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History and heritage

The origins of radiotherapy: Discovery of biological effects of X-rays by Freund in 1897, Kienböck's crucial experiments in 1900, and still it is the dose

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ABSTRACT

The discovery of X-rays by Wilhelm Conrad Röntgen (1845–1923) was triggered by pursuing an anomalous phenomenon: arousal of fluorescence at a distance from tubes in which cathode rays were elicited, a phenomenon which suggested the existence of a new kind of ray other than cathode rays. The discovery of biological effects of these X-rays by Leopold Freund (1868–1943) was triggered by pursuit of the purportedly useless phenomenon of epilation and dermatitis ensuing from X-ray-diagnostic experiments that others had reported. The crucial experiments performed by Robert Kienböck (1871–1953) entailed the proof that X-ray-dose, not electric phenomena, was the active agent of biological effects ensuing when illuminating the skin using Röntgen tubes. For both the discovery of X-rays and the discovery of their biological effectiveness, priority did not matter, but understanding the physical and medico-biological significance of phenomena that others had ignored as a nuisance. Present discussions about the clinical relevance of improving the dose distribution including protons and other charged particles resemble those around 1900 to a certain degree.

Different views have been proposed concerning the priority of applying Röntgen rays for therapeutic purposes [1–5]. Here it will be argued that not priority of an observation or application is the decisive event advancing science or medicine, but discovery and experimental characterisation of an unusual phenomenon. This fully applies in making use of biological effects of X-rays. Radiotherapy in its early days – well before the discovery of effective antibiotic and tuberculostatic treatment – was a treatment modality providing a perspective for numerous diseases of the skin. Its social significance by rendering treatable diseases such as favus, sycosis, lupus vulgaris, and many others, was well recognised by the pioneers [6]. The basic principles of biological actions of X-rays on tissue were clearly not described in the context of cancer treatment, which was initiated as a realistically effective treatment option later, but in dermatology.

Diagnostic implications immediately realised

When Wilhelm Conrad Röntgen discovered a new kind of rays in 1895, he at once also realised the potential of these X-rays in medical diagnostics [7–9]. Within the first days or weeks after 8 November 1895, the day he first realised fluorescence of a barium-platincyanur screen, Röntgen among other experiments showed that holding a hand between a Hittorf- or similar tube and a fluorescing screen or photographic plate made the bones of the hand visible. At the first public demonstration of his discovery at the Physical-Medical Society in Würzburg, Germany, on 23 January 1896, the society's president, the anatomist August Kölliker discussed the likely significance for medical diagnostics of the new rays [7]. Even in the front-page note of 5 January 1896 in the Vienna newspaper "Die Presse" the sensational discovery is denoted as potentially epoch making for both physics and medicine [10]. Thus, practical implications of the discovery of X-rays, which had resulted from serendipity, clearly non-goal-directed scientific curiosity, were immediately recognised.

In order to put the discovery of the biological effects of X-rays in context it is necessary for a moment to reconsider Röntgen's discovery of X-rays motivating the first physics Nobelprize in the history (in 1901). Röntgen was attempting to better understand cathode rays generated in Hittorf or similar tubes. Cathode rays, yielding in turn the fifth Nobelprize in physics in 1905, had been discovered some 20 years before and were among the most investigated physical phenomena towards the end of the 19th century. The triggering observation Röntgen made concerned the hitherto

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unappreciated phenomenon of fluorescence of a barium-platincyanur screen even at a distance from the tube and even behind black non-transparent paper, when cathode-rays were elicited in a Hittorf tube. As experiments with cathode-rays had been performed for more than two decennia by numerous physicists, it is beyond doubt that others had already seen such fluorescence phenomena or darkening of photographic plates before, but abandoned them as anomaly, not worth noticing, let alone pursuing [11,12]. But still, had Röntgen just observed and described fluorescence of barium-platincyanur by producing cathode-rays, he would not have discovered X-rays as a new physical entity. What turned his observation into a discovery was the characterisation of their properties by way of numerous experiments, performed in unbelievably short time – he performed the decisive first series of experiments alone in his laboratory between 8 November and 28 December 1895 – and published in three papers [7–9].

What matters and rendered Röntgen the discoverer of X-rays was thus not the priority of observation or production of X-rays. The discovery consisted in placing the phenomenon in the context of contemporary physical theory – electrodynamics, optics – and therewith noticing its peculiarity. To accomplish this, Röntgen performed the experiments.

Freund's experiments discovering biological effects of X-rays

A newspaper note of unknown provenance and an article by Marcuse describing epilation and dermatitis caused by repeated and extensive fluoroscopy experiments aroused Leopold Freund's attention [13–15]. He was thus evidently not the first who had observed epilation due to X-rays [1–4], just like Röntgen was not the first to observe X-rays. Marcuse had described these phenomena as harmful and unintended side-effects of attempted diagnostic use of X-rays, disregarded them as nuisance and was happy to report the restitution of the effects after some time [13,14]. Freund's patient, a girl with an extensive hairy naevus on the back, had already been demonstrated at the Vienna Medical Club and the Vienna Dermatological Society in May 1896 [16,17]. The first report of the treatment was in the proceedings of the Vienna Dermatological Society of 13 January 1897 [18]. Due to limited physical understanding of the physicians involved, the rays are repeatedly falsely called "cathode-rays or Röntgen rays" in these first reports. In the full paper from 1897, Freund argued convincingly that X-rays and not electric discharge was the active agent causing epilation [19,20]. Set up as an experiment beginning on 24 November 1896, using a 5-year-old girl as "experimental object" (his words), Freund primarily intended to demonstrate that illumination using Röntgen tubes did in fact lead to hair loss, and that X-rays were the active agent and could therefore be used as a new therapeutic modality for diseases involving hair and skin. He experimentally excluded the effect to be due to anode rays that could have been elicited, because Freund had connected the tube wrongly just the day before he observed the first hairs fall out. Secondly, he excluded electric discharge being responsible for the effect by placing an earthed aluminium foil between tube and skin. The illuminations were repeated every day for several hours, and epilation as well as erythema, moist desquamation, and ulceration at last were seen only days, weeks, and months after the experiment. Freund thus concluded that the biological effects of X-rays were cumulative and administration needed to be stopped before the full effect was observed. Whether the epilating effect was secondary to inflammation he deemed rather unlikely, because hair loss occurred before the first signs of dermatitis. The way of action of the rays he suggested to be likely chemical, having to do with the loss of electric charge of objects irradiated with X-rays, as described by Röntgen [8]. Because ions played an important part in chemical reactions, a strong influence of X-rays on chemical reactions might be expected, Freund speculated. This suggested that X-rays could act on deeper layers of the skin, which would however require more research. Freund did not speculate about eventual treatment of internal organs with X-rays.

From an ethical point of view it is questionable why these experiments were performed on a child and not on a haired animal. Evidently, the fear that nothing would happen predominated, any risks were not foreseen by the 28-year-old just graduated doctor. The reason why none of the university professors at the Vienna University Hospital had permitted Freund to use one of the Röntgen tubes at their departments for his experiments was also certainly not their concern regarding eventual risks for the child. Rather, they believed the idea was futile and harmless [21]. The experiments were thus performed outside the University Hospital at the Royal Institute of Photography and Reproduction in Vienna [19].

Doubting the effective agent

Shortly after the publication of his experiments, Freund was invited to discuss his findings at the Chemical-Physical Society in Vienna [6]. There, two eminent physicists Ernst Mach (1838–1916) and Ludwig Boltzmann (1844–1906) started a lively controversy about the agent causing the biological effects. Mach would rather agree with Freund and render X-rays responsible for the effects, while Boltzmann vividly opposed and stated that electric discharge or oscillations, not X-rays, were the only possible agent causing biological phenomena. Freund adopted Boltzmann's view and contrary to his clear – and in hindsight correct – statements in his 1897 paper, came to believe for several years that electric phenomena caused the biological effects following illumination with Röntgen tubes. Even in the first comprehensive book on what he called radiotherapy [22,23], which deals with electrotherapy and light therapy for two thirds and with therapy using Röntgen tubes for one third, he leaves considerable doubt about the active agent of this therapy. Moreover he deleted the reference to the potential use of X-rays for the treatment of cancer of the mucosa in the English translation that had appeared one year after the German edition (pages 236 and 291, respectively [22,23]). Of note, there is no reference in this book to the paper from 1900 by Robert Kienböck describing the crucial experiments proving X-rays as the active agent [24]. Only several years later Freund returned to his own original position from 1897.

Kienböck's crucial experiments

The long, comprehensive, and stringently argued paper by Kienböck was set up to experimentally address the decision between the two then existing camps: those who held X-rays responsible for epilation, dermatitis, and eventually ulceration, and those who believed these phenomena to be due to electric discharge and waves around and originating from Röntgen tubes [24].

Kienböck performed experiments on rabbits to demonstrate that the biological effects decreased with the distance of the skin from the tube: perpendicular under the focus of the tube the reaction was an ulcer, as the distance increased towards the periphery, it became moist desquamation, erythema, and just epilation at the most distant regions. Thus, the effects depended on the dose of the X-rays. The hypothesis that qualitatively different tubes (hard versus soft) would yield the different effects was therewith refuted. To prove that the effective agent was the X-rays originating at the focus of the tube, Kienböck placed lead squares or circles at half the distance between focus and skin: sharp geometrically enlarged projections of the figures were spared from erythema suggesting

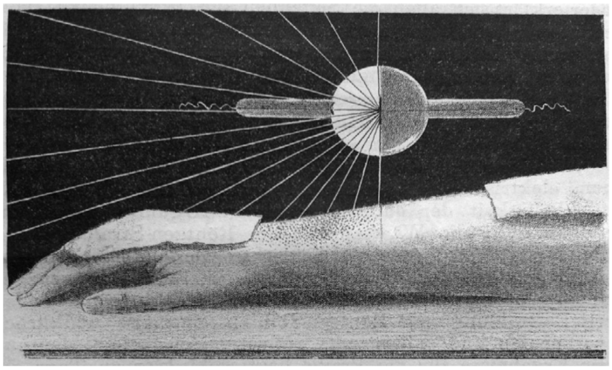

Fig. 1. Crucial experiment performed 1900, proving X-ray dose as the biologically effective agent. Fig. 6 from [24].

rays originating at the tube's focus to be responsible, and not electric discharge, which occurred unfocussed all around the tube. Only non-shielded skin exposed to the part of the tube that had not been covered with lead became erythematous (Fig. 1). This finding could not be explained assuming electric discharge or oscillations as the agent causing the biological reactions after illumination with Röntgen tubes. This was thus a classical crucial experiment to decide between two rivalling theories.

As a conclusion from his experiments Kienböck made clear recommendations on how patients and physicians could avoid skin reactions when X-rays were used for diagnostics, namely to avoid longer than necessary exposition, and to use lead shielding. The most crucial conclusion for radiotherapy with X-rays was that purportedly large inter-individual variations of radiation sensitivity – one individual should need 15, the other 100 sessions to achieve epilation – were rather due to uncontrolled conditions of the tube: uncontrolled electrical voltage, uncontrolled degree of the vacuum, and thus due to changes in dose administered rather than to individually different radiation sensitivity. Kienböck beyond reasonable doubt demonstrated that the dose of X-rays was the biologically effective agent and furthermore drew some thirteen conclusions he called general laws of X-ray effects on the skin [24]. These insights included dose-time-fractionation, the cumulative nature of effects, focus-skin-distance, even acceleration resulting in more pronounced effects, and formed the basis for rational radiation protection as well as for radiotherapy.

Resemblances: discovery of X-rays, biological effects, and the present discussion

The discovery of the biological effects of X-rays by Freund and Kienböck resembled the discovery of X-rays by Röntgen to a high degree: both discoveries were based on their discoverers' paying attention to phenomena that others had disregarded as being anomalies or just disturbing nuisance. In both instances, discovery, not priority mattered: the discoverers were not the first to observe, but the first to understand the respective new phenomena by experimentally characterising them. Röntgen put X-rays in the context of contemporary physics, Freund and Kienböck put the biological effects on skin of X-rays into the context of contemporary medicine. This, not the earliest attempts to irradiate deep-seated tumours with the weak unstable tubes available at the end of the 19th century, was the origin from which radiotherapy evolved as a therapeutic modality. Dose had been established as the crucial agent for biological effects in 1900 [24]. Today's challenge regarding new technologies including protons and other charged particles is how to prove that dose distribution is the crucial agent determining tumour control and toxicity. Trivial as this may sound, discussions comparable with discussions around 1900 are lead today about the clinical significance of optimising the gradient between target and normal tissue dose [25,26].

Conflict of interest

None.

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