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The earliest experiments on radioactivity and bacteria, 1897–1901

Despite its importance, a comprehensive history of the use of radioactive substances for medical purposes, especially in the early years, still has to be written. This research note—based on the original literature in French, Italian, and German—covers the first experiments on the bactericidal effect of radioactive substances from 1897 to 1901, a topic that has rarely been covered in the literature,[e.g., 1; 2:188ff; 3:215; 4:92] and never completely and with correct references to all the original publications.

As is quite well-known, the immediate interest in Henri Becquerel's (1852–1908) discovery of radioactivity in 1896 was much less impressive than the one shown in Wilhelm Conrad Röntgen's (1845–1923) discovery of X-rays a few months earlier.[4:5] As far as medical therapy is concerned, the first attempts with X-rays were made by Victor Despeignes (1866–1937) in Lyon and Leopold Freund (1868–1943) in Vienna already in 1896,[5; 6] whereas the earliest treatments using radioactivity, in the form of radium salts, had to wait until 1901,[7] more than two years after the discovery of radium by Marie Skłodowska-Curie (1867–1934) and Pierre Curie (1859–1906) in Paris.[8]

However, research on one aspect of radioactivity did begin earlier—and earlier than has hitherto been assumed: the possible bactericidal nature of the Becquerel rays. In his 1903 textbook on radiology Freund mentions about 20 studies on the effects of X-rays on bacteria, many from 1896 to 1898,[9:251ff] so it should not be surprising that at least some people at that time also tried to find out whether Becquerel rays might be bactericidal.

1897

On 29 July 1898 Pierre Joseph Teissier (1864–1932), *agrégé* at the faculty of medicine in Paris, reported at a congress on tuberculosis in Paris that he and Pierre-Carl-Édouard Potain (1825–1901), one of the eminent professors at that faculty, had in 1897 studied the effect of certain "fluorescent substances" on tuberculosis bacilli, prompted by Becquerel's comparison of X-rays and uranium rays. They fixed pulverized uranium dioxide and, alternatively, zinc sulfide with gum arabic between sheets of celluloid and of glass, exposed them to sunlight, and put the celluloid side on petri dishes with tb culture in glycerine broth for three hours. Then they injected the bacteria subcutaneously into four guinea pigs, with a further two being injected with a normal tb culture. They also transferred one irradiated culture to a new petri dish. However, three of the guinea pigs died about a month before the control animals, under comparable circumstances; the transferred culture grew normally. The tests were then repeated with an exposure time of four days, with the fluorescent substances being put into sunlight every morning for ten minutes, but again the animals died quite quickly and the transfers were positive. So they came to the conclusion that the uranium radiation and the rays from zinc sulfide had no effect on tuberculosis bacilli.[10]

1898

On 12 July 1898, Giuseppe Pacinotti (born 1855?), professor of medicine at the University of Camerino, and V. Porcelli, physics teacher at the Liceo of Camerino, finished their booklet “Azione microbicida esercitata dai raggi Becquerel su alcuni microrganismi patogeni” (“Microbicidal activity of Becquerel rays on some pathogenic micro-organisms”; 26 pages and a table), which likely was the first monograph on any biological/medical aspect of radioactivity. In the foreword they explain that the idea to study the effect of Becquerel rays on bacterial cultures and the physical aspects were Porcelli’s contribution, the bacteriological research methods and the writing Pacinotti’s.[11:3]

After recapitulating the history of research on the effects of light on bacteria, they also cover the studies of the bactericidal effects of X-ray, including those by Giuseppe Sormani (1844–1924) in Camerino, whom Porcelli had provided with apparatus.[11:5ff]

Beginning in April 1898 Pacinotti and Porcelli used metallic uranium (obtained from the chemical company of Theodor Schuchardt in Görlitz/Germany) in several series of experiments. They first produced small glass “cells”, which could be made airtight and into which they could fill about one cc of either broth or chicken egg albumen stained green with raw coffee beans. Initially, their objects of study were Proteus vulgaris, Staphylococcus pyogenes aureus and Streptococcus pyogenes.

In the first series they put a thin layer of freshly pulverised uranium on the lids of some of the inoculated cells and put them in the sun on the ground of the garden of Pacinotti's Institute of Pathological Anatomy. As a control, they also put cells without uranium into the sun, and further cells into an incubator at 25° to 35°. Yet the bacteria in those cells with uranium and those kept in the incubator developed equally well, nearly as much as those kept in the sun without uranium. Pacinotti and Porcelli reasoned that under the influence of the sunlight the Becquerel rays had somehow taken the direction of least resistance: anywhere, but not into the middle of the bacterial development.[11:12ff]

In their next series in May, they therefore changed the set-up. They now spread the, always freshly pulverised, uranium in a thin layer on a glass plate on a table and put their cells on it. At seven in the morning they began exposing this combination to direct sunlight for three hours, until the temperature on the table reached 39°. Then the cells and the uranium powder were put into the incubator and kept at 35° to 38° for up to 48 hours. The bacteria in these cells did not grow and their protoplasm, when examined under the microscope, had "certainly suffered a profound degeneration". Moreover, Gram staining and dyeing with aniline no longer took effect uniformly, if at all. Those bacteria in the control cells (some kept in the sun without uranium and then transferred to the incubator, some kept in the incubator from the beginning), on the other hand, did proliferate. "Transplanting" the irradiated bacteria to new cells led to the same results. Therefore, they argue, "the Becquerel rays, excited by the action of the sun, have exercised a manifest and rapid microbicidal action".[11:14ff]

Pacinotti and Porcelli then continued their experiments in May and June in a similar way and with similar results with bacilli of typhus, diphtheria, and cholera; Escherichia coli; and Pseudomonas aeruginosa.[11:18ff] In addition, they used a sputum culture from a person infected with tuberculosis, irradiated some samples, and injected them into the peritoneal cavities of several guinea pigs. Those injected with the untreated culture died, the others showed no abnormalities and even gained weight. They also injected some of this sputum culture—in one case irradiated in the usual way in the sun, in the other only exposed to sunlight, both for ten hours, at temperatures of up to 44°—into the anterior chambers of the eyes of two rabbits. After nearly two months the eyes of the rabbit injected with the irradiated culture showed no signs of any tuberculous process, in contrast to the other rabbit, where three or four small nodules could be seen.[11:21ff]

Finally they injected a “quite virulent” culture of Streptococcus pyogenes subcutaneously into both ears of a rabbit and brought one of them into contact with the freshly-made uranium powder, heated beforehand in the sun, on a bed of potassium silicate on a copper plate for three hours. Inflammation and finally a superficial scar developed on the rabbit’s ear not exposed to the uranium powder, whereas the other one only temporarily showed a spot and then an eschar at the injection point.[11:23ff]

Pacinotti and Porcelli concluded that Becquerel rays emitted by freshly pulverised uranium that had been exposed directly to sunlight helped kill bacteria in a humid state quite fast at temperatures of 35° to 44°C, also if contact (of the bacteria) with air and thus “superoxidation” was prevented. In their opinion, the Becquerel rays had most likely degenerated and chemically changed the bacterial protoplasm. They saw their results as encouraging further research on Becquerel rays as a possible means against bacterial development in animal tissues.[11:25]

It should be noted, however, that their finely pulverised “metallic” uranium was black—they once controlled for a possible effect of the black surface by using pulverised carbon[11:21]—and thus likely uranium dioxide which is pyrophoric as a powder. This might provide an explanation for their results, which can hardly be credited to the weak radioactivity of natural uranium. In one somewhat obscure passage Pacinotti and Porcelli write of their interest in getting the Becquerel rays emitted “in large amount, quasi tumultuously”.[11:15] They also mention that the Becquerel rays had to be “provoked” or “excited” by sunlight,[11:15,17] and that the “irradiation power” of the uranium powder would decrease depending on the time it was kept in the sun.[11:19f] It is thus quite possible that what they presumably took for phosphorescence, and the concomitant activity of Becquerel rays, was in fact the ignition of the uranium dioxide when heated by sunlight to temperatures above 40°. The bactericidal effect they observed would then have been due, not to radioactivity, but to the glass cells being heated from below beyond the temperature measured by the thermometer on the table.

Digression: Reporting research, 1898–1899

Pacinotti's and Porcelli's research was reported quickly and internationally. One of the earliest reports appeared in the Italian journal "La Settimana medica dello sperimentale";[12] the Italian "Gazzetta degli ospedali e delle cliniche" repeated it nearly verbatim on 25 September 1898.[13] The latter became the basis for the report which appeared in the "Journal of the American Medical Association" on 26 November 1898,[14] which in turn was reprinted nearly completely in "The Clinical Journal" of 14 December 1898[15] and seems to have served as inspiration for the Austrian journal "Wiener Medizinische Blätter" at the beginning of 1899.[16]

The German "Münchener Medicinische Wochenschrift", on the other hand, referred to "La Settimana medica" in its brief report on 8 November 1898[17], whereas a "medical correspondent" covered Pacinotti's and Porcelli's research for the French "Revue Internationale d'Électrothérapie et de Radiothérapie" in March 1899.[18] The annual review of Italian publications for the German "Centralblatt für allgemeine Pathologie und pathologische Anatomie" on 15 July 1899[19:533] apparently used the report in "La Settimana medica", while the source for the very brief summary of the "[...] curious observation made by Professor G. Pacinotti and Professor von[!] Porcelli [...]" in "The Lancet" on 30 December 1899 cannot be ascertained.[20:1830]

All reports mentioned above (there were more) contained the main claim by Pacinotti and Porcelli that Becquerel rays from pulverised uranium could kill various bacteria within three to twenty-four hours. Most also gave additional details, but only "La Settimana medica"[12] and the "Centralblatt für allgemeine Pathologie"[19:533] actually mentioned the publication details. Some reports praised the researchers for their diligent work;[12–14] others, such as the "Revue Internationale d'Électrothérapie", were only slightly hesitant: "If these experiments were verified, one could use plasters made of phosphorescent substances, at least for skin diseases caused by pyogenic microbes."[18] None was overtly critical. (Even an attempt as late as 1913 to understand these experiments, based on the garbled report by Freund,[9:284] gave Pacinotti and Porcelli the benefit of the doubt and assumed that their uranium sample probably had been "quite radioactive".[1:134])

Yet, many of the reports contained inaccuracies. One of the most wide-spread was, in fact, introduced already by “La Settimana medica”: it gave the temperature range at which the bacteria had been kept by Pacinotti and Porcelli as “55°–44°”,[12] instead of 35°–44°. This misprint was copied by several reports based on “La Settimana medica” or “Gazzetta degli ospedali”, but mostly in the reverse form “44°–55°”, as in the “Journal of the American Medical Association”.[14] (Not all journals, for example the “Münchener Medicinische Wochenschrift”,[17] did state the temperature range. “The Lancet” gave the correct one.[20:1830]) Another mistake, also found in the “Journal of the American Medical Association“ and other reports based on it, was the claim that the uranium powder had been kept “without contact with the air”, instead of the bacteria being kept thus.[14–16] But after the review in “La Settimana medica” few went back to the hard to find original publication—an exception in 1899 was the Italian “Archives Italiennes de Biologie”[21], which provided an accurate report—, so mistakes and misunderstandings could prevail.

1900

Inspired by the report in the “Wiener Medizinische Blätter”[16] (but stating a temperature range of 44°–45°), Leopold Freund, who at the time was carrying out similar experiments with X-rays and various forms of electricity, attempted to ascertain the bactericidal effects of radioactive substances. He used several samples of radium salts, obtained from colleagues in Vienna (including one used by the Curies), enveloped in parchment paper and an aluminium sheet to keep them from getting moist. Putting the samples on cultures of Staphylococcus pyogenes aureus and of Salmonella typhi showed no influence on their subsequent growth in an incubator, whether the exposure took three hours or three days. Another experiment on developed bacteria also ended negatively. Similar negative results were achieved with phosphorescence.[22:630ff] (Freund also referred to these experiments in his textbook in 1903: at that time he quoted the “Wiener Medizinische Blätter” “correctly” with a temperature range of 44°–55°.[9:284])

The German dentist Otto Walkhoff (1860–1943) was also experimenting with, quite potent, radium, on loan from Friedrich Giesel (1852–1927). After discovering the physiological effect of radium on the skin in autumn 1900,[23] he turned to the effect on micro-organisms, working at the Institute of Hygiene of the University of Munich. However, these experiments were stopped by the head of the institute, Paul Buchner (1850–1902), because he considered radium a “fraud and completely unimportant”.[24]

In a notice published on 22 November 1900 in the “Deutsche Medizinische Wochenschrift”, the Munich general practitioner Hermann Strebel (1868–1943) stated that he was, among other things, experimenting on the possible bactericidal effects of Becquerel rays of uranium and radium.[25] (It is quite possible that he had heard a speech by Walkhoff in Munich and/or had read his article on radium in October 1900.[23]) In a lecture in Munich on 17 December 1900 Strebel mentioned that he was now able to show the bactericidal, or at least growth arresting, effect of radium.[26]

1901

In spring 1901 Strebel published a paper in the journal “Fortschritte auf dem Gebiete der Röntgenstrahlen” in which he explained his experiments with radium and Micrococcus prodigiosus (Serratia marcescens). Strebel had received samples of radioactive substances from two professors at the University of Munich, found from tests with photographic plates that radium (originally from the chemical company de Haën near Hanover) was the most potent, and after several false starts got one positive result: a tube containing radium and covered with paraffinated paper was brought upside-down into contact with a flat tin stencil which had been put on paraffinated paper covering a glass block with a Serratia marcescens culture on agar inside. After some time (presumably 48 hours), bacteria had grown heavily in the places that had been covered by the stencil, whereas they had scarcely developed outside its “shadow”. Therefore Strebel expressed the hope that Becquerel rays might help in fighting bacterial infections like lupus vulgaris (cutaneous tuberculosis). He was, however, careful to qualify his result at the end of the note, stressing that “under favourable conditions” Serratia marcescens could be prevented from growing or even be killed with radium, although results might vary with place and time.[27]

Likely after Strebel’s publication, the physicist Emil Aschkinass (1873–1908) and the physician Wilhelm Caspari (1872–1944), respectively *Privatdozent* at Berlin University and *Assistent* at the Agricultural University in Berlin, started their experiments with radioactive material. Testing its effect on tissue respiration of frog muscles (also employing X-rays) yielded only an equivocal result, so they decided to study the effect on bacteria, namely Serratia marcescens. Using a sample of barium radium bromide crystals in a brass capsule with an aluminium cover, on loan from a professor at Berlin Technical University, they undertook a whole battery of tests to find that only those Becquerel rays which were easily absorbed, i.e. α rays, had an effect on the growth of Serratia marcescens. (They did not exclude, however, that in a stronger radioactive sample the β rays might also be effective.) Like Strebel, they don't seem to have used a microscope; in contrast to him, they tried to ascertain that neither "radium emanation" (the not yet identified element radon) nor bromine evaporations were responsible for their results. Moreover, they ran tests to ensure that the radiation had actually affected the bacteria, not the agar, and that the slight fluorescence of the barium radium bromide had not been involved.[28]

Aschkinass and Caspari finally reached the conclusion that their radium sample had certainly damaged Serratia marcescens after a minimum exposure of one hour, presumably by ionisation. However, the bacteria had not been killed completely, as was proved when the irradiated bacteria, inoculated on fresh agar, grew again, if slower and less intensive in colour.[28:617] (A quarter of a century later, Caspari interpreted this as a radiation-induced impairment of the vital functions of the bacteria.[29:376]) While they assumed that longer exposition would kill Serratia marcescens, the hygroscopic nature of their sample made this impossible to test. For the same reason, they could not extend their research to pathogenic bacteria, even though they argued that this might prove useful for the internal therapy of bacterial diseases by letting the body take up radioactive substances.[28:617f]

At a large congress in Hamburg, Aschkinass gave a summary of their results on 26 September 1901. In the following discussion Freund mentioned his experiments in 1900, and Strebel pointed out that he had already published on this topic. Aschkinass then replied that Strebel had had only one positive result, which did not entitle him to his claim of priority.[30:447ff] A similar statement can be found in a footnote in the article by Aschkinass and Caspari, which had been published a week earlier, claiming that they had noticed Strebel's publication only after having written up their experiments, and using some of his own admonitions against him.[28:608] Yet, at another large congress in Karlsbad the following year Strebel again insisted on his priority regarding the effect of radium on bacteria.[31:176]

After 1901

Aschkinass and Caspari can be regarded as the first to have proved convincingly that radium/radioactivity could keep a bacterial culture from growing. Yet much remained obscure, e.g. the role of the β and γ rays, how radioactivity would affect other bacteria, especially pathogenic ones, and whether one could kill developed bacteria by irradiating them. For some reason, probably the difficulty of getting hold of strongly radioactive substances, a rush of publications on such topics started only in 1903 in France, Britain, the United States, and not least in Germany.[e.g., 32–35] By then, however, the destructive power of radium on human tissue also began to be recognized, so in April 1904 even Caspari, who tried to employ the bactericidal effect in therapy by injecting radium salts, began to sound despondent about its likely benefits in that direction.[36:40f] In his 1912 textbook on radium therapy, Siegfried Loewenthal (1869–1951) pithily dismissed radium and radium emanation as bactericides for therapeutical purposes "for the time being" because they were ineffective at low dose and destroying tissue, too, in higher doses.[37:44]

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