The History of Modern Time-Dose Relationships

A. 1895-1900: In the beginning, there were...The Pioneers!

1. In his laboratory in Wurtzburg, Germany, Dr. Roentgen discovers X-rays in 1895

![Dr. Roentgen](image)

Dr. Roentgen and one of his early x-rays...of his wife’s hand.

When shown the ghostly image, she freaked out and never set foot in his lab again.

2. By 1896, French scientist Dr. Becquerel discovers that there also exists a type of radiation capable of exposing photographic film that emanates from naturally-occurring chemical compounds (uranium salts in his case)

![Dr. Becquerel](image)

Dr. Becquerel figuring out what happens when a bottle containing uranium salts is left sitting on top of photographic film.

3. In 1898, fellow Frenchmen Drs. Marie and Pierre Curie were hard at work trying to chemically isolate a novel, naturally-radioactive element, ultimately named radium, from about two tons of pitchblende (coal) dumped on their front lawn
4. By 1900, ionizing radiation was already a big business and in widespread use both for medical imaging and radiation therapy

a) arguably, in terms of radiation’s use as therapy (in the US), the original pioneer was probably Emile Grubbe (1875-1960), a Chicago electrotherapist who irradiated several patients during 1896, although he didn’t publish his results (“reasonable palliation” of extensive skin cancers) until years later

1] morbid factoid: by the time of his death, Grubbe had already had large chunks of his body amputated secondary to tumors and other normal tissue injuries associated with his decades of radiation exposure, especially during the early years when nobody gave much thought to radiation protection
b) using ionizing radiation for imaging was a no-brainer...yet what in the world possessed early practitioners to think it could be used as a toxin for cancer therapy?

ANSWER:

Pierre Curie wows his friends and colleagues with a deliberate demonstration (on himself, no less) of the toxic effects of radium.

c) X-ray machines or radium sources...which was preferred?

1) in those early days, nationalism was such that the Germans developed and marketed X-ray machines, whereas the French continued to extol the virtues of radium; in fact, to this day, it is the French who are best known for their expertise in all-things brachytherapy!

2) internationally however, X-ray machines were generally preferred since they were readily available (NOT the case with radium), relatively convenient to use (also not the case with radium), and capable of high radiation output (definitely not the case with radium)

Early radiotherapy with X-ray “machines” (tubes, actually).

Radium applicators for brachytherapy used by French physicians (friends of the Curies) to eradicate a large angioloma.
B. “The Massive Dose Era”: 1900-1920

1) X-ray tubes with high outputs made it attractive for physicians (and quacks) to treat large numbers of patients with one, or at most a few, large radiation doses

2) the rationale for using very large, single doses was to wipe out the tumor while marginally avoiding sterilization of the surrounding normal tissues, emphasis on “marginally”

"...It is also reasonable to assume that recovery from radiation injury depends on cellular metabolism, and further that a rapidly growing tumour cell is better able to effect recovery than a connective tissue cell with its comparatively slow metabolism. Therefore, the difference in response will favor the tumour if the cancricidal dose is not delivered in the first treatment...."

>Dr. Wintz of Erlangen, Germany, massive dose proponent

(a) unfortunately, not only did normal tissues get sterilized anyway (with resulting horrible complications)...

(but frankly, the rate of local tumor control wasn’t all that good either

3) meanwhile, the French continued to pursue radium therapy, even though treatments took forever to reach comparable “cancricidal” doses, due to the low activity of the sources

(a) despite the inconveniences for both patients and physicians inherent in protracted, multi-session treatments, clinical results were often noticeably better than those obtained after large, single doses

(b) and by 1906, two nascent radiobiologists, Drs. Bergonié and Tribondeau, came up with an idea as to why protracted radiotherapy might prove superior: that rapidly growing, relatively undifferentiated cells—like those found in many tumors—were more sensitive to radiation, and that by spacing out treatments, more of them could be “caught” in sensitive stages than by delivering the total dose all at once

C. The First Fractionation Era: 1920’s / Early 1930’s

1) figuring that the increase in overall treatment time was the critical factor that made radium therapy work better than massive dose, X-ray users started to experiment with fractionation
2) but again, the French were ahead of the game...seminal experiments (in both the lab and the clinic) conducted by Drs. Regaud and Coutard ultimately hammered the last nail into the Massive Dose Era's coffin, such that, by 1930, almost everybody world-wide was giving many, small dose fractions as the standard of care for radiation therapy.

(a) Dr. Claudius Regaud, possibly the field's first "physician-scientist"

1) building on the ideas of his colleagues Drs. Bergonie and Tribondeau, Regaud attempted to develop a model system that he could use to study both tumor and normal tissue responses to either large, single doses, or many small fractions of X-rays.

2) using the testes of a rabbit, and later, a ram, as his model (since the rapid and unlimited proliferation of spermatogenic cells reminded him of the behavior of cells in tumors), Regaud posed the following question: Under what irradiation conditions would it be possible to "cure the tumor" (i.e., render the animal sterile), yet without causing "unacceptable normal tissue complications" (i.e., causing necrosis of the scrotum—ouch!

Answer: The only way to sterilize a rabbit without producing severe injury to the scrotum was to use multiple, small radiation doses spread over at least a couple of weeks.

(b) upon completion of his animal experiments, Regaud briefed his department Chair, Dr. Henri Coutard and colleague Dr. François Baclesse, who immediately started treating head and neck cancer patients with small, daily fractions over several weeks, with spectacularly improved results, including:

1] much better regression of primary tumors
2] much better disease-free survival at five years
3] many fewer normal tissue complications

Coutard almost immediately went out on the international lecture circuit and published widely, such that news traveled very fast about this new way to do X-ray therapy.

(Meanwhile, work continued in France on ways to improve radium therapy as well)
D. The Second Era of Fractionation: 1930's and 1940's

1) once just about everybody agreed that multiple dose fractions over a several week period was the way to go for radiation therapy, lots and lots of clinical papers began to appear in journals...only problem being that everybody had their own way of doing fractionation, and there were no standards whatsoever as to how best to compare and contrast different treatment protocols

(a) one idea that did seem to catch on was to report, if you had the information available, treatment "equivalents", that is, treatment schemes that seemed to match in terms of tumor control or normal tissue complication frequencies (the literature of the time is filled with papers talking about "equivalents")

2) it wasn't until a decade later that somebody got the bright idea to plot these equivalents in graphical form; the resulting graphs are now referred to as ISOEFFECT CURVES, that is, plots of the total dose required for various "equivalents" giving the same level of effect in a particular tissue, as a function of one of the varied treatment parameters (such as overall treatment time, number of fractions, etc.)

(a) the first published isoeffect curves (1944) are credited to Strandqvist (Acta. Radiol. Suppl. 55: 1-300, 1944), a body of work whose influence has been rarely equalled in the annals of radiation therapy

Swedish isoeffect curves for various skin reactions and the cure of skin cancer, plotted as the log of the total dose versus the log of the overall treatment time. All lines were drawn parallel, and have a common slope of 0.33. No actual data points were included at the time.

(b) important implications of Strandqvist's isoeffect curves

1. total dose and overall treatment time are related by a power function (i.e., curves are linear when plotted on a log-log plot)

   \[ \text{Total Dose} = (\text{constant}) \times \text{Overall Time}^{\text{raised to a power}} \]

2. "overall time" includes the influence of both fraction number and overall time (that is, longer treatment times generally meant a larger number of fractions, and vice versa), although, as presented, the relative contributions of each cannot be determined

3. the various isoeffect curves appear parallel, implying that there would be NO therapeutic advantage to using highly fractionated treatment compared to a few, large fractions
(c) Strandqvist's isoeffect curves were widely heralded as the best thing since sliced bread, and were so popular as to still form the basis of isoeffect formulae developed some 25 years later (and beyond!); this was rather ironic considering that the curves had some rather serious limitations:

1. they were based solely on skin reactions (which were dose-limiting at the time) and skin cancer cures, and as such, what to do about late effects and other tumor types remained largely unknown (and "unmodeled")

2. it was already known that these isoeffect curves were kind of "approximate," and that they probably weren't parallel...otherwise, the use of many, small dose fractions would NOT have been found to be superior to a few, large dose fractions

(d) however, these limitations were trumped by the fact that isoeffect analysis was a way to make order out of chaos, not to mention that they were very good at what they were intended for: predicting skin reactions--in fact, they can still be used today, provided the treatment parameters are within the bounds of Strandqvist's original sets of data

A modern-day isoeffect curve for skin tolerance (solid line), with Strandqvist's curve superimposed on top of it (dashed line). Notice the excellent agreement between the two, except at extremes of fraction number/size.


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Skin reaction and squamous cell carcinoma cure isoeffect curves constructed in later years based on clinical data from the 1950's, onward, indicating that isoeffect curves may not be quite as parallel as initially thought by Strandqvist. The slope of the cancer cure curve is 0.22, and that for skin reactions, 0.33.


1) during these years, major technological advances in physics and dosimetry, and the dawning of the modern era of radiobiology provided new avenues of investigation, and new problems, for radiation therapy

(a) innovations in physics included: (finally) a standardized concept of dose, better dosimetric methods, and most significantly, the advent of megavoltage radiotherapy

1. this meant, among other things, that early effects (i.e., skin reactions) were no longer dose limiting, making late effects more the focus of attention

(b) meanwhile, great strides were also being made in radiobiology, that likewise had implications for the practice of radiation therapy, including: better understanding of the effects of radiation on specific tissues and organs; the entire concept of cellular radiosensitivity, and survival curve analysis; the identification of DNA as the critical cellular target for radiation-induced death and mutagenesis; advances in the understanding of the cell cycle and cell cycle kinetics in tissues; the early days of radiosensitizers, radioprotectors and combined modality therapy; and last but by no means least, the “discovery” of sublethal damage recovery

2) likewise significant was the growing body of knowledge about the natural history and clinical response of different cancers...meaning that “radiation therapy” was already well on its way to becoming “radiation oncology”

3) Selected Great Moments in the History of Clinically-Oriented Radiation Biology!

(a) sublethal damage recovery as the explanation for the sparing effect of dose fractionation - arguably, (still) the single most important radiobiological contribution to the advancement of the practice of radiation oncology

1. because of this discovery, more emphasis gradually began to be put on survival curves and survival curve shoulders, and doses per fraction and number of fractions, than in previous years

(b) Fowler and Stern’s Pig Skin Experiments (Br. J. Radiol. 36: 163-173, 1963 — recommended reading!)

1. Fowler and Stern set out to answer the vexing question: How much of Strnadqvist’s isoeffect curve slope (0.33) was due to the fraction number, and how much was due to the overall treatment time?

2. their first experiment was to determine isoeffective fractionation schemes in terms of producing moist desquamation on the flanks of pigs; the authors found that the following were “equivalents”:

| A single dose of 20 Gy (1 x 20 Gy) | 30 Gy given as 5 fractions over 5 days (5 x 6 Gy) | 50 Gy given as 20 fractions over 28 days (20 x 2.5 Gy) |
3. the second, decisive experiment asked: What total dose, given as 5 fractions, but over 28 days, gave the same degree of moist desquamation?

a] reasoning: if the answer turned out to be about 30 Gy, that would imply that the fraction number (5) was more important in determining the isoeffect; if the answer turned out to be closer to 50 Gy, that would mean that the overall treatment time (28 days) was more important

b] The Result? 35 Gy, leading to the conclusion that fraction number contributed more to the shape of the isoeffect curve for moist desquamation than overall treatment time...by a factor of approximately two, in fact

(c) Ellis' NSD Concept (Clin. Radiol. 20: 1-7, 1969)

1. the results of Fowler and Stern's pig skin experiments were not lost on a clinical colleague of theirs named Frank Ellis, who had had a long-standing interest in isoeffect curves and isoeffect curve theories dating back to the 1930's (more than a decade before Strandqvist); armed with this new information on the relative contributions of fraction number and overall treatment time, Dr. Ellis developed a new "refinement" of Strandqvist's ideas, which he called the Nominal Standard Dose (NSD) model

2. the NSD equation related the total dose (D), the number of fractions (N) and the overall treatment time (T) in the form of a power function (not unlike Strandqvist's isoeffect curves):

\[ D = (NSD) N^{0.24} T^{-0.11} \]

2:1 ratio as per the pig skin experiments and Strandqvist's common isoeffect curve slope of 0.33

...where NSD is a proportionality constant related to normal tissue tolerance; it is expressed in units called "reths" or "radiation equivalents for therapy"

a] naively, the NSD value can be thought of as the single dose equivalent to produce normal tissue tolerance (emphasis on "naively")

3. important assumptions inherent to the NSD model

a] the equation was based on Strandqvist's and Cohen's isoeffect curves, as well as the data from Fowler's pig skin studies; as such the NSD model is only applicable over the range of fraction numbers (4-30) and overall treatment times (up to about 50 days) used in the studies upon which it was based

Ellis spelled this out explicitly, lest anyone misuse the model. But guess what? They did anyway!
4. The NSD model revolutionized radiation oncology...and had a good 15-20 year run of popularity thereafter

a) Important innovations of the NSD model:

(1) It provided a way of calculating isoeffective treatments in terms of normal tissue tolerance

(2) Allowed the pooling of data from many different individuals/institutions provided all treatment protocols were deemed isoeffective according to the NSD model; this was a boon to multi-institutional clinical trials

(3) And perhaps of greatest importance: the NSD model allowed a particular prescription to be "recalculated" in the event of an unexpected treatment interruption, a common scenario

b) However, perhaps the major drawback of the NSD model was its mathematical complexity (this was the era of the slide rule after all!), and calculation errors were common

(d) Orton and Ellis' TDF Concept ("Time-Dose-Factor" or "Time-Dose-Fractionation Factor") - Br. J. Radiol. 46: 529-537, 1973

1. In response to the difficulties with the NSD calculations, Ellis' graduate student Colin Orton published a "simplification" of the NSD equation that he called the TDF Concept (at almost the same time, a nearly identical model called CRE ["Cumulative Radiation Effect"] was published by James Kirk in the UK)

2. Without belaboring the point, the TDF equation represents a rearrangement of the NSD equation in such a way that all the power terms cancel out, and what's left are "partial tolerances", whole number terms that can be added or subtracted

a) In other words, all combinations of fraction size and number that have the same TDF value are considered isoeffective, and one schedule with a TDF = 100, would be equivalent to two different schedules each having a TDF = 50

<table>
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<tr>
<th>Time, Dose, and Fractionation Factors for Five Fractions Per Week</th>
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<td><strong>Dose/Fraction (rdm)</strong></td>
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**Isoeffective Treatments:**

- 30 fractions of 2.0 Gy
- 26 fractions of 2.2 Gy
- 20 fractions of 2.6 Gy

...all give TDF = 99
Another common scenario: A patient is planned for 30 fractions of 2.0 Gy given once per day, 5 days per week (overall time of 40 days), corresponding to a TDF of 99. After 20 fractions, the patient announces that, due to family obligations, she will be unable to continue treatment for an additional 2 weeks, but wonders whether there might be a way to finish up her treatment in one week instead.

Solution:

After 20 fractions of 2.0 Gy, TDF = 66.

Therefore, any new treatment that adds up to a TDF ~ 33 (and can be completed in one week) could be substituted, such as:

5 fractions of 3.2 Gy, TDF = 34 (close enough!)

And an even more common scenario: Same original treatment prescription as above (30 x 2.0 Gy, TDF = 99), however in this case, the patient likewise receives the first 20 fractions, but then goes off on a bender and disappears for the next 2 weeks. Assuming the patient does return to continue treatment thereafter, what do you do to get back to the originally-intended TDF = 99?

Solution:

After 20 fractions of 2.0 Gy, TDF = 66 (and elapsed time of about 25 days into treatment)

Apply a split-course decay correction of 0.95 (see table below) to account for the 2 week interruption, so TDF = 66 x (0.95) = 63

Come up with a new fractionation schedule that has a TDF = 99 - 63 = 36, such as:

14 fractions of 1.7 Gy, TDF = 36
10 fractions of 2.1 Gy, TDF = 36
8 fractions of 2.5 Gy, TDF = 37 (close enough!)

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Normal Tissue Tolerance in Radiation Oncology: What goes around, comes around!

Courtesy of Dr. Albert van der Kogel
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