/ inhibitory | |
| Johnson[69] | 1936 | X-rays | 1 | NA | 1500 r | Wild potato | Tubers | | Tuberization of potato | No stimulation | Inhibitory | Favourable in pilot study but not in follow-up; experiments over five seasons with 17,000 tubers |
| Saeki[70] | 1936 | X-rays | 6 | 50–1200 MAM/21[2] at 30 KV | 50, 100, 200, 400, 800, 1200 | *O. sativa* | Seeds Seedlings | G | Growth Germination Yield | ⩽200 MAM/21[2] stimulatory depending on endpoint | Stimulatory | |
| Zankevich and Brunst[71] | 1937 | X-rays | 7 | 250–10 000 r | 250, 500, 750, 1500, 3000, 6000, 10 000 r | Tobaco Poppies Flax Rhubarb | | | Growth | 500 and 750 r stimulatory to tobacco and flax | Stimulatory | |

*(Continued)*

**Table 1** *(Continued)*

| *Author* | *Year* | *Type of radiation* | *No. of doses* | *Dose range* | *Specific doses* | *Plant name* | *Plant part exposed* | *If seed, D S G UK* | *Endpoint* | *Results* | *Conclusion* | *Comments* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bless[72] | 1938 | X-rays | 8 (radish) 6 (beans) 10 (lettuce) | 0.25–7 sec (radish & lettuce) 0.25–6 sec (beans) | 0.25, 0.50, 0.75, 1, 2, 3, 4, 5, 6, 7 s | Radish, beans, lettuce | Seeds | D, S | Growth | Radish: 10% increase in pod wt– not thought to be significant. Bean: no significant effect with dry seeds; 25% increase with spouted seeds. Lettuce: 60% increase in 5 min dry seed group; later repeat showed 2—30% increase | Stimulatory | Radish: 20 plants per treatment; Bean: 25 plants per treatment; Lettuce: 10 plants per treatment |
| Zaurov[73] | 1937 | X-rays | 5 | 125–4000 r | 125, 500, 1000, 2000, 4000 r | Indian hemp | Seeds | | Stem length Growth | Insignificant increase in stem length at 500 r; insignificant increase in growth at 2000 r | Stimulatory | |
| Breslavets[74] | 1937 | X-rays | 10 | 50–1000 r | 50, 100 200, 250, 350, 450, 550, 650, 750, 1000 r | Peas | Seeds | D | Growth Pods | Excellent stimulation of growth at 350 and 1000 r; increase in pods | Stimulatory | |
| Breslavets[74] | 1937 | X-rays | 6 | 250–16,000 r | 125, 250, 500, 750, 1000, 2000, 4000, 8000, 16,000 r | Spring wheat | | D, S sprouts | Growth | Dry and soaked seeds did not respond; sprouts not stimulated (50–8000 r) | Inhibitory | |
| Wort[75] | 1941 | X-rays | 7 | 19–22 r | 19, 38, 57, 76, 114, 152, 228 r | Spring wheat Winter wheat | Seeds | D | Growth | Enhanced growth | Stimulatory | Attempted to closely follow Shull & Mithell 1933 |
| Breslavets (as reported in Breslavets[44]) | 1942 | X-rays | 9 | 200–8000 r | 200, 300, 400, 600, 750, 1000, 2000, 4000, 8000 r | Meadow grasses | Seeds | | Germination No. of roots Root length Stem length | Stimulation of all parameters | Stimulatory | Typical of β-curve |

Abbreviations: H = Holzknecht's Unit; HED = Erythema dose; designated by Seitz and Wintz as the Hauteinheitsdosis; S = soaked; D = dried; G = germinating; UK = unknown

**Table 1** *(Continued)*

| |
|---|
| Summary of data |
| 70 species of plants were tested in a total of 64 publications |
| 43 publications were conducted with seeds, 7 with sprouts, and 1 with bulbs |
| Of the 43 publications conducted with seeds, 15 involved air-dried seeds, 15 water-soaked seeds, and 5 germinating seeds |
| Of the total 64 publications, 44 showed stimulation, 17 inhibition, and 3 both stimulation and inhibition |

how X-rays affected plant growth culminating in interim conclusions provided in U.S. National Academy of Science publications on this topic.

### *X-rays*

*Early studies on rice* During the early decades of the 20th century several authors investigated the capacity of X-rays to stimulate the germination of rice seeds and the growth of rice seedlings. Six such studies have been typically cited in review papers as providing support to the radiation hormesis hypothesis.[31,32,37,38,70] Four of the six papers which utilized *Oryza sativa* as the plant species, included three doses and a control; the study of Yamada[31] employed four doses and a control, while Saeki[70] used six doses plus a control. Four of the six studies defined the X-ray dose in H units and they were quite similar in dose range (i.e., 3, 5, 7 and 11 H; 5 to 15 H; and 3, 5, and 7 H). The latter study by Saeki[70] defined dose as MAM/21$^2$ at 30 KV (i.e., 50 – 1200 MAM/21$^2$ at 30 KV). It should be noted that the international roentgen (r) as a radiation unit was in general use since 1928. Its equivalence to other units previously used is as follows: (1) skin erythema dose (SED) is considered to be equivalent to about 600 r and equivalent to 1 S.-N unit as introduced by Sabournud and Noire. The Holzknecht (H) unit has two values. As initially given by Holzknecht it equalled 1/3 SED (200 r), but later is equalled to 0.25 N or 125 r. Kienbock divided his scale into unites of X (i.e., Kienbock units) and considered 10 × =1 S.-N=5 H. Thus, X is about 60 r (see Hudson;[77] Taliaferro and Taliaferro[78]).

The principal difference in earlier studies involved how the seeds were handled prior to and after ovulation. In general, the seeds were either air-dried or steeped (soaked) in water for variable time periods prior to irradiation [e.g., Yamada[31] for 168 h and Komuro[38] for 12 h]. In some studies germination was considered or growth or both parameters. In general, the data indicate that air dried seeds were stimulated by the X-ray treatments.[37,38] In the 1924 study of Komuro several experiments indicated a consistent acceleration of germination, especially at 5 and 10 H.[38] The number of seeds in each of these experiments was modest, ranging from 10 – 25 per treatment group. Nonetheless, the integration of the three experiments indicates that the acceleration was considerable and approached twofold at the 10 H dose. Statistical analyses were not conducted on the data by the authors. Komuro also claimed that soaked rice seeds were also stimulated by low doses of X-rays. These findings were, however, generally marginal increases and are not as reasonably established as with dry seeds.[38]

With respect to growth, the findings of Yamada[31] and Nakamura[32] provide support for the hypothesis that crop yield could be enhanced by X-ray treatment. However, their conclusions were directly challenged by Komuro[37] based on the inadequacy of the control group of these two investigations and especially in light of his generally better study design and non-stimulatory response as far as yield was concerned. However, Komuro reported that the plants displayed 'precocious' growth, meaning that they developed more quickly and were able to be transplanted earlier.[37] Later investigations by Komuro[38] and Saeki[70] supported the hypothesis of X-ray treatment enhanced crop yield in studies with more powerful designs (e.g., six doses in Saeki[70]) and with the magnitude of enhancement being generally in the 10 – 30% range depending on the endpoint measured.

*Other early research on non-rice species* In research that both preceded and was contemporaneous with the Japanese work on rice, Koernicke[21,30] assessed the effects of X-rays on the germination and growth of multiple species of plants. Early findings[21] gave some hint that X-rays may enhance germination during certain experimental conditions. More specifically, Koernicke[21] reported a reproducible acceleration of germination in air dried seeds of *Vicia faba*, a phenomenon that was not observed in soaked seeds (see next section).

This initial research of Koernicke[21] was noteworthy not only for the stimulatory response, but also because it involved methodological advances, including the use of multiple species as well as larger numbers of seeds in the investigations. Nonetheless, the study was still limited to only three doses (16, 20 and 24 H) with only the 20 H dose providing evidence of a stimulatory response.

In follow-up experimentation published over a decade later, Koernicke[29] extended his research to include ten species, employing air dried seeds, water soaked seeds (1, 2 or several days), germinated seeds into radicals, and potted seedlings. The range of doses was markedly increased, with now ten doses (5 H to 1/100 H) in contrast to the 16–24 H dose ranging study. The sample size was also increased to include from 200–3000 seeds per experiment. In general, air dried seeds and those soaked for 1 or 2 days that were more strongly irradiated germinated sooner than weakly or non-irradiated seeds. Other stimulatory growth was reported for seedling responses to low doses of X-rays (1/60 to 1/20 H). These findings of Koernicke[29] were generally consistent with the more limited study of Schwarz,[27] who observed that irradiated air dried *V. faba* seeds resulted in enhanced growth (5 doses) by 3 weeks. While the magnitude of the enhancement was approximately twofold, the sample size was only three plants per treatment.

Other findings published in the early years of the 20th century provided support for the premise that X-rays could stimulate either germination and/or growth. Most notable were those of Euler,[20] Guilleminot,[23] Schmidt,[24] Promsy and Drevon,[26] Miege and Coupe,[28] and Pfeiffer and Simmermacher.[79] These early studies were distinguished by the wide range of species tested, the use of up to 16 doses by Guilleminot[23] and five doses by Schmidt.[24] Nonetheless, most of these investigations had important limitations, including small sample size, such as only ten seeds/treatment,[28] lack of statistical analysis and often inadequately controlled environmental conditions.

Nonetheless, the first two decades of the 20th century witnessed the recognition that low doses of X-rays, especially to seeds in an air dried but also water soaked state, had the potential to have their germination accelerated. Growth was also stimulated depending on the study as measured by enhanced early development, shorter time to blooming[20] and increase in height and weight.[24,28] There was also the progressive improvement in the standardization and reporting of X-ray exposures, and in the quality of the study design. While these studies lacked the capacity to derive definite conclusions about the capacity of X-rays to stimulate germination and/or growth, the data clearly support the hypothesis that stimulation could occur and that follow-up research was necessary to resolve the question. Such findings ushered in an expanded level of research on this topic that would continue over the next several decades.

*Vicia faba* Perhaps the most tested plant in X-ray stimulation studies is *Vicia faba*, the broad bean. By 1936 fifteen studies were found in the open literature concerning whether X-rays could stimulate seed germination or growth of this plant. It was believed that a more careful consideration of the responses of *V. faba* were warranted since this would more effectively speak to the issues of robustness of the database, endpoint variation, reproducibility and dose range studied.

Of the fifteen studies, six were reported as clearly providing no support to a stimulation hypothesis. Of the remaining nine studies which produced some evidence of an X-ray-induced stimulatory response, one was criticized by other investigators for either lack of controlled conditions (see Komuro's criticism[37] of Schwarz[27]) while another study suggesting stimulation could not be replicated (see Ancel's criticism[43] of Altmann *et al.*[36]). The stimulatory study of Bersa[51] was also criticized as having too small a sample size ($n$=10) to draw firm conclusions, while Patten and Wigoder[56] presented evidence of a stimulatory response in an abstract-like note without research methods. Of the five remaining articles providing evidence of stimulatory responses, Koernicke[21,22] and Jungling[80] report only one dose in the stimulatory zone, thereby not providing an adequate characterization of the possible stimulatory zone. Of the remaining two studies, Koernicke[30] and Iven[45] ultilized ten (1/20–25 HED) and nine (1/250–5½ HED) X-ray doses, respectively, plus controls. In the case of Koernicke,[30] stimulation was reported at 1/12, 1/8, and 1/5 HED, while in the Iven[45] report the stimulatory range was from 1/250–½ HED. In her major review of the effects of X-rays on plants Breslavets[44] indicated that both of these studies provide support for the Arndt-Schulz Law.

Of particular interest was the fact that Iven[45] provided repeat measures data that revealed that the growth stimulation which appeared within 10–20 days following treatment and then regressed to become equal with the control values. Thus, as Johnson[58] noted, the stimulatory effect with the low dose X-ray treatment was a transitional one. Johnson[81] concluded that Iven[45] was reporting an acceleration of growth following retardation, 'a phenomenon commonly reported after radiation'. Such an interpretation was consistent with the views of Stebbing,[82] that hormesis represents an overcompensation to a disruption in homeostasis. This overcompensation phenomenon was carefully documented for u.v. radiation on fungal growth by Smith.[83,84]

Of further note is that several of the more strongly designed studies which display no evidence of stimulation and/or clear inhibition utilized doses in the inhibitory area of the dose-response of Koernicke[30] and Iven[45] or even apparently higher. For example, Gambarov[42] employed doses of 1–10 HED, Czepa[39] used doses at 2.5–125 HED. Consequently, the fact that they were negative does not conflict with the observations of Koernicke[30] and Iven[45] who reported stimulatory responses at lower levels. In her review of the *V. faba* data, Breslavets[44] offers four explanations of why the array of papers presented a confusing picture of stimulatory and inhibitory responses: (1) *V. faba* was viewed as an inappropriate biological model because its threshold for stimulation was too low. It was believed to be so radiosensitive that even with normally weak doses a retardation response would ensue; (2) Insufficiently accurate measurement of dose, especially those early studies in which dosage was measured in skin erythemas; (3) The *V. faba* experiments also employed inadequate numbers of seeds. This was principally due to the large size of the seeds coupled with the use of the limited field in the Coolidge tube thereby providing an important barrier for conducting such experiments; and (4) These studies were also criticized for their use of a generally small range of doses. According to Breslavets,[44] the most significant flaw in many of the experiments may have been the *a priori* bias of the investigator. Much was made of the remarks of Seide[85] and Johnson[58] who displayed obvious bias against the theory of X-ray-induced stimulation by ignoring or discounting data inconsistent with their views. On the other hand, Breslavets[44] noted (without being specific) that investigators supportive of the theory may have at times designed experiments that could lead to this favorable (i.e., stimulatory) response.

While many of the conclusions of Breslavets[44] such as low dose sensitivity, poor sample size and limited dose range are valid in their criticisms of the early studies on X-ray-induced changes in *V. faba*, the present analysis indicates that the general pattern of response is consistent with the Arndt-Schulz Law. However, at the time the research was conducted there appears to be considerable confusion over the nature of the low dose exposure dose-response relationship. This is reflected in the major review by Johnson[81] who was accused of bias against the theory of radio-stimulation and in the writings of Breslavets[44] who was a supporter of the low dose stimulatory theory. However, *in toto*, an analysis of the body of data on *V. faba* up through the 1930's is remarkably in agreement with those seen for the sunflower and wheat responses in which analysis of reported studies was consistent with the hormetic perspective.

*Wheat* Another plant species commonly used to evaluate the effects of X-rays on plant growth has been wheat. However, in contrast to other plants evaluated such as rice which assessed as early as the first decade of the 20th century, research with wheat did not occur until the 1930's. In the assessment of the X-ray plant research with wheat ten studies were identified. Of these ten, four involved exposure to seeds while six involved exposure to seedlings. Attention will be directed here to the responses of seedlings due to the more substantial nature of their research protocols. Research concerning X-rays on seeds will not be followed due to the fact that one of the four papers did not address growth endpoints and two foreign articles require translations.

Of the six studies assessing the effects of X-rays on wheat seedling growth, three studies utilize high doses (i.e., $\geqslant$550 R) and reported dose dependent growth inhibition.[58,64,86] In contrast, two studies providing low doses displayed low dose stimulatory responses.[62,75] Figure 1 indicates the dose-response relationship of the X-ray treatments for multiple endpoints including wet and dry weights.[75] In each case a marked stimulatory response was observed consistent with the hormetic dose-response curve. Similar findings using low dose X-ray exposures were noted for other species tested for corn, wheat, oats, and sunflower.[62] The final article, which covered 150–1100 R, bridged the gap of the higher end of the low dose area and high dose exposure zone.[57] The findings of Cattell[57] displayed suggestive evidence of a weak stimulatory response at the lower doses for coleoptiles, and strong inhibition at the higher end of the doses administered consistent with the hormetic dose-response relationship.

The quality of these post 1930 studies represents substantial progress over those of the early decades

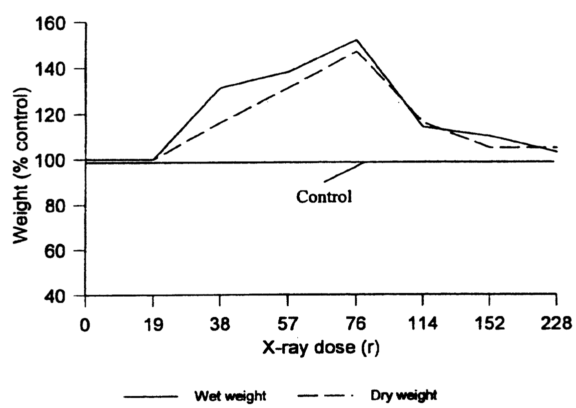


**Figure 1** Wet and dry weights (% control) of Marquis spring wheat 56 days after exposure to various doses of X-rays. Exposure was conducted on 24-h seedlings (data from Wort[75])

of the 20th century in terms of study design and adequacy of sample size. For example, the report of Wort[75] involved seven doses plus an unexposed control with 35 plants per group. This experiment, which was replicated, also included a repeated measures component over three consecutive weeks. Wort[75] also provided data from two identical studies using 57 and 9 month old seeds in order to assess the effect of seed age.

Despite their generally strong study designs, the reports of Wort[75] and others during this time period lacked important and more recently emphasized features such as random allocation of subjects (e.g., seedlings) to group and formal statistically-based hypothesis testing techniques. Despite these limitations, the findings of X-rays on wheat seedlings were remarkably consistent with the Arndt-Schultz Law, a phenomenon also clearly mirrored in studies with other plants such as rice, sunflower and broad bean, which were assessed over a wide dose range.

*Sunflower* One of the most influential figures in the US affecting the acceptance of the Arndt-Schultz Law (i.e., hormesis) was Edna Johnson at the University of Colorado, Boulder. She was perhaps the first American scientist to publish research findings on the topic of X-ray stimulation of plant growth and did so over a span of several decades (mid 1920's to late 1940's). She published a series of original research papers that displayed better design features and attention to detail than most of the previous efforts. In these more credible articles up through the 1930's she consistently found no convincing evidence to support the hypothesis of a direct stimulation of plant growth by X-rays. So substantial was her research in this area that she was invited to author a major review of the topic under the auspices of the NRC and the oversight of such prestigious individuals as Gino Failla, Charles Packard and Benjamin Duggar.

Despite the influence of Johnson on the topic of radiation hormesis on plant growth, a paper published by Shull and Mitchell[62] had the potential to challenge the basis of her denial of evidence of radiation hormesis. In this paper Shull and Mitchell[62] hypothesized that past studies used doses that were far in excess of a potentially stimulating dose range. Consequently, they undertook a series of investigations with corn, wheat (three varieties), oats and sunflower to assess whether X-ray exposures over a broad but lower dose range could be stimulating to recently germinated seeds. While Shull and Mitchell[62] reported stimulatory responses for all species of plants tested, the most significant feature of their work was their inclusion of sunflower since Johnson had studied the response of this same species in three different published papers. Despite the fact that both research groups used sunflower, there were some differences in the research methodologies employed. In two of Johnson's papers[52,53] she irradiated seeds soaked in distilled water, while the third paper[58] utilized 7 day old seedlings. In the Shull and Mitchell[62] paper the X-rays were applied to very recently germinated seeds that had been soaked in distilled water. Thus, the first two reports of Johnson[52,53] were most directly relevant (although not a perfect match) for the Shull and Mitchell study.[62] The doses of radiation used by Johnson in studies one and two ranged from 100 – 1000 R,[52,53] while the dose range used by Shull and Mitchell ranged from 38 – 380 R.[62] In the Shull and Mitchell report stimulation was observed over 38 – 190 R; inhibition was reported at the highest dose (i.e., 380 R).[62]

The follow-up study of Shull and Mitchell[62] should have been used to clarify the alleged discrepancy with the earlier work of Johnson.[52,53,58] However, Shull and Mitchell never attempted to do so.[62] Only limited reference was made to Johnson's work, and even in such instances the discussion was not directed towards the principal issue of low dose stimulation. Why they did not seek to clarify an obvious and important issue is unknown. However, it should be emphasized that Johnson knew Shull, and specifically states in her acknowledgment that she expressed appreciation to Professor CA Shull for assistance during the progress of her studies as at doctoral student at the University of Chicago and as a new faculty member at the University of Colorado. It is possible that Shull did not want to challenge the position of a former student. Similarly, in her influential review for the NRC, Johnson[69] summarizes the paper of Shull and Mitchell[62] but never links it to her work, nor attempts to clarify the obvious discrepancy between her high dose inhibition and the low dose stimulation of Shull and Mitchell.[62]

Despite the central role that Johnson had in affecting the direction of scientific attitudes to radiation hormesis in the US and the potential significance of the Shull and Mitchell paper,[62] no other reviewer has brought forth the proposition offered here as to the scientific reason why Johnson[53,58] did not observe stimulation and why it may not have been resolved.

The work of Johnson continued to be cited in the most prestigious reviews on the topic of radiation stimulation of plant growth. For example, Sax's reviews in 1955 and 1963 cited the work of Johnson[81] and Shull and Mitchell[62] favorably without resolving their apparent conflicting conclusions.[87,88] The book entitled 'Plants and X-rays' by

LB Breslovets[44] directed considerable space to both Johnson[81] and Shull and Mitchell,[62] yet again without an attempt to resolve their apparent conflicting conclusions. Furthermore, Packard, co-editor of the 1936 NRC report in which Johnson strongly emphasized the lacking support for the Arndt-Schulz Law for X-rays on plant growth, reported her incorrect conclusions that X-ray treatment does not stimulate plant growth, citing her 'extensive summary of this topic.'[89]

*Summary* This section of the historical development of the radiation hormesis hypothesis has considered the effects of X-rays on plant material [i.e., seeds (dry, soaked, germinating) or seedlings (sprouts)]. Due to the substantial diversity of articles, plant species tested, exposure techniques and experimental protocols employed, it was decided that the most effective way to provide clarity to this array of information was to be guided by the premise that the review would focus greatest attention on those plant species which were tested most substantially. This would permit the greatest likelihood of having the broad array of doses applied as well as the most substantial sample sizes and capacity to review independent replication of earlier findings. To that end, reseach on rice, sunflower, broad beans and wheat were selected. Despite the wide range of experimental protocols and perspectives from different investigative teams, the most striking observation is that at low doses of X-rays (as defined for each plant species), a stimulatory growth response was observed, while at high doses inhibitory responses occurred. The dose-response range was similar to the $\beta$-curve of the hormesis phenomenon and of course, therefore, consistent with the Arndt-Schulz Law. The present analysis is also important because the reviews of the literature that address these early findings never resolved the obvious challenge of how to properly integrate stimulatory and inhibitory responses within a dose-response continuum. Even the reviews of Sax,[87,88] who helped usher in the modern age of plant cytogenetics, were more descriptive than explanatory. As noted earlier, the review of Breslavets[44] which was quite analytical for the time, ultimately blamed investigator bias as the most important factor affecting proper interpretation of the low dose effects area. Despite potential investigator bias, there is little doubt that the clear weight of evidence should have supported the conclusion that the dose-response relationship supports the theory of hormesis. Nonetheless, it seems clear that the scientific community of the 1930's and 1940's had not resolved the issue of low dose X-ray effects on plant growth. The Arndt-Schulz hypothesis was earlier criticized by fair-minded scientists because of studies using inadequate sample sizes along with poor replication of findings. Such criticisms of weak studies were then contrasted with more convincing high dose studies which unequivocally noted dose dependent inhibition. The combination of the legitimate criticism of weak studies, suggesting stimulatory responses and clear findings indicating inhibitory responses at high doses, lead investigators such as Johnson[69] to relegate the Arndt-Schulz Law to a scientific irrelevancy. The substantial criticism of Johnson had its impact on American leaders in the field of radiation (Failla, Hollender, etc.) even though such criticism lacked a proper perspective. Nonetheless, such a flawed perspective (see Packard[89] for his continued reaffirmation of the flawed conclusions of Johnson[69]) delayed the acceptance of hormesis as a legitimate biological hypothesis. Such criticism as reported in a NAS document is comparable to the harsh attack on the Arndt-Schulz Law by AJ Clark in his 1937 publication, 'Handbook of Pharmacology', in which 15% of this book is explicitly devoted to challenging the Arndt-Schulz hypothesis.[90] Thus, the theory of hormesis has had strong opponents who occupied influencial positions in the scientific community at precisely the same time.

### *Radium*

*Studies by Gager* Perhaps the first claim that radium exposure could stimulate plant processes such as seed germination and seedling growth was reported in 1908 by Gager in a nearly 300 page report documenting some 93 experiments.[91] As a result of the magnitude of this study, its claims of radium-induced stimulation and the long-term advocacy of Gager[92,93] of the low dose stimulatory hypothesis, this paper will receive a detailed assessment. These experiments addressed a wide range of questions including the effects of radium on seeds (either dry or soaked) (i.e., 31 experiments), plants grown in soil (eight experiments), plants grown in water treated with radium (nine experiments), carbohydrate synthesis in plants (ten experiments), respiration (i.e., aerobic and anaerobic) (six experiments), 12 miscellaneous areas and experiments on yeast fermentation. In general, negative findings were typically noted for soaked seeds, plant growth in treated water and experiments on anaerobic respiration. Limited suggestive evidence of stimulation was reported in some experiments using dry seeds, plants grown in soil, and studies of aerobic respiration. The most consistently reported stimulatory responses occurred with yeast fermentation.

*Effects of radium on seeds (dry or soaked)*

Studies by Gager with seeds involved 14 experiments with *Lipinus alba*, four with Timothy, three with *Phaseolus*, two with oats, and one each with wheat, alfalfa, buckwheat, *Linum* (flax), *Brassica*, and corn.[91] These experiments were generally characterized by a single treatment and concurrent control with modest numbers of seeds treated. Typically, the sample size was ten or less, but on occasion up to 20 seeds in a treatment were used. The duration of the experiments was typically for one to several weeks. The radium was often in the form of a sealed glass tube of $RaBr_2$ with the radium tube lying against the hilum edges of the seeds. The radiation intensity was variable depending on the experiment, ranging from a low of $7000\times$ to $1.8\times10^6$. Such values meant that the preparation was that much stronger than an equal weight of uranium. However, at the time of the experiment no universally recognized unit of radioactivity had been formulated. Note that in 1910 the International Congress for Radiological Electricity proposed a unit (i.e., the curie) of radium emanation (i.e., radon gas) as the amount of emanation in an enclosed container which is in equilibrium with one gram of metallic radium.

Of the 31 experiments with seeds, four displayed evidence of stimulation including two with Timothy and two with *L. alba*. Gager summarized his findings with Timothy by stating that 'when Timothy grass seeds were exposed to radium of weak activity ($7000\times$) an initial retardation was followed by apparent recovery after an interval of five days.[91] At the end of this period the exposed seeds averaged even taller than those of the control culture'. Examination of the experimental procedure revealed that Gager did not indicate the number of seeds in either the treatment or controls, nor were individual or group averages presented.[91] Thus, even though Gager stated that the seedlings had a 'decidedly' larger average growth than the controls, no data were available to confirm the author's statement. The second experiment with Timothy involved a comparison of seed germination and seedling growth in relationship to the distance of the plants from the source of radiation, which varied from 5, 10, 25, 20 and 25 mm. The control growth ($n$=not reported) ranged from 9–14 mm in length over the five locations. However, those exposed to the radium displayed a low dose stimulation and high dose inhibition. While these findings are suggestive of stimulation, the limited and inadequate reporting of experimental details does not permit the drawing of a definitive conclusion except that the results warrant more careful follow-up experimentation.

In another experiment, Gager stated that the 'germination of seeds of *L. albus* and the subsequent growth of the radicle was appreciably accelerated' by exposure to $10\,000\times$ for 120 h (5 days).[91] In this case Gager provided the sample size ($n$=8) and the data for the individual control and treatment plants at day 5, the final day of the study. The difference between the two groups was 62.7 *vs* 53.9 mm (16%). A follow-up experiment with *L. albus* employing eight dry seeds/group exposed seeds for different lengths of time (2, 3, 4, 6, and 14 h) to $RaBr_2$ ($1.5\times10^6$) and later planted the seeds in soil. Measurements at 6 and 9 days after treatment indicated that low exposures were associated with enhanced growth. Although measurements continued, the author did not present further data except to conclude that at the end of 5 weeks there were no appreciable differences related to treatment.

The four experiments were the only ones presenting evidence to support the potential for radium to stimulate the growth of plants. In all cases the seeds exposed were dry. Despite the findings and conclusions of the author, the study designs and reporting, even for 1908, were poor. However, even nearly 30 years later the author concluded that 'this 1908 report provided for the first time experimental evidence that radium rays may, under suitable conditions, accelerate the growth of seedlings'.[93] He stated further that these results lead to the broad generalization that radium rays act as a time stimulus to metabolism.

*Effects of radium on the growth of plants in soil*

In the next set of experiments, Gager assessed the effects of radium in the soil on the germination and growth of oats, *L. albus*, Brassica, peas, beans, wheat and Timothy.[91] As such, there was one experiment for each species, except for oats for which there were two experiments. In general, the author placed seeds into potted soil. The radium source was inserted into the soil at the center of the pot to a depth of 15 cm. Depending on the experiment, seeds were placed in concentric rows around the radium source. In some experiments there was one source (intensity), while in several experiments multiple (up to 3) levels of radium intensity was employed. Thus, in most of the experiments it was possible to have the potential for a dose-response relationship. Of the eight experiments, four displayed evidence of a stimulatory response. However, two of the four studies in which Gager reported stimulatory responses using *Brassica alba* (white mustard) and peas, no measurements were either taken and/or provided. Of the remaining two stimulatory experiments, the one with oats utilized a single $RaBr_2$ intensity, ($1.5\times10^6$) with seeds planted at three locations from the source of radium. While Gager reported the height of the three treaments no mention was made of the control height, nor was the number of plants employed in the experimental and control groups stated.[91]

The most important experiment involved wheat at two doses of $RaBr_2$ and one dose of radiotellurium. The radium treatment involved exposure to beta and gamma rays while the radiotellurium involved exposure to alpha rays. In this experiment Gager provided information on sample size ($n$=12) as well as the values for each individual plant at day 4 of growth.[91] All treatment groups displayed greater growth than the controls by approximately 35–45%. As in the case of his results with seeds, Gager was inconsistent in his description of his methodology and reporting of his data.[91] In this present set of eight experiments, only one of the four experiments that Gager claims is stimulatory have adequate data upon which to make a reasonable preliminary determination.[91]

While attention has been directed towards radium, Gager reported on an experiment concerning the effects of alpha rays from polonium on the germination and growth of wheat ($n$=16).[91] The results indicated an initial slight growth deficit after 4 days (10%), followed by a more vigorous growth in the treated plants (125.3 *vs* 75.5 mm ave.).

*Other investigators* Based on the research of Gager,[91] there was great interest in assessing the hypothesis that crop production could be enhanced by adding radioactive substances to the soil with or without ordinary fertilizers. This interest was encouraged further by the research of Stoklasa in 1913 on the response of cultures of nitrifying and denitrifying bacteria to the emanation from pitchblend. It was believed that response to the radioactive substance in soil might increase soil fertility by increasing nitrogen circulation. However, a series of reports by Ewart in Australia,[94] Sutton in England,[95] and Ross,[96] Hopkins and Sachs,[97] and Ramsey[98] in the United States did not support the hypothesis that radium treatment of soil was likely to have any commercial agricultural significance. This lack of enthusiasm for the application of radium and/or perhaps other radioactive preparations needs to be seen within the context of commercial interest rather than scientific inquiry. In fact, Hopkins and Sachs, who were clearly not supportive of the commercial application of radium to agriculture, presented data on 36 experiments (with four doses and a concurrent control), nineteen of which offered evidence of stimulatory responses (Figure 2).[97] Rather than being discouraged, the agricultural research community should have been interested in the interspecies differences in response and the nature of the dose-response relationship. However, the lack of a more universal stimulatory response across all species at the same applied dose, the limited magnitude of stimulation and the difficulty in pinpointing the optimum stimulatory zone discouraged further commercial interests.

While the lack of enthusiasm for the commercial application of radium must have adversely affected research interest in this area, a number of papers continued to be published between 1910 and the early 1930's which were supportive of the premise that low dose exposures to radium may affect plant biological processes. Most notably during this period was the continuing work of Stoklasa who reported that various radioactive sources (e.g., naturally occurring radioactive water, pitchblend and radium enclosed in vessels) enhanced seed germination in multiple species,[99–101] growth of cucumbers, mint and tobacco seedlings, growth as evidenced by increase in photosynthesis, dry weight, earlier flowering, and greater seed production,[102] and bacterial metabolism and yeast fermen-

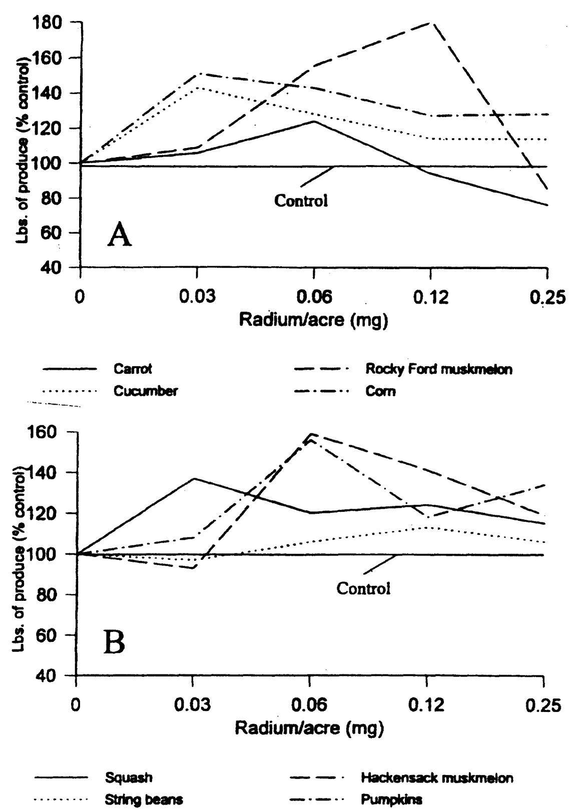


**Figure 2** Increase in pounds of produce (% control) of representative crops exposed to various concentrations of radium in the soil (data from Hopkins and Sachs[97])

tation.[102,103] Of relevance to the hormesis hypothesis was that Stoklasa's findings displayed the typical $\beta$-curve of a low dose stimulation/high dose inhibition.[100] In further support of the fermentation findings, Kotzareff and Chodat reported a clear $\beta$-curve in response to radium exposure.[104] Likewise, the findings of Doumer,[105] Agulhon and Robert,[106] and Montet[107-109] were consistent with the observations of Stoklasa[99,101] that seed germination could be enhanced by exposure to radium sources. It should be noted that an influential paper by Failla and Henshaw reported dose-dependent inhibitory responses in wheat by radium using a very powerful study design.[86] The doses of radium were normalized to that provided by an X-ray exposure. Thus, the lowest dose of radium in X-ray equivalents used in this inhibitory study was 550 R, a dose that is known to be inhibitory in wheat (see wheat section).

The above summary of findings represented the current state of scientific development as of 1936 (see Gager[93]). As could be seen, European researchers continued to study the effects of radium on biological systems especially as related to plant growth and seed germination. As happened in 1915, and again in the late 1930's, the research on radium became a victim of both World Wars I and II with essentially no published findings during these periods.

*Major USDA study* Two important developments occurred as a result of World War II that were to have a major impact on the assessment of radium on plant growth. The first is that cobalt-60, a gamma source, became readily available as a result of nuclear technology. In fact, the nearly entire focus of gamma rays from radium on plant growth would switch to cobalt-60 from the 1950's onward. Secondly, in 1948 the USDA and a large number (i.e., 13) of state agricultural experiment research stations under a contract with the Atomic Energy Commission (AEC) undertook a large and coordinated study to determine 'whether radioactive material does indeed stimulate plant growth.' This broad goal included the practical aim of whether the farmer would reasonably expect to obtain an increased crop yield by adding one or several naturally radioactive materials to the soil. The impetus for this study was based, at least in part, on reports from Japan of greatly increased crop yields in the vicinity of the bombed areas due to the radioactivity. The study involved three radioactive sources: radium, uranyl nitrate, and alphatron. The alphatron had an alpha ray disintegration rate of $8 \times 10^6$/s principally from actinium; the radium source was radium bromide; the radium and uranium sources were used since most of the past studies were with these two agents.[110]

The experimental design involved three doses for the alphatron source and one each for the radium and uranyl nitrate. Each experiment had its own control and each agent was tested on all plant species. In all, the results of 46 experiments on 20 crops (i.e., corn, wheat, barley, oats, clover, soybeans, white beans, red Mexican beans, sugar beets, table beets, carrots, sweet potatoes, spinach, tomatoes, cotton, seed cotton, bright tobacco and peanuts). No information was provided on how the doses were selected. In general, the data did not provide support for the hypothesis that crop yield would be significantly enhanced and provide consistent commercial value. On occasion, there were some instances of 5–10% increases in yield, but it was not possible to determine whether this was a treatment effect or normal variation.[110] European research conducted concurrently or a few years later likewise did not establish any clear effect on yield,[111-115] but according to Kaindl and Linser was not sufficient to deny any stimulatory effect hypothesis.[116] In fact, studies by Linser and Pelikan[117] and Kaindl,[118] using a radium bearing preparation from a French firm and fertilizing at the rate of $10^{-9}$ grams of radium/kg of soil, reported increases of 16% in yield for buckwheat. However, according to Kaindl and Linser, the generally negative findings of the American research[110] had a dominating influence on the course of both research and further international testing.[116]

Thus, the findings of the USDA had a major impact on the future of US and international research in this area. In retrospect it would appear that the strategy of the USDA was to consider a broad range of plants, but a very limited focus on dose. In fact, such a limited focus on dose and the non-recognition of interspecies differences in response to low doses of radioactive agents was an extremely poor strategy for testing the hormesis hypothesis. Yet, as noted earlier, the essentially negative findings of such an otherwise impressively large study was uncritically accepted as answering the question of low dose stimulation from a US government perspective. While such a conclusion did not end international or US research on the topic of radiation as a plant stimulant, it marked the end of an area for radium with the first stimulatory reports of cobalt-60 on plant growth occurring but a few years later.

## Fungi

*Introduction*
Fungi have long been the object of study concerning the effects of radiation. These studies have en-

compassed the broad spectrum of radiation, including visible and u.v. radiation, X-rays, and radiation from naturally occurring elements such as radium and uranium. In general, such studies have revealed that the typical dose-response relationship was consistent with the monomolecular dose-response (i.e., linear) curve. On occasion, deviations from such a dose-response curve have been reported and usually attributed to factors such as the age of the culture in the study. Despite the broad consistency of the linear and S-shaped dose-response realtionships, low dose stimulation was occasionally reported, although there were disputes about the reproducibility of the findings and/or their interpretation.

*U.V. radiation*

U.V. radiation induced stimulation of fungal activities has been reported with respect to mycelium growth rate, fruiting structure growth rate and spore production. In the case of mycelium growth rate, Nadson and Philippov reported much greater yeast colony growth around the edges of an irradiated zone, whereas growth in the middle (i.e., higher dose zone) was diminished.[119] The authors believed that the stimulation was due to small amounts of scattered radiation. However, attempts to confirm these observations were unsuccessful as reported by Luyet[120] and Schreiber[121] who obtained no evidence of stimulation with low doses of u.v. irradiation. However, Smith[83] argued that the lack of replication may have been the result of a limitation in study design, since reports by Chavarria and Clark[122] and herself[83] revealed that the key feature in observing the u.v-induced mycelium growth stimulation was the incorporation of an adequate temporal dimension. More specifically, Smith, working with *Fusarium* cultures, reported temporary mycelium growth stimulation which only occurred after a previous toxic or retardation effect.[83] In her nine dose experiment (0.05 – 15 min exposed) all doses yielded inhibitory effects on mycelium growth at 24 h (Figure 3A). By 48 h, all but the highest dose were displaying compensatory stimulation growth, with two doses greater than the control (Figure 3B). By 72 h, all but the highest dose had exceeded the controls by 15 – 40% (Figure 3C).

Such observations of Smith,[83] which were later supported by Sperti *et al.*,[123,124] are consistent with the hypothesis that hormesis represents an overcompensation to a disruption in homeostasis. According to these authors, in their experiments, yeast or other cells which become injured can synthesize growth factor agents which stimulate other cells to divide thereby providing a possible mechanistic explanation.[123–133]

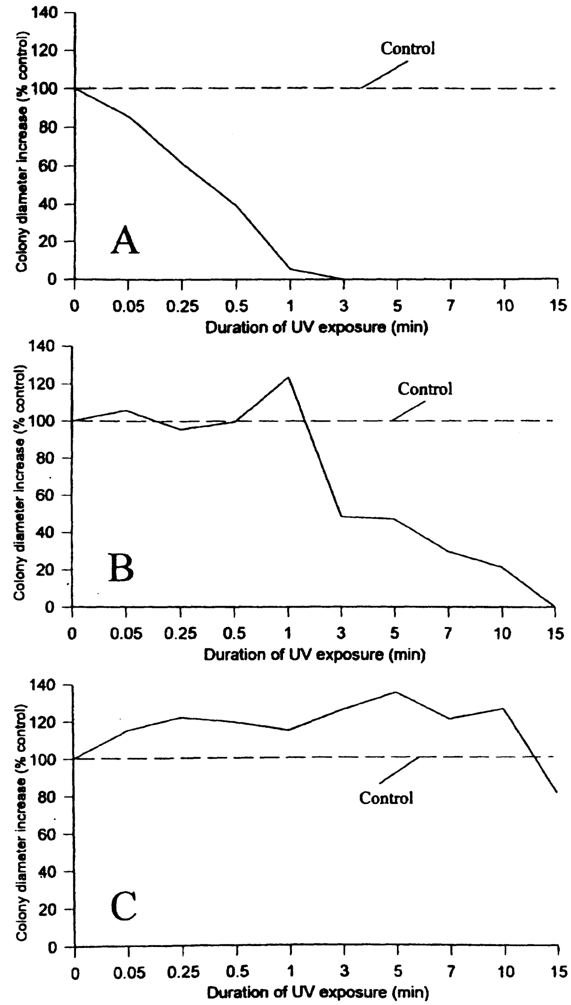


**Figure 3** Changes in diameter (% control) of *Fusarium eumartii* Carp. colonies exposed to various durations of ultra-violet (u.v.) irradiation at **(A)** 24 h, **(B)** 48 h, and **(C)** 72 h following irradiation (data from Smith[83])

Stevens, conducting experiments with a large number of fungal species exposed to the full irradiation from a quartz-mercury vapor lamp, observed that the u.v. light may stimulate the formation of reproductive structures.[134–137] Perithecia production was enhanced in cultures of *Glomerella cingulata*,[134,135] *Colletotrichum lagenarium*,[138] and various *Coniothyrium* species.[136] Pycnidia formation was stimulated in *Coniothyrium*.[136] Such stimulatory responses were caused by exposures of less than 1 min at a distance of 20 cm from the lamp.

Consistent with the findings of Stevens is the general observation that long exposures to u.v. irradiation diminish spore production while short exposures stimulate it. Perhaps the earliest report of stimulation of spore production with low doses of radiation was in 1907 by Purvis and Warwick, working with a *Mucor* culture.[138] They exposed the culture for 10–20 min to direct radiation from a Bach quartz energy vapor lamp located at 30 cm from the culture. The portion of the culture below the center of the opening was killed, but at the edge of the irradiated region spores were stimulated in great numbers. Since that initial discovery, an impressive number of reports were published in which short exposures to u.v. irradiation affected a marked stimulation of spore production in a broad range of fungal species.[83,139–143]

Of particular interest are the findings of Smith[83] since the experiment employed up to ten doses along with a concurrent control. Furthermore, this experiment was conducted at three different temperature settings (21, 25 and 30°C). While the basic trend of an hormetic response was clearly present at each temperature, the temperature had a profound effect on the control number of spores, with the number of control spores increasing as the temperature increased. In addition to the capacity of radiation at low level exposures to increase the number of spores, it may also enhance their formation as seen in the work of Hutchinson and Ashton who reported that sporulation in *Colletotrichum phomoides* was earlier with a brief u.v. exposure duration but delayed with longer duration exposures.[140]

*X-rays and naturally occurring radionuclides*
Considerably less research on the potential for X-rays and rays emitted from radioactive substances to cause a stimulatory response was conducted in the early decades of the 20th century as compared with u.v. radiation. In the case of X-rays, Lacassagne and Holweck[144] and Wycoff and Luyet[145] reported no evidence of stimulation with low doses of X-rays on yeast. However, Zeller suggested that fermentation may be temporarily increased.[146] In the case of radium, Gager,[91] Kotzareff and Chodat,[104] and Fabre[147] reported that low level exposures were associated with a stimulation of cell division while Ingber[148] reported that small doses of radium may enhance spore production. Likewise, Stoklasa[103] and Kayser and Delaval[149] noted that small doses of radiation enhanced fermentation.

Despite the substantial legitimate criticisms of the presentation by Gager[91] on the stimulatory findings of radium on seeds in culture and for plant growth in soil, the findings provided on alcohol fermentation are his strongest. Of the six experiments, all provide evidence of stimulation and in all cases the data are provided. In general, radium treatments were from 50% to several-fold greater than the control. However, on occassion, the difference between the treated and control was modest (10%), a factor that appeared related to an atypically high value in the control. Nonetheless, of the 14 reported experimental trials involving $RaBr_2$, eight were equal to or greater than twofold that of the control, while five exceeded 40%, and only one was less than 10% (8%). This type of consistency over such a large number of experimental trials provides strong evidence that the radium treatment provided *bona fide* stimulation of alcohol fermentation in yeast. While less extensively evaluated (four experiments) than radium, experiments with radiotellurium which emits alpha rays all displayed stimulatory responses greater than 10% (i.e., 14, 13, 15 and 13).

*Summary*
Taken collectively, the data as of the mid 1930's supported the conclusion that low doses of u.v. radiation enhanced the growth of the fungal mycelium and spore production. The research with mycelium growth was essentially limited to only three studies.[83,119,122] However, the Smith[83] study was extremely well designed and given heightened credibility as a result of her invitation to singly author a chapter on the effects of radiation on fungi for the National Academy of Sciences in 1936 in which she reaffirmed the hormetic hypothesis.[84] In fact, she linked her observations of the initial reduction in mycelium growth followed by stimulation to several previous reports in different biological models including bacteria,[150] some plant species,[151] and the fungus *Colletotrichum phomoides* using u.v.[140]

The data that u.v. light enhanced spore formation at low doses appears stronger than for mycelium growth since it was more extensively explored by other researchers in addition to Smith. Thus, it appears to be a reproducible and marked response. One major difference with the u.v.-induced stimulation of spores was that the u.v. appeared to act as a direct stimulant, thereby contrasting itself with that observed for the stimulation of growth fungal rate. As in the case of growth stimulation, this stimulatory conclusion was again emphasized by Smith in her 1936 article for the NAS.[84] In contrast to these stimulatory effects induced by u.v. exposure, no general consensus seemed to emerge on the effects of X-rays and naturally radioactive materials on fungal activities. One possible factor that may have affected the broader acceptance of these papers in the US is that each was published in French or German, a factor of uncertain but possible considerable importance in affecting their impact on US scientists.

## Algae

The first reports in the literature claiming that u.v.-irradiation accelerated colony development of algae were given by Meier.[152–156] During the earlier investigations on the lethal effect of 21 wavelengths of the ultraviolet radiation spectrum ranging from 2250–3130 A on a given algal strain, Meier occasionally noted an accelerated increase in cell mass with slightly less exposure than the minimally lethal exposure that destroyed the algal cells.[152–154]

These results lead to follow-up experimentation with the unicellular green algal *Stichococcus bacillaris* to assess whether u.v. radiation could stimulate cell division under various experimental settings. This model offered a variety of attractive experimental features with respect to precise and accurate counting, measurement of the size and method of reproduction. The algae were grown under conditions of regulated temperature and controlled lighting with fluorescent lamps. The algal cultures were grown for 2 weeks following irradiation, at which time a determination of growth rates was made. Separate experiments were conducted at different u.v. wavelengths (i.e., 2352A, 2483A, 2652A, and 2967A) for varying periods of time (i.e., 20 to approximately 300 s exposure depending on the wavelength). The quantity of ergs/s-cm$^2$ was also specified for each wavelength studied. The growth rate was defined as the final count made 2 weeks after the irradiation divided by the initial count made directly after irradiation. Each growth rate of an irradiated culture was then divided by the growth rate of the control to derive the final growth rates. Duplicate cultures were made of each exposure and control group. The cells of three drops of the culture from each flask were counted and the mean of the three cell counts was used for response determination. Based on the data, there was a strong tendency for a short duration exposure enhancement of growth rates along with a decrease relative to controls at longer durations. While this was the case for each wavelength tested, each wavelength displayed a unique duration of exposure response. Nonetheless, regardless of the unique duration response curve, the maximum stimulatory point for all the tested wavelengths was a duration approximately 65–75% of the toxicity threshold. The magnitude of stimulation varied between approximately 150–225% of the controls with the 2652A wavelength displaying the highest stimulatory response. No statistical analyses of the data were provided. These findings [i.e., magnitude of stimulation (50–125% above controls) and range of stimulation (3–8-fold) depending on the wavelength used] indicate a striking similarity to the recently reported findings with chemical hormesis.[12]

Of significance was that the stimulatory action in the 1939 report of Meier[155] appeared to be sustained with subsequent measurement some 2–3 years later indicating a marked increase in dry weight of the irradiated culture (40 s) for the 2628 A dose, the maximum response group. This and related findings lead Meier-Chase[156] to determine the influence of successive (i.e., repeated) treatments of the algal cells to the original four wavelengths studied (i.e., 2352A, 2483A, 2652A and 2967A). The methodology employed was similar to that used earlier by Meier.[155] However, the time between the successive or repeat exposures varied between the wavelengths used. Likewise, the time or duration of u.v. exposure was different across the wavelengths. However, regardless of the wavelength used, the algal cells were stimulated to approximately 4–5-fold, with the increase appearing as a type of step function with each successive exposure. Follow-up analyses of the algal cells revealed a decrease in length with each stimulatory response along with a general increase in width. Meier-Chase[156] indicated that the decrease in length was predictable because the rate of cell division was so considerably greater in the treated algae that the cells did not have time to achieve the length seen under normal conditions.

The stimulated algal cells were then exposed to lethal doses of u.v. radiation. In all cases the stimulated algal cells were less sensitive to the lethal u.v. doses. In general, the previously stimulated algae required approximately twice as long to display radiotoxic regions as compared to controls.

The findings of Meier[155,156] are striking in their consistency across wavelengths, their repeatability, and their similarity with the copious data available on chemical hormesis. In addition, the follow-up studies display a remarkable similarity to the concept of adaptive response with radiation. However, the long term stimulatory response is more difficult to explain and would require follow-up study.

## Protozoans

Experimentation concerning the effects of radiation on protozoans during the early decades of the 20th century was problematic because of their relative insensitivity. Numerous early investigators were unable to induce any notable effects of X-rays on any protozoan species, despite rather prolonged exposures (see Crowther[157] for review). In fact, it was not until the mid 1920's that investigators began to report on the capacity of X-rays to both stimulate[158] and harm protozoan species.[157] Despite the reported apparent stimulation of Markowits[158] with X-rays on paramecia, this section concerns the effects of u.v. radiation on paramecia, since this received greater attention and is more substantial than other protozoan areas of potential inquiry.

The earliest indication that u.v. radiation may stimulate paramecia was reported by Bovie and Hughes,[159] who noted that the cell division rate of *Paramecium caudatum* could be enhanced or delayed depending on dosage. More specifically, as the duration of exposure increases so does the extent of inhibition. However, and of relevance to the present assessment, the inhibition may be followed by an acceleration of the division rate. These authors hypothesized that acceleration following short periods of inhibition was due to the formation of a 'toxic photoproduct which is gradually removed from the cell' and subsequently 'acts as a stimulant to cell division when the amount becomes very small'. It was not until some 10 years later that the observations of Bovie and Hughes[159] were confirmed and extended by Hinrichs,[160] MacDougall,[161,162] Roskin and Romanowa,[163] and more impressively by Alpatov and Nastiukova.[164] In the case of Hinrichs,[160] cell division rates were assessed over 3 days in paramecia exposed for different durations (1 – 80 s) and at different distances from the u.v. source (26.5 – 56.0 cm). In addition, there were differing numbers of paramecia exposed at the same time (i.e., singly, paired, and multiple). Hinrichs summarized her findings by stating that of the 36 experiments conducted, half displayed a u.v.-induced stimulation while the remaining half had a depressive effect.[160] More specifically, in the stimulatory experiments the increase ranged from 7 – 70.6% over the controls. In these experiments, the exposures were conducted for 5 – 30 s at 26.5 cm from the u.v. lamp source and for 6 – 20 s at 37 – 45 cm from the u.v. source. The number of cases where stimulation occurred was greater in those instances when exposures were conducted at ⩾38.5 cm away from the lamp. In fact, nearly 80% of the exposures conducted ⩾45 cm from the lamp produced a stimulatory division rate, while only 45% of the exposures at closer range showed an increase in the division rate and total offspring produced. Moreover, depression of the rate of division was often observed during the initial 24 h after exposure, with stimulation occurring not until day 2 of observation.

The research of Hinrichs[160] was criticized by Alpatov and Nastiukova[164] because of her use of limited numbers of organisms and the lack of objective means (e.g., hypothesis testing) to guide decisions on stimulation or depression. Despite these legitimate criticisms, it should be emphasized that the value in the work of Hinrichs[160] was that it established an experimentally based framework to test the influence of dose as a function of time of exposure and distance from the u.v. source. Likewise, her findings were consistent with the statements of MacDougall[161] that the cultures of her animal model, *Chilodon uncinatrus*, that were exposed for less than 5 s appeared to be more vigorous and the individuals larger than in the control cultures. It should be noted that in her 1931 paper, MacDougall indicated that her research was being supported by the Committee on Radiation at the NRC.[163]

In their study Alpatov and Nastiukova[164] assessed the effect of u.v. radiation on the division rate of *P. caudatum* with different durations of u.v. exposure while keeping distance from the u.v. source constant. They presented their findings of 14 experiments with typically three doses (i.e., durations of 5, 10 and 20 s) for ten experiments, and longer durations for the remaining four experiments (up to 120 s). The number of organisms involved 20/treatment (i.e., totaling approximately 1000 in the 14 experiments). The findings revealed that at low doses (5 – 20 s) the division rate of the paramecia was increased, while with the higher durations of exposure (i.e., ⩾40 s) there was a marked decrease. Of significance is that the authors performed statistical testing and claimed that the enhanced responses at the 5 – 20 s durations were statistically significant.

The collective findings of the stimulatory effects of u.v. radiation on the cell division rate of paramecia up to the mid 1930's were limited to six studies. These studies provide consistent indications that at low doses and/or durations of exposure, the division rate was enhanced, while at high doses (or longer durations) the division rate was diminished. Of these six studies only two provide a quantitative basis for evaluation. In these cases the stronger of the two studies is that of Alpatov and Nastiukova[164] as a result of clearer focus, more powerful study design, enhanced statistical power, and inclusion of hypothesis testing. However, the Alpatov and Nastiukova study[164] was limited to only 24 h of observation after u.v. exposure, whereas the Hinrichs[160] study followed the paramecia for 3 days.

Despite the obvious differences in study design and the various strengths and limitations of the respective studies, it appears that the data clearly suggest that low doses of u.v. radiation can enhance the rate of cell division in Paramecia. The data of Alpatov and Nastiukova[164] were impressive with respect to the dose range employed and statistical power, while those of Hinrichs[160] which were generally consistent with Alpatov and Nastiukova,[164] also offers a dose-temporal relationship. Her observation of an initial inhibition followed by a stimulatory response are consistent with the overcompensation stimulatory response of Smith,[83] Colley,[150] Townsend,[151] and others. In fact, the low dose stimulatory response reported by Alpatov and Nastiukova[164] was a modest, although statistically significant, response probably because it only included a 24 h period of observation. In the Hinrichs[160] experiment displaying stimulation, the irradiated paramecia had a 5% lower division rate than controls after 24 h. This decrease reversed itself to a stimulatory mode, being some 19 and 38% greater than controls at 2 and 3 days, respectively. Even in the inhibitory response groups the 3rd day displayed a marked acceleration in the division rate over the controls by 40%, although it was insufficient to overcome the earlier inhibitory response.

The findings, while consistent with the concept of low dose stimulation within the context of a compensatory response, would greatly benefit from follow-up experimentation such as a study like that of Alpatov and Nastiukova[164] which included a temporal framework in order to clarify the nature of the dose-response. Nonetheless, these findings, though not conclusive of an hormetic response, were supportive of this relationship as the mid-1930's approached.

It should be noted that the acceleration of division in organisms such as paramecia by small doses of radiation was viewed with skepticism by Kimball nearly two decades later in his generally comprehensive review of the literature of the effects of radiation on protozoa.[165] He cited the well-recognized authority Giese[133] in his review of the effect of radiation on cell division as concluding that 'most of the evidence is of questionable significance' with the effects being small and lacking statistical significance. In some cases Kimball[165] concluded that Giese[133] seemed to accept the validity of several reports of the older literature concerning acceleration by ionizing radiation. Nonetheless, Kimball concluded that 'further investigation seems necessary before accepting stimulation of division by low doses of radiation a real phenomenon.'[165]

The review of Kimball,[165] which was published in a highly authoritative monograph and edited by the renowned Alexander Hollander and therefore given certain enhanced credence, misrepresented the assessment of Giese.[133] Giese's[133] assessment of the acceleration of biological processes by u.v. radiation was presented on pages 263–265 with particular attention directed toward u.v. radiation. In his review, Giese was critical and skeptical of the theory of mitogenic rays (i.e., short u.v. radiation emitted from cells that were hypothesized to stimulate other cells to divide more rapidly).[133] However, he appeared to be supportive of the findings of others when a defined u.v. source induced acceleration of cell division in a variety of models [i.e., Alpatov and Nastiukova;[164] MacDougall;[161,162] Hutchinson and Ashton;[140] Chase;[166,167] Meier;[155] Meier-Chase;[156] Sperti *et al.*;[123,124] Loofbourow *et al.*[128]]. In general, the review of Giese[133] was quite favorable to the stimulatory hypothesis of low doses of radiation with particular focus on u.v. radiation. Consequently, it was unfortunate that the authoritative review of Kimball[165] incorrectly characterized not only the report of Giese[133] but also the broader scientific field and thereby undermined the development of research in this area.

## Insects

The evidence associating X-ray exposure with the concept of hormesis in insects during the early decades of the 20th century was extremely limited. In fact, the only research that will be discussed in this context is that of Davey,[168,169] a researcher at General Electric. Despite the limited relevant studies on insects that alleged hormetic effects during this time period, the studies of Davey[168,169] were noted for their unusual quality and remain widely cited references demarcating perhaps one of the first generally convincing earlier experiments presenting evidence consistent with the ionizing radiation hormetic hypothesis.

Perliminary work by Davey[168] explored the effects of a wide range of X-ray doses on the longevity of the confused flour beetle (*Tribolium confusum*). This was initially assessed by comparing the latency period from the time of a single X-ray exposure to death. Davey[169] employed five doses [i.e., 500–8000 milliamperes/min at 25 cm at 50 kilovolts (MAM/$25^2$ at 50 KV)] and an unexposed control. To the surprise of the author, the lower dose treatments displayed enhanced survival relative to the controls, thereby prompting a follow-up investigation of this stimulatory phenomenon,[169] the frequently cited reference.

The initial report of Davey[168] was unusual in its attention to detail and in its overall intellectual rigor. For example, since the study used mortality as an endpoint, preliminary experiments assessed and eliminated possible confounding factors such as issues of injury due to overcrowding, high temperature due to overcrowding, presence of $NO_2$ due to high voltage connections of the X-ray tubes, effects of air ionization, humidity and other factors. There was also considerable attention given to the development of an effective, reliable and reproducible quantitative X-ray exposure system. The author also incorporated the concept of keeping the technicians blind to the study hypothesis as well as attempting to assess uniformity of age distribution of the beetles across exposure and control groups. The sample size was also substantial, making use of several thousand beetles. Furthermore, Davey,[168] while not employing hypothesis testing, did attempt to mathematically model the data using regression techniques. It should be remembered that analysis of variance was not discovered and published until 1918, a year after the report of Davey.[168] Thus, for the numerous reasons cited above, the findings of Davey[168,169] attracted both attention and high regard.

In the initial experiments the dose range studied was 500–8000 MAM/$25^2$ at 50 KV, as mentioned above. The findings revealed the typical S-shaped mortality curve with no evidence of a stimulatory response. Subsequent experimentation using 1100 beetles assessed the dose range of 100–500 MAM/$25^2$ at 50 KV. This experiment confirmed that the minimum dose needed to kill all the beetles was 500 MAM/$25^2$ at 50 KV, but the curves for 100 and 200 MAM/$25^2$ at 50 KV displayed a death rate lower than that observed in the controls. It was this finding that was presented in the 1917 paper by Davey.[168]

In the follow-up study of Davey,[169] the effects of X-rays on lifespan were assessed following either a single dose, as in the Davey[168] study, or via low daily X-ray exposures. In the daily exposure experiment, five doses were employed ranging from 6.25–50 MAM/$25^2$ at 50 KV daily, with approximately 950 beetles per group. After 5 months nearly all the beetles had died. The mortality rates indicated that the three lowest groups displayed a 25–40% decrease in mortality by 30 days after the start of the study (Figure 4A). The second experiment, using about 850 beetles/group, utilized a single dose involving four doses (100–400 MAM/$25^2$ at 50 KV) plus a control (Figure 4B). In contrast to the earlier experiments, the author indicated that these beetles were old, with the controls dying by 40 days. As in the earlier experiments the lowest exposed groups again displayed a reduced mortality rate by 20 days after dosing. According to the author, the 1919 experiments provide a 'direct confirmation' of the previous paper. It is interesting to note that Davey[169] referred to the daily X-ray exposure as 'a series of small 'homeopathic' doses, thereby linking the hormetic findings of his work to the medical practice of homeopathy.

Despite the striking and reproducible findings of Davey,[168,169] it was not until some 40 years later that Cork[170] set forth to reinvestigate the findings of Davey using the same animal model, but using a gamma ray source (Cesium-137) for either single or chronic daily doses. As in the case of Davey,[168,169] Cork[170] likewise reported a marked extension of the lifespan in a well-designed study with large numbers of beetles.

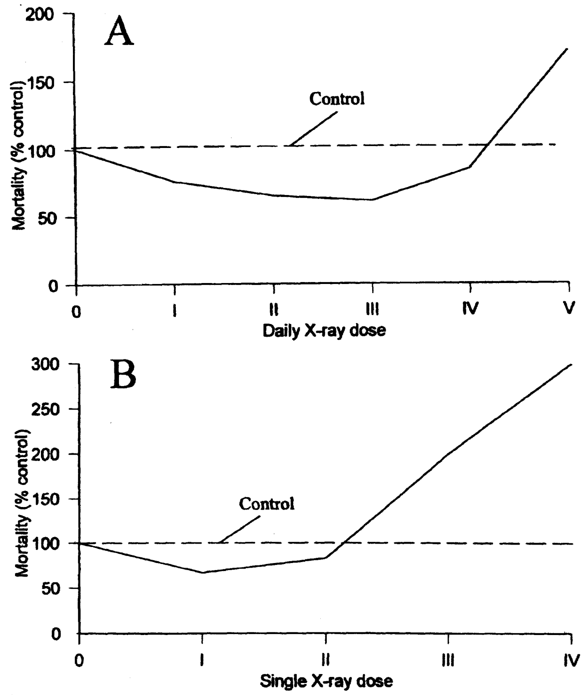


**Figure 4** (**A**) Mortality (% control) of confused flour beetles following 30 days exposure to daily doses of X-rays (dose I=6¼ MAM/$25^2$ at 50 KV; dose II=12½ MAM/$25^2$ at 50 KV; dose III=25 MAM/$25^2$ at 50 KV; dose IV=50 MAM/$25^2$ at 50 KV; dose V=100 MAM/$25^2$ at 50 KV). (**B**) Mortality (% control) of confused flour beetles at 20 days after a single exposure to X-rays (dose I=100 MAM/$25^2$ at 50 KV; dose II=200 MAM/$25^2$ at 50 KV; dose III=300 MAM/$25^2$ at 50 KV; dose IV=400 MAM/$25^2$ at 50 KV) (data from Davey[169])

## Avian embryos

Several studies have been published concerning the effects of X-rays on the development of the avian embryo.[171–174] While each of the studies reported a stimulatory response, the paper by Gilman and Baetjer[171] did not present any data but rather descriptive findings and conclusions. The remaining three studies provided markedly more information on research methods and were capable of receiving more detailed attention. In the case of Essenberg[172] the effects of X-rays were assessed for several endpoints: incubation period, time to mating for males and females, and number of eggs produced per month. The author used three treatment groups (30 r, 80 r, 400 r) plus a concurrent control with a total of 600 chicken eggs. It is assumed (but not stated) that there were 150 eggs/group. No tables or figures were presented, nor were statistical analyses provided. The author claimed that the incubation period varied directly with the X-ray dosage, with the small dosage accelerating development. However, this conclusion appears untenable since the average difference amongst the control and treatment groups is minor (496 h for the controls *vs* 484 h for the 30r group) and no data are presented on variation in response within a group.

The second avian endpoint that the author claimed was accelerated by X-ray treatment of the eggs was 'time to sexual maturity'. In the case of the female, the average control duration was 167 days, while the irradiated eggs required only 134 days (i.e., about 20% accelerated). In the case of the males, the average control was 75 days, while the irradiated males were 69 days (8% acceleration). In both the male and female cases, the author did not provide information on group specific findings, but combined all irradiated groups. Again, no information on variation in response was provided. While it would appear that these findings merit further experimentation, the lack of adequate presentation of the data does not permit a firm conclusion to be drawn. With respect to egg laying, the author reported an acceleration of this process during early weeks followed by a marked reduction, then later accelerations. As in the case of the previous two endpoint assessments, this one also suffers from lack of data presentation thereby precluding any definitive statement.

In contrast to the data presentation limitations of Essenberg,[172] Bless and Romanoff[173,174] offered well-designed and clearly presented studies in which X-rays were administered to 1200 chick eggs across 21 different doses ranging from 1.5–5000r units. For ease of presentation they combined the 21 doses into 7 r-units (8–3000 r). The 24 h blastoderm stage displayed evidence that low doses exerted a stimulatory effect (6–25%) regardless of whether the eggs were exposed in cool beakers, shells, or in preheated shells. Despite the stimulatory response at the blastoderm stage, there was a dose-dependent decrease in the hatchability of eggs.

The studies of Bless and Romanoff[173,174] offer clear evidence that the blastoderm stage is differentially affected by X-rays depending on the dose. However, given the generally negative effect on hatching success, it is uncertain what the biological significance of the stimulation is. Of interest were the poorly reported findings of Essenberg,[172] since it suggested that the developmental processes could be accelerated by low doses of radiation. This finding, while suggestive, represents one area of possible follow-up research some 65 years later.

## Salamanders

*Morphologenetic stimulation*

Stimulation of morphologenetic processes by X-ray treatment has been reported in regions that possess the capacity to form new limbs and when that capacity has not been suppressed by a relatively large dose of radiation. This observation becomes linked to the Arndt-Schulz Law based on reports that stimulation of target tissue is most commonly observed when the target has received less than the intended dose. Under such circumstances the radiation not only does not suppress limb formation, but even stimulates the formation of new limbs. In fact, Brunst[175] reported that animals may grow up to four asymmetrical, but large, hind limbs as well as secondary tails in the salamander. The development of such a radiation-induced secondary tail is what Brunst referred to as the 'zone of stimulation'.[175–177] This zone is characterized by a great mitotic activity in many cells of the narrow boundary zone of the irradiated field. This zone of stimulation represents a very transitory phenomenon and may be easily missed by investigators if they do not adequately sample tissue over time.

In addition to the temporary stimulation there are also cases of late, long continuing stimulation, possibly resulting from stimulatory influences of disintegration products which were referred to as 'necrohormones' orginating from the inhibition zone (see Caspari;[178] Strelin;[179] Zawarzin;[180] Scheremetjewa and Brunst;[181] Brunst and Scheremetjewa[182]). In fact, in the case of irradiation of Triton limbs by Brunst and Scheremetjewa,[182] the beginning of the new regeneration was observed after a period of reduction. Such observations lead to the tentative conclusion that the stimulatory effect can proceed only after a sufficient quantity of disintegration product has accumulated. This interpretation is remarkably similar to the hypothesis of Stebbing[82] that hormesis is an overcompensation to a disruption in homeostasis.

## Clinical

*Immunological responses and clinical perspectives*

There is little question that the concept of 'low dose stimulation, high dose inhibition' as embodied in the Arndt-Schulz Law and subsequently into the concept of hormesis, became the object of clinical verification and application in the early decades of the 20th century in the treatment of human diseases and other conditions by researchers of both traditional and homoepathic perspectives.[183,184] Such attempts of clinical verification and application of the Arndt-Schulz Law were principally linked to the use of various types of radiation, but especially X-rays. This follows from the timing of the initial reports of Schulz[14,15] in the late 1880's and the discovery less than a decade later of the X-ray by Roentgen. Given the immediate scientific/medical interest in the application of X-rays (i.e., 1000 papers were published on it within 1 year of the discovery!) and the relative ease of creating the condition to produce X-rays, there was little doubt that the testing of the Arndt-Schulz Law in clinical practice would be driven by the X-ray. In fact, by 1897 Leopold Freund became the first person to employ X-rays for therapeutic purposes. He also was the first to report the disappearance of inflammatory symptoms following treatment.[185,186] Such activities of Freund ushered in what was to become the beginning of the medical practice of X-rays for therapeutic application, but also the notion that X-ray treatment can include both beneficial and harmful effects, an hypothesis that was soon to be referred to by the phrase 'depending on the dose.'

As early as 1907, Crane demonstrated that the opsonic index (i.e., a mathematical ratio characterizing the ability of white blood cells to kill specific bacteria[187]) was increased in patients irradiated for infections, an observation that was repeatedly confirmed by well-recognized researchers of that era.[188–193] Such findings lead to the early general conclusion that the bacteriocidal quality of blood was enhanced by small doses of radiation, with the effects peaking some 48–72 h following irradiation. Furthermore, such stimulatory responses on the capacity to opsonize bacteria following low doses of irradiation were consistent with subsequent observations that low doses of X-rays induced reticuloendothelial stimulation likewise at low doses.[194,195] As Pendergrass and Hodes[196] emphasized, these suggestions of beneficial responses applied to small quantities of irradiation, while heavier doses or repeated smaller doses were observed to be harmful, lead to widespread therapeutic applications.

While the effects of low doses of radiation on normal physiological processes such as opsonization and reticuloendothelial stimulation were noted, radiotherapy was also widely employed for the treatment of various inflammatory conditions such as furuncle (boil), carbuncle (suppurating inflammation of the skin and subcutaneous tissues due to Staphylococci), pyrogenic (pus) infections, pneumonia, trachoma, parotitis, nephritis, and numerous other inflammatory conditions (see reviews by Desjardins[197–201]). In the case of pyrogenic infections, the preponderance of the published data indicate that the majority of patients reported rapid and substantial benefit, that is, pain was markedly reduced within a day. Furthermore, the radiotherapy greatly interrupts the predicted progression of the infection, thereby preventing the need for subsequent clinical interventions. The magnitude of the clinical literature, especially in the early decades of the 20th century, was substantial. For example, the 1926 report of Heidenhain[202] reviewed some 855 cases with 76% recovering without surgical intervention. The key factors associated with these initial clinical successes of the therapeutic application of X-rays for inflammatory symptoms was both the striking rapidity of improvement and the low nature of the radiation dose. More specifically, a dose of moderately filtered rays ranging from 50–150 r was demonstrated to be highly effective in a large number of cases.[186]

In the case of pneumonia, the first report of a beneficial response from radiotherapy was given by Musser and Edsall in 1905.[203] This involved the case of a delayed pneumonia resolution in which radiation was followed by immediate resolution and recovery (see Desjardin[197]). Within a year, Edsall, who later became dean of the Harvard Medical School and director of Massachusetts General Hospital, and Pemberton reported beneficial responses from radiotherapy for three additional cases in which moderate irradiation of the lungs was soon followed by recovery.[204] In 1916 the highly regarded Quimbys verified the above mentioned findings with 12 additional cases of delayed resolution.[205] These authors concluded that 'no pathologic process in the body responds quicker to an X-ray exposure that the nonresolution following pneumonia.' Numerous follow-up confirmatory studies over the next several decades were published demonstrating a comparable beneficial effect of radiotherapy on postoperative pneumonia, as well as on pneumonia unrelated to surgical intervention.

The eye disease, trachoma, which involves the sclerotization of eyelids, was first reported to be cured by X-ray treatment by Mayou[206,207] reporting on the findings of 16 patients. These initial striking results were confirmed and extended by numerous investigators (Table 2). Particularly impressive were the findings of Thielemann,[246] Cochard,[250] and Sabbadini.[254] As in the cases of therapeutic application, the beneficial effect is most likely when treatment is administered during the early stages of the disease process.

The issue of what is a low dose has always been problematic. However, in the case of X-ray treatment of inflammatory conditions the guidance offered by Desjardins[197–201] and Borak[186] is informative. They indicate that if the dose needed to cause

**Table 2** Studies demonstrating a beneficial effect of low dose X-ray treatment on specific diseases in humans

| *Furuncle, carbuncle, and other pyogenic infections* | *Pneumonia* | *Trachoma* | *Gas-bacillus, peritonitis* |
|---|---|---|---|
| Coyle 1906[208] | Musser and Edsall 1905[203] | Mayou 1902, 1903[206,207] | Kelly 1933, 1936[255,256] |
| Dunham 1916[209] | Edsall and Pemberton 1907[204] | Stephensen and Walsh 1903[238] | Hubeny and McNattin 1938[257] |
| Ross 1917[210] | Quimby and Quimby 1916[205] | Bettremieux 1903[239] | Kelly and Dowell 1936, 1941[258,259] |
| Richards 1922[211] | Krost 1925[226] | Cassidy and Rayne 1903[240] | Altemeier and Jones [260] |
| Lewis 1923[212] | Torrey 1927[227] | Geyser 1903, 1904[241–242] | Bates 1937[261] |
| Hodges 1924, 1925[213,214] | Heidenhain 1917[228] | Pardo 1904[243] | Faust 1934[262,263] |
| Heidenhain and Fried 1924[188] | Heidenhain and Fried 1924[188] | Horniker and Romanin 1905[244] | Kelly et al. 1938[264] |
| Pordes 1923, 1923–24, 1926, 1929[215–218] | Kaess 1925[229] | Stargardt 1905[245] | |
| Holzknecht 1926[219] | Fried 1926[230] | Thielemann 1905[246] | |
| Gerber 1926[220] | Holzknecht 1926[219] | Newcomet 1912[247] | |
| Fraenkel and Nissjewitsch 1926[221] | Gadjanski 1927[231] | Jacqueau et al. 1920[248] | |
| Solomon and Blondeau 1927[222] | Glas 1927[232] | Rollet and Bussy 1927[249] | |
| Carp 1927[223] | Holtz 1929[233] | Cochard 1921[250] | |
| Light and Sosman 1930[224] | Merritt and McPeak 1930[234] | Meldolesi and Sabbadini 1923[251] | |
| King 1937[225] | McIntire and Smith 1937[235] | Meldolesi 1924[252] | |
| | Powell 1938, 1939[236–237] | Lane 1924[253] | |
| | | Sabbadini, 1926[254] | |

erythema of the skin is assumed to be 100%, the dose successful in treating inflammatory conditions has been generally less than 50%, and at times even less than 10%. In fact, they emphasize that the results obtained with doses approaching the SED (skin erythema dose) are less successful than those treatments following the lower dose.

Given the substantial amount of clinical data indicating a beneficial effect of low doses of X-ray treatment on various inflammatory diseases, a number of speculative discussions ensued during the 1930's and 1940's on the possible underlying mechanisms. It has generally been shown that the beneficial X-ray treatment does not have a direct killing effect on the invading bacteria; consequently, the hypothesis that the X-ray treatment was beneficial because it destroyed the known causative agent was discredited. It has also been shown that X-rays act to enhance the bactericidal capacity of the blood as a result of the stimulation of both antibody production and phagocytosis of the reticuloendothelial system. This low dose stimulatory response hypothesis was challenged by Borak[186] who argued that if the stimulatory hypothesis were correct, one would expect that a beneficial effect should be obtained by radiating any region of the body. However, the X-ray treatment works only when the inflamed site is treated. Thus, if a patient has furuncles on both axillae and only one is irradiated, the irradiated region is the only one that will improve. A third hypothetical mechanism involved the enhanced radiosensitivity of leukocytes. This position was challenged by Borak[186] who claimed that the leukocytes do not decrease in cell number unless the blood forming organs are exposed; that if the effect of X-rays were directly related to leukocyte destruction, their effectiveness would be enhanced as the dose increases, yet clinical practice indicates just the opposite. Furthermore, the neutrophils (polymorphonuclear leukocytes) which are major factors in affecting the inflammatory process are relatively insensitive to X-rays. A fourth hypothesis assigns the principal effects caused by X-rays on inflammatory conditions to effects on the blood vessels. This hypothesis argues that the X-rays caused dilation of the capillaries which increase the permeability of the capillary walls, thereby increasing the entrance of antibodies and phagocytes to the inflamed area(s). The enhanced edema results in an increase in tension of the inflamed area. This provides an opening of the lymphatic capillaries. The dilation of the lymph vessel leads to an increase of their resorptive function. In contrast to the X-ray induced effects on blood capillaries, the arteries and veins become narrowed by the same dose due to the swelling of endothelial cells into the lumen. According to Borak,[186] a small dose of X-rays is able to produce dilation of the capillaries and a narrowing of the arteries in the inflammation process since the blood vessels exhibit a greater irritability in an inflammatory condition. Thus, a small dose will produce a further enlargement of the capillaries while reducing the dilated arteries to the normal lumen size.

Marked success was reported by Kelly and Dowell[259,265] in the treating of patients with gas bacillus infections and/or acute peritonitis. Such success had been initially reported by Kelly[255] as early as 1931 based on a presentation at the Radiological Society of North America. These authors used doses of 75 r per day for two days

(150 r total). These findings were substantiated by Dowdy and Sewell,[266] Merritt *et al.*,[267] and Cantril and Buschke.[268] Prior to the 1930's the mortality rate for gas gangrene had been ⩾50% along with substantial amputations. However, with the adoption of X-ray therapy the mortality rate and the need for tissue removal markedly decreased (Figure 5).

This brief review of the clinical literature concerning the beneficial aspects of X-ray therapy is based on numerous studies over the initial four decades of the 20th century. The clinical research was conducted at the most prestigious medical institutions in Europe and the United States and was published in the most mainstream and leading journals in the field. For example, the critical reviews by Desjardins, Chief Radiologist at the Mayo Clinic, were published in the journals *Radiology*, the *Journal of the American Medical Association*, and the *New England Journal of Medicine*[197–201] Likewise, the review by Borak[186] was published in *Radiology*, that of Pendergrass and Hodes[196] in the *American Journal of Roentgenology*, and that of Taliaferro and Taliaferro[78] in the *Journal of Immunology*.

The findings of the clinical researchers, especially in the early years of the 20th century, were often criticized because of the lack of rigorously designed blind clinical trials that are typically conducted today. However, this criticism was often mitigated by the citation of multiple animal model studies that supported the clinical investigations as well as the sheer magnitude of consistent findings from clinical investigations by multiple independent investigators.

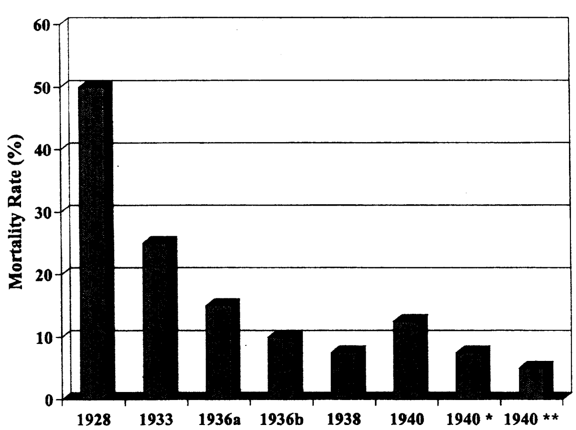


**Figure 5** Mortality rate since X-ray therapy was introduced in 1928. Note: mortality associated with patients receiving surgery, serum, and one or more X-ray treatments unless indicated otherwise; (*) indicates mortality associated with patients receiving surgery, serum, and three or more X-ray treatments; and (**) indicates mortality associated with patients receiving three or more X-ray treatments with no surgery or serum treatments. Reports: 1933=Kelly;[255] 1936a=Kelly;[256] 1936b=Kelly and Dowell;[258] and 1938=Kelly *et al.*;[264] 1940=Kelly and Dowell[259]

While the weight of evidence strongly favored a causal relationship of the X-ray treatments and the range of beneficial effects, the issue of whether the response is consistent with the hormetic hypothesis is difficult to resolve within the context of epidemiological studies since often only one dose is evaluated in clinical settings. In the case of the therapeutic use of X-rays to treat a wide range of inflammatory diseases, it appears fairly conclusive that there was a low dose benefit, high dose toxicity, thereby being consistent with the hormetic perspective.

Two papers by Glenn[269,270] provided the capacity to more formally assess the capacity of X-rays to affect immunological parameters with respect to the hormesis evaluation index, and thereby afford the possibility of providing an experimental corroboration of the above cited clinical observations. The initial study by Glenn[269] was of a preliminary nature in assessing the effects of X-rays on the phagocytic capacity of rabbits exposed to hemolytic *Staphyloccus aureus*. Of particular relevance to the hormesis hypothesis was that Glenn used five treatments plus a concurrent control. In this experiment there was a clear low dose stimulation (6.5-fold) followed by a sharp return toward control value as the dose increased. In the follow-up study,[270] nine doses were employed along with the concurrent control. As in the pilot experiment, there was a low dose stimulation of sevenfold followed by a return to control value as the dose increased.

While the collective findings clearly support the perspective that low doses of X-rays have a marked and reproducible therapeutic benefit to patients with various inflammatory diseases, there was still debate even among supportive researchers on how to interpret such findings. More specifically, there were two schools of thought concerning interpretation of the beneficial response. While both agree that functional activity followed low dose X-ray treatment, they markedly differed with respect to the mechanism involved. In the case of Fraenkel and his followers, it was believed that small doses of radiation cause a direct stimulation. In contrast, Holzknecht and Pordes argue that the X-ray treatment causes stimulation via a depressing factor which then releases the cells from a restraining influence.[183,184]

These different perspectives on hormesis have been periodically noted over the past century. The Holzknecht and Pordes perspective is highly consistent with subsequent reports of Hektoen[192] and

Bloom and Jacobson[271] who, also studying X-ray effects on biological systems, concluded that the 'stimulation was an example of reparative overcompensation after initial damage.'

## Discussion

This review has demonstrated that the hypothesis that is today called radiation hormesis has been evaluated by numerous investigators, using highly diverse plant and animal models over the initial decades of the 20th century. Particularly noteworthy were the highly consistent findings of a low dose stimulation, high dose inhibition for an exceptionally wide range of plant species. Likewise, convincing evidence of hormetic response were seen in the research on various fungal species, protozoans, algae and insects. While some of the findings would be considered inadequate or even poor by current standards, many other supportive experimental findings would be considered quite impressive even today. As in the case with that observed with historical features of chemical hormesis,[12] these observations of low dose stimulation were usually quite unexpected. For example, the observations of Davey[168,169] that low doses of X-rays enhanced longevity in the confused flour beetle were at first totally unexpected, but then highly reproducible in subsequent confirmatory experimentation. In fact, this type of process of initially observing an unexpected stimulatory response with follow-up confirmation and extension of the hormetic finding is a general feature of the database of the early decades of the 20th century. This combination of unexpected initial observation and reproducibility are important factors enhancing the credibility of the hormetic hypothesis, since they speak both to a lack of bias on behalf of such investigation and to the consistency of the initial observations.

The assessment also reveals that a large number of reports of hormetic-like findings were conducted by highly prestigious investigators, residing at some of the most outstanding research institutions in Europe, the United States and Japan, and published in the leading journals of that period, such as the *Journal of the American Medical Association*, the *New England Journal of Medicine*, and the *Journal of Immunology*.

Of particular importance is that the stimulatory responses were remarkably similar across the various biological models evaluated following exposure to various types of radiation with respect to stimulatory dose range, maximum stimulatory response, and distance of maximum stimulatory response to the threshold for toxicity (NOAEL). In fact, such responses were also highly consistent with that observed with the developing chemical hormesis database, as well. Further, the stimulatory response was often seen after an initial inhibitory response, thereby suggesting an overcompensation response to an initial disruption in homeostasis.

Despite the extensive earlier findings of a low dose stimulation, high dose inhibition to radiation exposure in numerous models, including humans, the belief that radiation hormesis was a general biological phenomenon came to be severely questioned in the mid 1930's and eventually became a marginalized hypothesis at best, and often the source of ridicule. Given the substantial initial scientific foundations of the hormetic hypothesis in the biological and medical sciences, it is important to consider how the concept of radiation hormesis evolved into a nearly forgotten concept, being ignored by leading radiological and toxicological texts, never the subject of technical sessions at society conferences, and with no place in the curriculum of toxicologists and biomedical scientists. The following article will explore the basis of the remarkable fall of the hormetic hypothesis from that of mainstream theory to an historical footnote and whether this was a justified demotion or whether a bona fide biological hypothesis with potentially profound toxicological and societal implications was inappropriately marginalized.

## Acknowledgements

We would like to thank Richard S Szczygiel, Jr. for his dilligent efforts as a library sleuth. This work has been sponsored in part by a grant to the University of Massachusetts (Edward J Calabrese, Principal Investigator) by the US Nuclear Regulatory Commission.

## References

1 Luckey TD. Hormesis With Ionizing Radiation. CRC Press, Inc.: Boca Raton, FL, 1980.
2 Luckey TD. Radiation Hormesis. CRC Press, Inc.: Boca Raton, FL, 1991.
3 Calabrese EJ (editor). Biological Effects of Low Level Exposures to Chemicals and Radiation. Proceedings of the First BELLE Conference, April-May, 1991, Amherst, MA. Lewis Publishers: Chelsea, MI, 1992.

4 Calabrese EJ (editor). Biological Effects of Low Level Exposures–Dose Response Relationships. Proceedings of the Second BELLE Conference, April 1993, Crystal City, VA. CRC Press: Boca Raton, FL, 1994.
5 Calabrese EJ (editor). Toxicological Defense Mechanisms and the Shape of Dose-Response Relationships. Proceedings of the Third BELLE Conference, November 1996, Research Triangle Park, NC. *Environmental Health Perspectives* 1998; **106**(Suppl.1): 275–394.
6 Liu SZ (editor). Proceedings of the International Symposium on Biological Effects of Low Level Exposures to Radiation and Relataed Agents. Cangchun, China. Princeton Scientific Publishers, Princeton, NJ, 1994.
7 Sugahara T, Sagan LA, Aoyama T (editors). Low Dose Irradiation and Biological Defense Mechanisms. Proceedings of the International Conference on Low Dose Irradiation and Biological Defense Mechanisms. July 12–16, Kyoto, Japann, 1992.
8 Calabrese EJ, Baldwin LA. Chemical hormesis: Its historical foundations as a biological hypothesis. *Toxicologic Pathology* 1999; **27:** 195–216.
9 Calabrese EJ, Baldwin LA. The marginalization of hormesis. *Toxicologic Pathology* 1999; **27:** 187–194.
10 Calabrese EJ, Baldwin LA. The dose determines the stimulation (and poison): development of a chemical hormesis database. *International Journal of Toxicology* 1997; **16:** 545–559.
11 Calabrese EJ, Baldwin LA. A quantitatively-based methodology for the evaluation of chemical hormesis. *Human and Ecological Risk Assessment* 1997; **3:** 545–554.
12 Calabrese EJ, Baldwin LA. A general classification of U-shaped dose-response relationships in toxicology and their mechanistic foundations. *Human and Experimental Toxicology* 1998; **17:** 353–364.
13 Southam CM, Erlich J. Effects of extracts of western red-cedar heartwood on certain wood-decaying fungi in culture. *Phytopathology* 1943; **33:** 517–524.
14 Schulz H. Zuhre Lehre von der Arzneiwirdung. *Virchows Archiv fur Pathologische Anatomie und Physiologie fur Klinische Medizin* 1887; **108:** 423–445.
15 Schulz H. Uber Hefegifte. *Pflugers Archiv fur die gesamte Physiologie des Menschen und der Tiere* 1888; **42:** 517–541.
16 Hueppe F. Principles of Bacteriology. Translated from the German by E.O. Jordan, The Open Court Publishing Company: Chicago, 1896.
17 Schober A. Ein Versuch mit Rontgen'schen Strahlen auf Keimpflanzen. *Berichte der Deutschen Botanishen Gesellschaft* 14, 1896; **No.7:** 108–110.
18 Maldiney E, Thouvenin S. De l'influence des rayons X sur la germination. *Revue generale de Botanique* 1898; **10:** 81–86.
19 Perthes G. Versuche ueber den einfluss der Rontgen- und Radiumstrahlen auf Zellteilung. *Deutsche Med. Wochenschrift Jahr* 1904; **30:** 632.
20 Euler. Uber die heilende Wirkung der Tontgenstrahlen bei abgegrenzten Eiterungen. *Veroffentlichungen Gebiete Des Militar-Sanitatswesen. Berlin* 1906.
21 Koernicke M. Uber die Wirkung von Rontgenstrahlen auf die Keimung und das Wachstum. *Berichte der Deutschen Botanishen Gesellschaft* 1904; **22:** 148–155.
22 Koernicke M. Weitere Untersuchungen uber die Wirkung von Rontgenund Radiumstrahlen auf die Pflanzen. *Berichte der Deutschen Botanishen Gesellschaft* 1905; **23:** 324–333.
23 Guilleminot H. Effets compares des rayons X et du radium sur la cellule [vegetale]. Valeur de l'unite M en physiologie vegetale. *Comptes Rendus Academie des Science (Paris)* 1907; **145:** 798–800.
24 Schmidt HE. Experimentelle Untersuchungen uber die Wirkung kleinerer und grosserer Strahlenmengen auf junge Zellen. *Berliner Klin. Wochenschrift* 1910; **47,** No. 21: 972–974.
25 Wetterer J. Beitrag zur Kenntnis der biologischen Wirkung der Rontgenstrahlen auf das Wachstum der Pflanzen. *Fortschritte auf dem Gebiete Roentgenstrahlen* 1912–1913; **14:** 172.
26 Promsy G, Drevon M. Influence des rayons X sur la germination. *Revue generale de Botanique* 1912; **24:** 177 197.
27 Schwarz E. Der Wachstumsreiz der Rontgenstrahlen auf pflanzliche [und tierische] Gewebe. *Munch. med. Wochenschr. 60,* 1913; **39:** 2165–2169.
28 Miege E, Coupe H. De l'influence des rayons X sur la vegetation. *Comptes Rendus Academie des Science (Paris)* 159, 1914; **4:** 338–340.
29 Koernicke M. Uver die Wirkung verschieden starker Rontgenstrahlen auf Keimung und Wachstum bei den hoheren Pflanzen. *Jahrbucher fur wissenschaftliche Botanik* 1915; **56:** 416–430.
30 Koernicke M. Wirkung der Tontgenstrahlen auf Pflanzen. *Fortschritte auf dem Gebiete Roentgenstrahlen* 27, 1920; **1:** 661.
31 Yamada M. On the effect of Roentgen rays upon seeds of *Oryza sativa. Journal of Physical Therapy* No. 6, referenced in *Journal of the College of Agriculture. Tokyo Imperial University* 1917; **8:** 2.
32 Nakamura S. Comparative experiments of the effect of X rays. Proceedings of Koto-Kwai No. 111, Japan, 1918; referenced in *Journal of the College of Agriculture. Tokyo Imperial University* 1923; **8:** 2.
33 Sierp A, Robbers F. Uber die Wirkung der Rontgenstrahlen auf das Wachsum der Pflanzen. *Strahlentherapie* 14, 1923; **3:** 538–557.
34 Lallemand S. Etude de l'action des rayons X sur le developpement des plantes. *Archiv D'anatomie, d'histologie et d'embryologie* 1929; **10:** 1–233.
35 Weber F. Fruhtreiben ruhender Plflanzen durch Rontgenstrahlen. *Biochemische Zeitschrift* 1922; **128:** 495–507.
36 Altmann V, Rokhlin D, Gleikhgevikht E. Uber [den] entwicklungsbeschleunigenden und entwicklungshemmenden Einfluss der Rontgenstrahlen. *Fortschritte auf dem Gebiete Roentgenstrahlen* 1923; **31:** 51–62.
37 Komuro H. Studies in the effect of Rontgen rays upon the development of *Vicia faba. Journal of the College of Agriculture, Imperial University, Tokyo* 1923; **8:** 253–292.

38 Komuro H. Studies on the effect of Roentgen rays upon the germination of *Oryza sativa. Botanical Magazine (Tokyo)* 1924; **38:** 1–21.
39 Czepa A. Das Problem der wachstumsfordernden und funktionssteigernden Rontgen-Radium-Wirkung. *Strahlentherapie* 1924; **16:** 913.
40 Martius H. Bohnenversuche an Rontgenstrahlen. *Fortschritte auf dem Gebiete Roentgenstrahlen* 1924; **32:** 361–365.
41 Geller FC. Die Wirkung der Tontgenstrahlen auf jugendliche Organismen. *Klin. Wochenschr.* 1924; **3:** 561–566.
42 Gambarov GG. The problem of the so-called 'irritating' effect of X rays. *Vestnik Rentgenol. i Radiol.* 1925; 3, **6:** 311–323.
43 Ancel S. Action de faibles doses de rayons X sur des graines seches. *Comptes Rendus Societe Biologie* 1924; **91:** 1435–1436.
44 Breslavets LB. Plants and X-rays. Translation by A. Elbl. A.H. Sparrow (editor). The American Institute of Biological Sciences: Washington, 1946.
45 Iven H. Neuere Untersuchungen uber die Wirkung der Tontgenstrahlen auf Pflanzen. *Strahlentherapie* 19, 1925; **3:** 413–461.
46 Ancel S. Les rayons X appliques sur des graines seches n'ont aucune influence sur l'epoque d'apparition du germe. *Bulletin Societe Botanique de France* 1925; **72:** 195–197.
47 Ancel S. Sur un phenomene de pseudo-excitation determine par les rayons X sur les bourgeons dormants cotyledonaires de la Lentille. *Bulletin Societe Botanique de France* 1925; **72:** 1084–1088.
48 Kol'tsov AV, Kol'tsov LI. The influence of radium emanations and X-rays on the growth and development of plants. *Zapiski Leningr, Sel'skokhoz. Institute* 1925; **2:** 205–222.
49 Ancel S. Recherche du meilleur test de la radio-reaction des graines des Legumineuses. *Bulletin Societe Botanique de France* 1926; **73:** 71–73.
50 Ancel S. De l'influence accelatrice des rayons X sur le developpement des plantes. *Archives de Physiologiques et Biologie* 1926; **5:** 106–118.
51 Bersa E. Strahlenbiologische Untersuchungen. I. Zur Frage der Rontgenreizwirkung bei Keimlingen. *Sitzungsbericgte Akademie der Wissenschaften In Wien, Mathematische–Naturwissenschaftliche Klasse* Abt. 1, 135, 1926; **1:** 425–451.
52 Johnson E. Effect of X rays on growth, development and oxidizing enzymes of *Helianthus annuus. Botanical Gazette* 1926; **82:** 373–402.
53 Johnson E. Growth and germination of sunflowers as influenced by X rays. *American Journal of Botany* 1928; **15:** 65–76.
54 Doroshenko AV. The influence of X radiation on the length of the vegetative period in plants. *Tr. Prikl. Bot., Genet. i Sel.* 23, 1929–1930; **2:** 511–535.
55 Sprague H, Lenz M. The effect of X rays on potato tubers for 'seed.' Science 69:606.Weber, F. 1922. Fruhtreiben ruhender Pflanzen durch Rontgenstrahlen. *Biochemische Zeitschrift* 1929; **128:** 495–507.
56 Patten R, Wigoder S. Effect of X rays on seeds. *Nature* 1929; **123:** 606.
57 Cattell W. The effect of X rays on the growth of wheat seedlings. *Science* 1931; **73:** 531–533.
58 Johnson E. On the alleged stimulating action of X rays upon plants. *American Journal of Botany* 1931; **18:** 603–614.
59 Johnson E. Effect of X radiation upon growth and reproduction of tomato. *Plant Physiology* 1931; **6:** 685–694.
60 Johnson E. The influence of X radiation on *Atriplex hortensis* L. *New Phytologist* 1933; **32:** 297–307.
61 Chekhov VP. The influence of X rays on plants. *Tr. Tomsk. Gosudarst. Univ. im. V. V. Kuibysheva* 1932; **85:** 67–135.
62 Shull C, Mitchell J. Stimulative effects of X rays on plant growth. *Plant Physiology* 1933; **8:** 287–296.
63 Benedict HM, Kersten H. Effect of soft X rays on germination of wheat seeds. *Plant Physiology* 1934; **9:** 173–178.
64 Francis DS. The effects of X-rays on growth and respiration of wheat seedlings. *Bulletin of the Torrey Botanical Club* 1934; **61:** 119–153.
65 Breslavets LP, Afanas'eva AS. Increase of yield under the influence of X rays. Rye. II. Irradiation of seeds. *Tr. Vsesosoyuznyi Institut Udobrenii Agropochvovedeniya I Agrotekhniki* 1935; **8:** 245–253.
66 Breslavets LP, Afanas'eva AS. The action of X rays on rye. II, Irradiation of seeds. *Vestnik Rentgenol. I Radiol.* 1935; **14:** 302–324.
67 Long T, Kersten, H. Stimulation of growth of soy bean seeds by soft X rays. *Plant Physiology* 1936; **11:** 615–621.
68 Frolov G. The action of X rays and ultraviolet rays on the growth of plants. *Tr. Sel'skokhoz. Akad. Im. Timiryazeva* 1, 1936; **2:** 189–206.
69 Johnson E. Effects of X rays upon green plants. In: *Biological Effects of Radiation*. BM Duggar (ed). **2.** pp. 961–985. McGraw-Hill: New York, 1936.
70 Saeki H. Studies on the effects of X-ray radiation upon germination, growth and yield of rice plants. *Journal of the Society of Tropical Agriculture [Taiwan]* 1936; **8:** 28–38.
71 Zankevich E, Brunst V. The influence of X rays on the individual development of tobacco, poppies, flax, and rhubarb. *Inst. Bot. AN UkSSR,* 1937; **10/18:** 77–98.
72 Bless AA. Effects of X-rays on seeds. *Plant Physiology* 1938; **13:** 209–211.
73 Zaurov EI. An experiment on the effect of X rays on Indian hemp. *Biologii Zhurnal* 1937; **6:** 479–486.
74 Breslavets LB. The present status of X-ray biology of plants. Byull. Moskov. Obshchestva Ispytatelei Prirody. *Otdel biol.* 1937; **46:** 359–369.
75 Wort DJ. X-ray effects on the growth and reproduction of wheat. *Plant Physiology* 1941; **16:** 373–383.
76 Porter TM. The Rise of Statistical Testing, 1820–1900. Princeton University Press: Princeton, NJ, 1986.
77 Hudson JC. Roentgen-Ray Dosimetry. In: O. Glasser, The Science of Radiology. Charles C. Thomas: Springfield, IL. Pp. 120–139, 1933.
78 Taliaferro WH, Taliaferro LG. 1951. Effect of X-rays on immunity: A review. *Journal of Immunology* 1951; **66:** 181–212.

79 Pfeiffer T, Simmermacher W. The influence of Rontgen rays on the seeds of *Vicia faba* as shown in the development of the plants. *Landwirtschaftlichen Versuchs-Stationen* 1915; **86:** 35–43.
80 Jungling O. Die praktische Verwendbarkeit der Wurzelreaktion von *Vicia faba equina* zur Bestimmung der biologischen Wertigkeit [der Rontgenstrahlen]. *Munch. med. Wochenschr.* 1920; **40:** 1141–1144.
81 Johnson E. Susceptibility of seventy species of flowering plants to X radiation. *Plant Physiology* 1936; **11:** 319–342.
82 Stebbing ARD. A theory for growth hormesis. *BELLE Newsletter* 1997; **6:** 1–11.
83 Smith EC. Effects of ultra-violet radiation and temperature on Fusarium. II. Stimulation. *Bulletin of the Torrey Botanical Club* 1935; **62:** 151–164.
84 Smith EC. The effects of radiation on fungi. In: *Biological Effects of Radiation, Vol. II.* Duggar BM (ed) pp. 889–918. McGraw-Hill Book Co., Inc.: NewYork. 1936.
85 Seide J. 1929.
86 Failla G, Henshaw PS. The relative biological effectiveness of X-rays and gamma rays. *Radiology* 1931; **17:** 1–43.
87 Sax K. The effect of ionizing radiation on plant growth. *American Journal of Botany* 1955; **42:** 360–364.
88 Sax K. The stimulation of plant growth by ionizing radiation. *Radiation Botany* 1963; **3:** 179–186.
89 Packard C. Roentgen radiations in biological research. *Radiology* 1945; **45:** 522–533.
90 Clark AJ. Handbook of Experimental Pharmacology. Verlig Von Julius Springer: Berlin, 1937.
91 Gager CS. Effects of the rays of radium on plants. *Memoires of the New York Botanical Garden* 1908; **4:** viii+278.
92 Gager CS. Present status of the problem of the effect of radium rays on plant life. *Memoires of the New York Botanical Garden* 1915; **6:** 153–160.
93 Gager CS. The effects of the rays of radium on plants. In: *Biological Effects of Radiation, Vol. II.* BM. Duggar (ed) pp. 987–1013. McGraw-Hill Book Co.: New York, 1936.
94 Ewart AJ. *Journal of the Department of Agriculture, Victoria* 1912; **10:** 417–421.
95 Sutton HF. Radium and plant growth. *Gardeners' Chronicle* 3rd Ser. 1915; **58:** 102.
96 Ross WH. The use of radioactive substances as fertilizers. U.S. Department of Agriculture Bulletin **149,** 1914.
97 Hopkins CG, Sachs WH. Radium fertilizer in field tests. *Science* 1915; **41:** 732–735.
98 Ramsey RR. Radium fertilizer. *Science* 1915; **42:** 219.
99 Stoklasa J. Influence du selenium et du radium sur la germination des grains. *Comptes Rendus Academie des Science (Paris)* 1922; **174:** 1075–1077.
100 Stoklasa J *et al.* Die Dynamik der physiologischen Wirkung der Radioaktivitat auf das Protoplasma. *Beitrage zur Biologie der Pflanzen* 1930; **18:** 185–224.
101 Stoklasa J, Penkava J. Biologie des Radiums und Uraniums. Paul Parey: Berlin, 1932.
102 Stoklasa J. Bedeutung der Radioaktivitat in der Physiologie. *Chemische Zeitschrift* 1913; **37:** 1176.
103 Stoklasa J. Bedeutung der Radioaktivitat in der Physiologie. *Centralblatt fur Bakteriologie* 2. Abt. 1914; **40:** 266–280.
104 Kotzareff A, Chodat F. De l'action exercee par l'emanation du radium sur les levures. *Compte Rendu Societe de Physique et d'Histoire Naturelle de Geneve* 1923; **40:** 36–39.
105 Doumer E. Radiumenanation und die Keimung der Samen. Beiblatter, VI. Internat. Kongress Allgem. Und Arztl. Elektrol. und Radiol. Prog., 1912.
106 Agulhon H, Robert T. The action of radium and radioactivity on germination in the higher plants. *Annales de l'Institut Pasteur, Paris* 1915; **29:** 261–273.
107 Montet D. Action des faibles radioactivities sur la germination des graines. *Comptes Rendus Hebdomadaires des Seances de l'Academie des Sciences* 1932; **194:** 304–306.
108 Montet D. L'action de la radioactivite dur la germination des bulbes. *Comptes Rendus Hebdomadaires des Seances de l'Academie des Sciences* 1932; **194:** 1093–1095.
109 Montet D. De l'influence des faibles radioactivities sur la germination. *Comptes Rendus Hebdomadaires des Seances de la Societe Biologie* 1932; **109:** 678–680.
110 Alexander LT. Radioactive materials as plant stimulants–field results. *Agronomy Journal* 1950; **42:** 252–255.
111 Lemmermann OG, Schmidt MOC. Die Wirkung von radiumhaltigen Dungemitteln. *Zeitschrift fur Pflanzenernahrung, Dungg und Bodenkunde* 1947; **38:** 185–195.
112 Burstenbinder R. Radioaktive Dungemittel. *Zeitschrift fur Pflanzenernahrung, Dungg und Bodenkunde* 1947; **38:** 200–201.
113 Marx TH, Salm U. Uber die Radioaktivitat und den Dungewert von Plantoradon. *Zeitschrift fur Pflanzenernahrung, Dungg und Bodenkunde* 1947; **38:** 195–200.
114 Gericke S. Dungungsversuche mit Planteondon. *Zeitschrift fur Pflanzenernahrung, Dungg und Bodenkunde* 1948; **42:** 143–147.
115 Baetge HH, Begemann E. Dungungsversuche mit Planteradon. *Zeitschrift fur Pflanzenernahrung, Dungg und Bodenkunde* 1949; **44:** 198–206.
116 Kaindl K, Linser H. Radiation in agricultural research and practice. Developments in the Peaceful Applications of Nuclear Energy No. 10, International Atomic Energy Agency, Karntner Ring, Vienna, Austria, 1961.
117 Linser H, Pelikan W. Gefassversuche mit radioaktiver Dungung. *Bodenkultur* 1951; **5:** 417–424.
118 Kaindl D. Verhalten von Radium in Boden und Pflanze. *Bodenkultur* 1951; **5:** 425–436.
119 Nadson GA, Philippov GS. Action excitante des rayons ultra-violets sur le developpement des levures et des moisissures. *Comptes Rendus Societe de Biologie [Paris]* 1928; **98:** 366–368.
120 Luyet BJ. The effects of ultra violet, X-rays and cathode rays on the spores of Mucoraceae. *Radiology* 1932; **18:** 1019–1022.

121 Schreiber H. Strahlenbiologische Untersuchungen besonders im ultravioletten Spektralbezirk an Saccharomyces turbidans Hansen. *Strahlentherapie* 1934; **49:** 541–595.
122 Chavarria AP, Clark JH. The reaction of pathogenic fungi to ultra-violet light and the role played by pigment in this reaction. *American Journal of Hygiene* 1924; **4:** 639–649.
123 Sperti GS, Loofbourow JR, Dwyer CM. Proliferation-promoting factors from ultraviolet injured cells. *Ins. Divi. Thomae* 1937; **1:** 163–191.
124 Sperti GS, Loofbourow JR, Lane MM. Effects on tissue cultures of intercellular hormones from injured cells. *Science* 1937; **86:** 611.
125 Loofbourow JR. Intercellular hormones. 7. Release of aminoacids by damaged living yeast cells. *Biochemical Journal* 1947; **41:** 119–122.
126 Loofbourow JR, Dwyer CM. Production of intercellular hormones. *Nature (London)* 1939; **143:** 725–726.
127 Loofbourow JR, Morgan MN. Intercellular wound hormones from ultraviolet injured cells. *Stud. Inst. Divi Thomae* 1938; **1:** 137–153.
128 Loofbourow JR., Cook ES, Stimson MM. Chemical nature of proliferation-promoting factors from injured cells. *Nature (London)* 1938; **142:** 573.
129 Loofbourow JR, Cronin AG, Lane MM. Proliferation producing intercellular hormones. I. Quantitative study of factors produced by injured animal tissue cells. *Biochemical Journal* 1940; **34:** 432–441.
130 Loofbourow JR, Englert ME, Dwyer CM. Increased yield of nucleic acid-like substances from irradiated yeast. *Nature (London)* 1941; **148:** 113.
131 Loofbourow JR, Oppenheim-Errera S, Loofbourow DG. Intercellular hormones. 8. Release of nucleotides and nucleosides by damaged living cells. *Biochemical Journal* 1947; **41:** 122–129.
132 Loofbourow JR, Webb AM, Abramowitz RK. Relation of aeration to the activity of proliferation promoting action of injured cells. *Nature (Lond.)* 1942; **149:** 272.
133 Giese AC. Radiations and cell division. *Quarterly Review of Biology* 1947; **22:** 253–282.
134 Stevens FL. Effects of ultra-violet radiation on various fungi. *Botanical Gazette* 1928; **86:** 210–225.
135 Stevens FL. The sexual stage of fungi induced by ultra-violet rays. *Science* 1928; **67:** 514–515.
136 Stevens FL. The effects of ultra-violet irradiation on various Ascomycetes, Sphaeropsidales and Hyphomycetes. *Centralblatt fur Bakteriologie (Abt. 2)* 1930; **82:** 161.
137 Stevens FL. The ascigerous stage of *Colletotrichum lagenarium* induced by ultra-violet irradiation. *Mycologia* 1931; **23:** 134–139.
138 Purvis JE, Warwick GR. The influence of spectral colors on the sporulation of Saccharomyces. *Proceedings of the Cambridge Philosophical Society* 1907; **14:** 30–40.
139 Dillon-Weston WAR. III. Studies on the reaction of disease organisms to light. The reaction of disease organisms to certain wave-lengths in the visible and invisible spectrum. *Scientific Agronomy* 1932; **12:** 352–356.
140 Hutchinson AH, Ashton MR. The effects of radiant energy on growth and sporulation in *Colletotrichum phomoides. Canadian Journal of Research* 1930; **3:** 187–198.
141 Ramsey GB, Bailey AA. Effect of ultra-violet radiation on sporulation in *Macrosporium* and *Fusarium. Botanical Gazette* 1930; **89:** 113–136.
142 Bailey AA. Effects of ultraviolet radiation upon representative species of Fusarium. *Botanical Gazette* 1932; **94:** 225–271.
143 Porter CL, Bockstahler HW. Concerning the reaction of certain fungi to various wave lenghts of light. *Proceedings of the Indiana Academy of Sciences* 1928; **38:** 133–135.
144 Lacassagne A, Holweck F. Sur la radiosensibilite de la levure *Saccharomyces ellipsoideus. Comptes Rendus Societe de Biologie [Paris]* 1930; **104:** 1221–1223.
145 Wycoff RWG, Luyet BJ. The effects of X-rays, cathode and ultra-violet rays on yeast. *Radiology* 1931; **17:** 1171–1175.
146 Zeller H. Wirkung von Arzneimitteln und Strahlen auf Hefe. III. Wirkung von Rontgenstrahlen auf Hefe. *Strahlentherapie* 1926; **23:** 336–353.
147 Fabre G. Effets de l'Activation de l'Atmosphere par l'Emanation de Radium sur la Germination et la Poussee de Divers Organisms Vegetaux. *Comptes Rendus Societe de Biologie [Paris]* 1911; **70:** 187–188.
148 Ingber E. Uber die Radiumsensibilitat des Actinomycespilzes. *Strahlentherapie* 1929; **28:** 581–588.
149 Kayser E, Delaval H. Radioactivite, fixateurs d'azote et levures alcooliques. *Comptes Rendus Academie des Science (Paris)* 1925; **181:** 151–153.
150 Colley MW. Stimulation phenomena in the growth of bacteria as determined by nephelometry. *American Journal of Botany* 1931; **18:** 266–287.
151 Townsend CO. The correlation of growth under the influence of injuries. *Annals of Botany* 1897; **11:** 509–532.
152 Meier FE. Lethal action of ultra-violet light on a unicellular green alga. *Smithsonian Miscellaneous Collections* 1932; **87:** 1–11.
153 Meier FE. Lethal response of the alga *Chlorella vulgaris* to ultraviolet rays. *Smithsonian Miscellaneous Collections* 1934; **92:** 1–12.
154 Meier FE. Lethal effect of short wave lengths of the ultraviolet on the alga *Chlorella vulgaris. Smithsonian Miscellaneous Collections* 1936; **95:** 1–19.
155 Meier FE. Stimulative effect of short wave lengths of the ultraviolet on the alga *Stichococcus bacillaris. Smithsonian Miscellaneous Collections* 1939; **98:** 1–19.
156 Meier-Chase FM. Increased stimulation of the alga *Stichococcus bacillaris* by successeive exposures to short wave lengths of the ultraviolet. *Smithsonian Miscellaneous Collections* 1941; **99:** 1–16.
157 Crowther JA. The action of X-rays on *Colpidium colpoda. Proceedings of the Royal Society of London,* 1926; **B100:** 390–404.

158 Markowits E. Cytologische Veranderungen der Einzeller Paramoecium nach Bestrahlung mit Mesothorium. *Arch. Zellforsch.* 1922; **16:** 238.
159 Bovie WT, Hughes DM. The effects of quartz ultra-violet light on the rate of division of *Paramecium caudatum. Journal of Medical Research* 1918; **39:** 223.
160 Hinrichs MA. Ultraviolet radiation and division in *Paramecium caudatum. Physiological Zoology* 1928; **1:** 394–415.
161 MacDougall MS. Modification in *Chilodon uncinatus* produced by ultraviolet radiation. *Journal of Experimental Zoology* 1929; **54:** 95–109.
162 MacDougall MS. Another mutation of *Chilodon uncinatus* produced by ultraviolet radiation with a description of its maturation processes. *Journal of Experimental Zoology* 1931; **58:** 229–236.
163 Roskin G, Romanowa K. Arzneimittel und ultraviolette Strahlen; die Chininwirkung auf die Zelle bei gleichzeitiger Bestrahlung derselben mit ultravioletten Strahlen. *Zeitschrift fur Immunitatforschrung* 1929; **62:** 147–158.
164 Alpatov NV, Nastiukova DK. The influence of different quantities of ultraviolet radiation on the division rate of *Paramecium. C. r. Acad. Sci. USSR* 1933; **1:** 290–291.
165 Kimball RF. The effects of radiation on protozoa and the eggs of invertebrates other than insects. In: Radiation Biology Vol III: Ultraviolet and Related Radiations. Hollander A (ed). McGraw-Hill Book Company, New York. Pp. 285–331, 1955.
166 Chase HY. The effect of ultraviolet light upon early development in the egg of *Urechis caupo. Biological Bulletin* 1937; **72:** 377–383.
167 Chase HY. The effect of ultraviolet light upon cleavage in certain marine eggs. *Biological Bulletin* 1938; **75:** 134–144.
168 Davey WP. The effect of X-rays on the length of life of *Tribolium confusum. Journal of Experimental Zoology* 1917; **22:** 573–592.
169 Davey WP. Prolongation of life of *Tribolium confusum* apparently due to small doses of X-rays. *Journal of Experimental Zoology* 1919; **28:** 447–458.
170 Cork JM. Gamma radiation and longevity of the flour beetle. *Radiation Research* 1957; **7:** 551–557.
171 Gilman PK, Baetjer FH. Some effects of the rontgen rays on the development of embryos. *American Journal of Physiology* 1904; **10:** 222–224.
172 Essenberg JM. Effect of X-rays on the incubation period, sexual development, and egg-laying in white and brown leghorn chickens. *Poultry Science* 1935; **14:** 284, 293, 317.
173 Bless AA, Romanoff AL. The effect of X-ray stimulation on the bioelectric potentials of the avian egg. *Proceedings of the National Academy of Science* 1942; **28:** 306–311.
174 Bless AA, Romanoff AL. Stimulation of the development of the avian embryo by X-rays. *Journal of Cellular and Comparative Physiology* 1943; **21:** 117–121.
175 Brunst VV. Influence of local X-ray treatment on the development of extremities of the young axolotl (*Siredon mexicanum*). *Journal of Experimental Zoology* 1950; **114:** 1–49.
176 Brunst VV. Histopathology of roentgen death of young axolotl (*Siredon mexicanum*). *American Journal of Roentgenology* 1957; **78:** 518–545.
177 Brunst VV. Effects of ionizing radiation on the development of amphibians. *The Quarterly Review of Biology* 1965; **40:** 1–66.
178 Caspari W. Physiologie der Rontgen und Radiumstrahlen. *Handbuch der norm. und pathol. Physiologie* 1926; **17:** 343–390.
179 Strelin GS. Rontgenologische Untersuchungen an Hydren II. Die histologischen Veranderungen im Korperbau vom Pelmatohydra oligactis unter der Wirkung der Rontgenstrahlen und ihre Bedeutung fur die Regeneration und Vermehrung. *Wilhelm Roux' Archiv fur Entwicklungsmechanik* 1929; **115:** 27–57.
180 Zawarzin AA. Rontgenologische Untersuchungen an Hydren I. Die Wirkung der Rontgenstrahlen auf die Vermehrung und Regeneration bei Pelmatrohydra oligactis. *Wilhelm Roux' Archiv fur Entwicklungsmechanik* 1929; **115:** 1–26.
181 Scheremetjewa EA, Brunst VV. Untersuchung des Einflusses von Rontgenstrahlen auf die Regeneration des Schwanzes bei den Kaulquappen von Pelobates fuscus. *Wilhelm Roux' Archiv fur Entwicklungsmechanik* 1933; **130:** 771–791.
182 Brunst VV, Scheremetjewa EA. Untersuchung des Einflusses von Rontgenstrahlen auf die Regeneration der Extremitaten beim Triton. *Wilhelm Roux' Archiv fur Entwicklungsmechanik* 1933; **128:** 181–215.
183 Gordon MB. The stimulative effect of roentgen rays upon the glands of internal secretion. *Endocrinology* 1930; **14:** 411–437.
184 Gordon MB. The stimulative effect of roentgen rays upon the glands of internal secretion. *Radiology* 1931; **17:** 1309–1311.
185 Freund L. Elements of General Radiotherapy (English translation). New York, Rebman Co.: New York, 1904.
186 Borak J. Theories on the effectiveness of roentgen therapy in inflammatory conditions. *Radiology* 1944; **42:** 249–254.
187 Chen W. The laboratory as business: Sir Almroth Wright's vaccine programme and the construction of penicillin. In: The Laboratory Revolution in Medicine. Cunningham, A. and Williams, P. (eds) Cambridge University Press: London, 1992.
188 Heidenhain L, Fried C. Rontgenstrahlen und Entzundung. *Klin. Wchnschr.* 1924; **3:** 1121–1122.
189 Fried C. Die Rontgenbehandlung der akuten Entzundungen. *Strahlentherapie* 1927; **26:** 484–506.
190 Hartley P. Effect of radiation on production of specific antibodies. *Journal of Experimental Pathology* 1924; **5:** 306–313.
191 Hektoen L. Influence of the X-ray on production of antibodies. *Journal of Infectious Diseases* 1915; **17:** 415–422.
192 Hektoen L. Further studies on the effects of roentgen ray on antibody-production. *Journal of Infectious Diseases* 1918; **22:** 28–33.
193 Westman A. Studies on influence of roentgen and radium rays on phagocytosis. *Acta Radiology* 1923; **2:** 57–69.

194 Castellino PG. L'azione dell'irradiazioni roentgen ed ultraviolette sul sistema reticulo, istiocitario cutaneo. *Arch. di radiol.* 1930; **6:** 681–689.
195 Tannenberg J, Bayer L. Der heilungavorgang von entzundlichen Veranderungen unter dem Einfluss von Rontgenstrahlen. *Strahlentherapie* 1933; **47:** 408–425.
196 Pendergrass EP, Hodes PJ. Roentgen irradiation in the treatment of inflammations. *American Journal of Roentgenology and Radium Therapy* 1941; **45:** 74–106.
197 Desjardins AU. Radiotherapy for inflammatory conditions. *Journal of the American Medical Association* 1931; **98:** 401–408.
198 Desjardins AU. The action of roentgen rays or radium on inflammatory processes. *Radiology* 1937; **29:** 436–445.
199 Desjardins AU. Dosage and method of roentgen therapy for inflammatory conditions. *Radiology* 1939; **32:** 699–707.
200 Desjardins AU. Radiotherapy for inflammatory conditions. *New England Journal of Medicine* 1939a; **221:** 801–809.
201 Desjardins AU. The action of roentgen rays on inflammatory conditions. *Radiology* 1942; **38:** 274–280.
202 Heidenhain L. Rontgenbestrahlung und Entzundung. *Strahlentherapie* 1926; **24:** 37–51.
203 Musser JH, Edsall DL. A study of metabolism in leukemia, under the influence of the X-ray. *Transactions of the Association of American Physicians* 1905; **20:** 294–323.
204 Edsall DL, Pemberton R. The use of X-rays in unresolved pneumonia. *American Journal of Medical Science* 1907; **133:** 286–297.
205 Quimby AJ, Quimby WA. Unresolved pneumonia: Successful treatment by roentgen ray. *New York Medical Journal* 1916; **103:** 681–683.
206 Mayou MS. A case of trachoma treated by X-rays. *Transactions of the Ophthamology Society of the United Kingdom* 1902; **22:** 95–95.
207 Mayou MS. The treatment of trachoma by X-rays. *Transactions of the Ophthamology Society of the United Kingdom* 1903; **23:** 10–23.
208 Coyle RR. Odds and ends of X-ray work, including some cases of carbuncle. *M. Electrol. and Radiology* 1906; **7:** 139–142.
209 Dunham K. Treatment of carbuncles by the roentgen ray. *American Journal of Roentgenology* 1916; **3:** 259–260.
210 Ross GG. X-ray treatment of carbuncle of face. *Annals of Surgery* 1917; **66:** 99–100.
211 Richards CE. Some of the less common uses of X-ray therapy. *Journal of Radiology* 1922; **3:** 271–273.
212 Lewis RW. A conservative treatment of carbuncles. *Annals of Surgery* 1923; **78:** 649–659.
213 Hodges FM. The roentgen ray in the treatment of carbuncles and other infections. *American Journal of Roentgenology* 1924; **11:** 442–445.
214 Hodges FM. Roentgen ray in treatment of local inflammations. Cellulitis and carbuncles. *Journal of the American Medical Association* 1925; **85:** 1292–1294.
215 Pordes F. Uber die Natur der Wirkung der Rontgenstrahlen, speziell uber das Verschwinden von Anurie nach Nierenbestrahlung. *Wien. Klin. Wchnschr.* 1923; **36:** 656–637.
216 Pordes F. Der Mechanismus der Rontgenwirkung: Ein Erklarungsversuch. *Fortschritte auf dem Gebiete Roentgenstrahlen* 1923–1924; **31:** 287–297.
217 Pordes F. Ueber Rontgenbehandlung entzundlicher Erkrankungen: Allgemeines und Spezielles. *Strahlentherapie* 1926; **24:** 73–86.
218 Pordes F. Die Verlaufsanderung akuter Entzundungen nach Rontgenbestrahklung. *Strahlentherapie* 1929; **33:** 147–151.
219 Holzknecht G. Roentgen treatment of spontaneous post-traumatic and postoperative coccus infections and suppurations. *American Journal of Roentgenology* 1926; **15:** 332–336.
220 Gerber I. Roentgen-ray treatment of superficial pyogenic infectioms. *Rhode Island Medical Journal* 1926; **9:** 33–38.
221 Fraenkel SR, Nissnjewitsch LM. Ueber die Rontgenbehandlung der chirirgischen entzundlichen Vorgange. *Strahlentherapie* 1926; **24:** 87–100.
222 Solomon S, Blondeau A. La roentgentherapie dans les affections inflammatoires. *J. de radiol. et d'electrol.* 1927; **11:** 465–469.
223 Carp L. Treatment of carbuncles. *Annals of Surgery* 1927; **86:** 702–706.
224 Light RU, Sosman MC. Treatment of carbuncles by the roentgen ray. *New England Journal of Medicine* 1930; **203:** 549–555.
225 King CO. Radiation therapy of carbuncles. *Southern Medical Journal* 1937; **30:** 903–906.
226 Krost GN. Unresolved pneumonia in choldren; treatment with roentgen ray. *American Journal of Diseases of Children* 1925; **30:** 57–71.
227 Torrey RG. Roentgentherapy in disorders of the respiratory tract, particularly those associated with enlargement or persistence of the thymus gland, and those associated with unresolved pneumonic exudates. *S. Clin. N. America* 1927; **7:** 221–235.
228 Heidenhain L. UeberKopfverletzungen durch stumpfe Gewalteinwirkung. *Munchen. Med. Wchnschr.* 1917; **64:** 600–602.
229 Kaess FW. Rontgenbestrahlung bei postoperativer Pneumonie. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* 1925; **38:** 509–515.
230 Fried C. Rontgentherapie der post-operative Pneumonie. *Klin. Wchnschr.* 1926; **5:** 15–18.
231 Gadjanski B. Ueber die Radiotherapie der akuten Entzundungen. *Serb. Arch. f. d. ges. Med.* 1927; **4:** 191.
232 Glas K. Rontgenbehandlung von Lungenstorungen nach Operationen. *Wien. klin. Wehnschr.* 1927; **40:** 1054–1055.
233 Holtz L. Ueber die Behandlung der Pneumonie mit Rontgenstrahlen. *Ztschr. f. klin. Med.* 1929; **109:** 698–713.
234 Merritt EA, McPeak EM. Roentgen irradiation in unresolved pneumonia. *American Journal of Roentgenology* 1930; **23:** 45–48.
235 McIntire FT, Smith JH. X-ray therapy in treatment of pneumonia. *Texas State Journal of Medicine* 1937; **33:** 422–426.
236 Powell EV. Roentgen therapy of lobar pneumonia. *Journal of the American Medical Association* 1938; **110:** 19–22.
237 Powell EV. Treatment if acute pneumonias with roentgen rays. *American Journal of Roentgenology and Radium Therapy* 1939; **41:** 404–414.

238 Stephenson S, Walsh D. Short note on the cure of trachoma by X-ray tube exposure and by high-frequency brush discharges. *Lancet* 1903; **1:** 237.
239 Bettremieux. Rayons X en therapeutiqueoculaire. *Clin. Opht.* 1903; **9:** 225–227.
240 Cassidy HF, Rayne FC. Trachome chronique tres ameliore par les rayons X. *Tr. Ann. d'electrobiol.* 1903; **6:** 617–619.
241 Geyser AC. The successful treatment of eighteen cases of granular lids by the X-ray and high-frequency vacuum electrodes. *American Therapist* 1903–1904; **12:** 41–43.
242 Geyser AC. The successful treatment of eighteen cases of granular lids by the X-ray and high-frequency vacuum electrodes. *Journal of Advanced Therapeutics* 1904; **22:** 299–302.
243 Pardo R. Due casi di tracoma trattati coi raggi di Rontgen. *Gazz. d. osp.* 1904; **25:** 459–460.
244 Horniker E, Romanin V. Ueber einen Hulfsapparat zur Behandlung des Trachoms mit Rontgenstrahlen. *Ztschr. f. Augenh.* 1905; **14:** 569–575.
245 Stargardt K. Ueber die Wirkung der Rontgenstrahlen auf Trachomfollikel. *Ztschr. f. Augenh., Ber.* 1905; **14:** 251–258.
246 Thielemann R. Zur Wirkungsweise des Radiumbestrahlung auf die trachomatose Bindehaut. *Ztschr. f. Augenh.* 1905; **14:** 559–569.
247 Newcomet WS. Radium and radioactive salts compared with X-rays. *Journal of Advanced Therapeutics* 1912; **30:** 72–77.
248 Jacqueau, Lemoine, Arcelin. Trachome et radiotherapie. *Lyon Med.* 1920; **139:** 869–870.
249 Rollet M, Bussy D. Conjunctive granuleuse grave: Radiotherapie amelioration. *Lyon med.* 1927; **129:** 458.
250 Cochard M. La radiotherapie du trachome. Thesis 128. Lyons, France, 1921.
251 Meldolesi G, Sabbadini D. Sulla terapia del con le radiazioni secondarie ottenute col metodo del Ghilarducci. *Radiol. med.* 1923; **10:** 222.
252 Meldolesi G. Sulla terapia del tracoma con le radiazioni secondarie (secondo il metodo del Ghilarducci). *Actinoterapia* 1924; **4:** 97–162.
253 Lane LA. Radium in ophthalmology, with special reference to its use in benign affections. *Journal of the American Medical Association* 1924; **83:** 1838–1845.
254 Sabbadini D. Le modificazioni cliniche ed anatomo-pathologiche della conguintiva tracomatosa in seguito all'azione delle radiazioni secondarie. *Arch. di Radio.* 1926; **2:** 584–688.
255 Kelly JF. The X-ray as an aid in treatment of gas gangrene. *Radiology* 1933; **20:** 296–304.
256 Kelly JF. Present status of the x-ray as an aid in treatment of gas gangrene. *Radiology* 1936; **26:** 41–44.
257 Hubeny MJ, McNattin RF. X-ray therapy: Evaluation of its use in treatment of diseases of non-malignant neoplastic nature. *Urol. and Cutan. Rev.* **42:** 436–441.
258 Kelly JF, Dowell DA. Present status of X-rays as aid in treatment of gas gangrene. *J.A.M.A.* 1936; **107:** 1114–1118.
259 Kelly JF, Dowell DA. Twelve-year review of X-ray therapy of gas gangrene. *Radiology* 1941; **37:** 421–439.
260 Altemeier WA, Jones HC. Experimental peritonitis: Its prevention by X-ray irradiation. *Journal of the American Medical Association* 1940; **114:** 27–29.
261 Bates MT. Gas gangrene; review of 32 cases with special reference to the use of serum, both prophylactic and therapeutic. *Annals of Surgery* 1937; **105:** 257–264.
262 Faust JJ. Radiation therapy of gas bacillus infecton. *Illinois Medical Journal* 1934; **66:** 547–551.
263 Faust JJ. Report on x-ray treatments in gas gangrene cases. *Radiology* 1934; **22:** 105–106.
264 Kelly JF, Dowell DA, Russum BC and Colien FE. Practical and experimental aspects of roentgen treatment of *Bacillus welchii* (gas gangrene) and other gas-forming infections. *Radiology* 1938; **31:** 608–619.
265 Kelly JF, Dowell DA. Roentgen Treatment of Infections. The Yearbook Publishers, Chicago, IL. 432 pp. 1942.
266 Dowdy AH, Sewell RL. Roentgen radiation in experimental *Clostridium welchii* ingection (gas gangrene) in dogs: Preliminary report. *Radiology* 1941; **37:** 440–442.
267 Merritt EA, Den AJ, Wilcox UV. The effects of radiation therapy in Clostridium infection in sheep. *Radiology* 1944; **43:** 325–332.
268 Cantril ST, Buschke F. Roentgen therapy in gas bacillus infection. *Radiology* 1944; **43:** 333–345.
269 Glenn Jr JC. Studies on the effects of X-rays of phagocytic indices of healthy rabbits. *J. Immunology* 1946; **52:** 65–69.
270 Glenn Jr JC. Further studies on the influence of X-rays of phagocytic indices of healthy rabbits. *J. Immunology* 1946a; **53:** 95–100.
271 Bloom W, Jacobson LO. Some hematologic effects of irradiation. *Blood* 1948; **3:** 586–592.