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EARLY FRACTIONATION METHODS AND THE ORIGINS OF THE NSD CONCEPT

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Abstract

The concept of the time factor in radiotherapy originated in the controversy surrounding single-dose and fractionated treatments during the first 20 years of this century. The success of Coutard's fractionated treatments of larynx tumors was an important factor in the abandonment of single-dose treatments. There was considerable research afterwards into the influence of dose rate and overall time of treatment on the responses of normal tissues. Recovery was modeled in terms of the Schwarzschild law of photochemistry, as exemplified by the analysis of Strandqvist in log dose–log time coordinates. Different conventions were followed in defining the time for a single-dose treatment. Subsequently the concept arose that the slopes of isoeffect lines relating dose and treatment time for normal tissues and tumors were different and moreover that the effects of fraction number and overall time could be separated; these developments constituted the foundation of the Ellis NSD model. It had an important influence on clinical practice and was reasonably successful in predicting isoeffective regimens for acute effects. It failed to predict severe late effects after large dose fractions. The dissociation between acute and late effects with altered fractionation led to recognition of the importance of the ratio α/β in characterizing the fractionation sensitivity of tissues.

Key words: Therapeutic radiology; fractionation methods, NSD concept, historical review.

The purpose of this paper is to outline the evolution of fractionation practices in the early years of radiotherapy, from which interest in the time factor arose, and to show how this led ultimately to the NSD concept. Attention will be directed toward the early evolution of fractionation practice, from multiple daily doses in the beginning, then treatment with single doses or a few fractions, and back again to treatment with multiple fractions in the 1920's and 1930's. The factors that influenced STRANDQVIST's (1944) monograph are outlined, with emphasis on the significance of the definition of treatment time and how this varied among the different authors. It was concluded that there was a difference in the time factors for normal tissues and tumors. The NSD model arose when this difference was made the basis for the separation of the time and fractionation factors.

Some of the discussion has been extracted from our recent book (THAMES & HENDRY 1987). The presentation is necessarily brief; readers interested in more detail can find it in the following sources. For the early Austrian period we recommend WEISS (1966), WYKLICKY (1980), WICHTL (1986), and GLASSER's (1959) biography of Röntgen. MIESCHER (1930) and SHINZ (1930, 1937) gave an account of the status of single-dose vs. fractionated treatments. The early years of the Radiumhemmet at Stockholm were described by FORSSELL et al. (1939). The history of radiology in England is the subject of a recent book by BURROWS (1986). The development of the Curie Institute in Paris may be followed through the lives of its famous members (DEL REGATO 1987, and references therein).

Evolution of fractionation practice through the 1940's

Fractionated vs. single-dose treatment (1896–1920's). X-ray therapy was first used for treatment of the hairy nevus by the Viennese dermatologist Leopold FREUND (1868–1943). His technique was to treat daily at the very low dose rate available from the x-ray tubes of that time, until the desired effect had been achieved. This required 2 or more weeks overall time, and thus the first radiotherapy treatments were given in daily fractions, at low dose rate (FREUND 1897a, b; 1937). Priority in the first treatments with x-rays has been claimed for others, notably

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E. H. GRUBBE, V. DESPEIGNES, F. H. WILLIAMS, and G. VOIGT. For the most part, however, these were one-of-a-kind attempts with little or no rationale and no subsequent follow-up.

Freund believed that x-rays were the active agent in epilation, but many thought the electric field generated by the tubes was more likely to be biologically active, including the physicist Ludwig BOLTZMANN. However, Freund himself came to doubt his original interpretation, and was only convinced (but slowly) by the later definitive experiments of Robert KIENBÖCK (1900a, b; 1901).

The first cures of skin cancer were reported by the Swedish physicians STENBECK (1900) and SJÖGREN (1901), who used a treatment technique similar to Freund's. In all of this the dose was undetermined, and treatment was guided by day-to-day observation of patient response, that is to say biologically. X-ray tubes of that time, however, were plagued by low (and often variable) output, and when technical improvements led to increased dose rates the advantage of following patient reactions was lost. The need for physical specification of the dose was first met by chemical dosimeters, e.g. Guido HOLZKNECHT's (1902) chromoradiometer; a mixture of salts changed from yellow to green when exposed to x-rays. This change, in proportion to dose, was compared to a colorimetric scale demarcated in Holzknecht (H) units, a dose in the neighborhood of 1 Gy. The ionization chamber was proposed as a dosimeter a few years later by the French physicist VILLARD (1908) but it was ignored subsequently. After modifications by other workers it was eventually adopted as the preferred dosimeter at the time of adoption of the standard unit of exposure, the 'Röntgen', at the first International Radiology Congress in Stockholm in 1928.

The higher dose rates available to therapists, together with quantitative means of assessing dosage now led to treatments in one or a few sessions. This change resulted in the loss of the advantage of following patient reactions daily. It was prompted by the fear that a fractionated dose might cause tissue injury because of the hypothesized 'cumulation' of radiation damage. PERTHES (1904) recommended treatment in one session or at most a few fractions, with close monitoring of the dose. This method, called the *expedited* or *massive-dose* treatment, led to toxic reactions of unexpected severity. There followed a growing awareness of the *time factor*—the influence of the time during which a dose was delivered on its biological effect. The first clinical demonstration of the diminished effect of a fractionated dose was published in the influential book by KRÖNIG &FRIEDRICH (1918). An early interpretation of the time factor involved the 'radioimmunization' of normal tissues and tumors (REGAUD 1921).

It was increasingly appreciated that cells in a state of growth, division, and reproduction were more radiosensitive than those in a resting state; this difference began to influence treatment in some centers. In Paris, REGAUD and colleagues extended the time of application of radium in the treatment of uterine carcinoma to one week; they were mindful of the law of BERGIONIÉ & TRIBONDEAU (e.g. REGAUD & FERROUX 1922) and possibly also of the work of the Austrians. In Vienna in December 1914, SCHWARZ (1914a, b) had published some critical observations just after the outbreak of World War I which prevented their dissemination outside of Germany and Austria: a mediastinal tumor that had been unsuccessfully irradiated with the single-dose method quickly responded months later to small doses given daily. He concluded: 'In the same tumor there will be cells more radiosensitive than others, depending on the phase of the division cycle. Therefore it is not recommended to use one, or a few large doses separated by long intervals, since the most advantageous time for irradiation may be missed entirely or occur during one of the intervals. Instead we recommend a method of small daily doses'.

The view favoring single-dose treatment, which was the more influential one until the 1920's, is illustrated by the arguments of WINTZ (1937): 'The cells of the human body are endowed with variable radiosensitivity and capacity for recovery from radiation damage. It is also reasonable to assume that recovery from radiation injury depends on cellular metabolism, and further that a rapidly growing tumor cell is better able to effect recovery from injury than a connective tissue cell with its comparatively slow metabolism. Therefore the difference in response will favor the tumor if the cancericidal dose is not applied in the first treatment'. Wintz was a leader of the *Erlangen school,* where it was believed that fractionated treatment was decisively inferior, to be judged as 'primitive method' and 'weak irradiation'.

The lives of the Austrian pioneers in radiology were marked by misfortune and exile (WEISS 1966). Kienböck suffered a fracture of the base of the skull in 1910, but after recovering was able to continue working until a partial paralysis forced him to stop. Over the years, Holzknecht suffered radiation burns on his arms and hands, which resulted in a series of amputations; he continued working, however, until his death in 1931. Freund achieved late recognition for his accomplishments, when invited to be a founding member of the Austrian Radiological Society (1934) and keynote speaker at its first meeting (1936). Two years later he was obliged to emigrate after the Anschluss and died impoverished abroad in 1943.

Early Radiobiological Research. Biological research in the first decade of the twentieth century emphasized the preeminent role of proliferative activity in the sensitivity of cells to radiation-induced injury and provided one of the rationales (among many others) for the eventual abandonment of single-dose treatments. Kienböck (1901) published the first observations concerning the higher radiosensitivity of cell populations with higher proportions of mitotic figures, and commented that organs in which active cell proliferation occurred were especially sensitive

to the effects of radiation. ALBERS-SCHÖNBERG (1903) showed that radiation could induce azoospermia after irradiation of the testicles. BERGONIÉ & TRIBONDEAU (1906) used the same system to develop their law of the proportionality of radiosensitivity to the reproductive activity of cells, a law that influenced Regaud and his colleagues in Paris.

A more precise linkage of radiosensitivity to degree of proliferative activity was made possible by demonstrations of concomitant changes in both, in the same biological systems. BENJAMIN et al. (1906) showed that intensive irradiation of the circulating blood of the rabbit did not produce aleukia, whereas exposure of the sites of production of leukocytes did. SCHWARZ (1909) showed that different degrees of sensitivity were manifest depending on the degree of proliferation in the same biological system: dry beans vs. sprouting beans. In his studies of the sensitivity of skin exposed to radiation during partial hypoxia, achieved by applying a tourniquet, he found a decreased sensitivity, which he attributed to lowered mitotic activity.

Biological evidence accrued for the superiority of fractionated treatments. The increased probability of irradiating cells in a sensitive phase with fractionated doses was confirmed by studies of the sterilization of testicles in the grasshopper (MOHR 1919) and ram (REGAUD & FERROUX 1927). Regaud and Ferroux demonstrated experimentally that more damage was done to the seminiferous epithelium when the same dose was given in 4 fractions rather than in one. On the other hand, there was less damage to the skin in the 4-fraction treatment. They concluded that cells in different physiologic states differed in their mitotic activity and in their response to fractionated radiation. On grounds that cell multiplication in the testis could serve as a model for tumors, a therapeutic benefit was proposed for fractionated treatments.

The saturation method. An interesting variation in fractionation technique, the saturation method, was used in the 1920's and 1930's. It was based on what was perhaps the first mathematical isoeffect model (KINGERY 1920; HOFFMAN & REINHARD 1934). Radiation injury was considered to arise from an accumulation of toxic products, with recovery the result of their removal. It was further assumed that the rate of loss would follow the same first-order (exponential) kinetics as had been observed in chemical and biochemical reactions. Working with low voltage, unfiltered roentgen rays Kingery found that a full dose could be repeated after 14 days, 75% of a full dose after 7 days, and 50% after 3.5 days. The idea behind saturation was that tissues could be kept near the tolerance limit by giving a certain fraction of the first dose each day. The saturation method was put into clinical practice, e.g. by PFAHLER (1927) and HOLFELDER (1930), but was abandoned in the 1930's because of toxic side effects and the increasing popularity of Coutard's method (see below).

The Stockholm technique. The Regaud method of protraction of radium treatment of uterine carcinoma contrasts with the early Stockholm technique, begun in the early 1900's by Gösta FORSSELL (treatment in two or three sessions). This technique, first described by Forssell in an address to the Swedish Medical Association in 1912 (B. FRANKENDAL 1986, personal communication), involved 3 insertions with intrauterine and vaginal radium. The intervals between the applications were 1 and 3 weeks respectively. Beginning in 1914 James HEYMAN began his collaboration with Forssell. Owing to an increasing patient load, Heyman in 1930 concentrated treatment to 2 applications with an interval of 3 weeks, and obtained results equivalent to those obtained with the old technique.

The Stockholm technique was used at the Radiumhemmet, at the Finsen Institute in Copenhagen, and elsewhere in Scandinavia. The most important result of its use was that for a long time in Sweden cervical cancer was treated by radiotherapy alone.

Regaud and Coutard. The controversy about which method of treatment, concentrated or fractionated, was best continued into the 1920's, each with biological justifications based on an improved therapeutic ratio: In favor of concentrated treatment, the supposition that recovery from injury was more efficient in rapidly growing tumor cells, and in favor of fractionated treatment, that the chance of irradiating cells in the more radiosensitive mitotic phase was higher. This was the situation when Coutard began his celebrated treatment of head-and-neck tumors with fractionated, low-dose-rate Röntgen therapy in 1919, the year of the founding of the Curie Institute in Paris.

Coutard's methods were designed to mimic the radium technique of Regaud, which had led to improved results in the treatment of uterine carcinoma: first, by giving treatment over an extended time and with correspondingly elevated doses, and second, by daily or twice-daily exposures at a low dose rate. Both Regaud (Paris) and Forssell (Stockholm) had used radium not only in the treatment of uterine carcinoma but also in the treatment of carcinoma of the tonsils, oral cavity, tongue, and lips, using applicators and teleradium (E. BERVEN, report at the congress of the German Röntgen Society, Vienna 1929). Coutard circumvented the technical difficulties of using radium to treat these head-and-neck tumors with external beam röntgen therapy, but maintained similar dosing conditions, i.e. treatment with 1 or 2 low-dose-rate fractions per day, extended over at least 2 weeks, and longer for the larger tumors. In this way he established the first treatment technique capable of lasting cures of deep-seated tumors, particularly of the larynx and tonsil.

As a guideline in his treatments, Coutard aimed for the skin reactions described by REGAUD (1927): 'Radioepidermitis', a very intense but fully repairable skin reaction (moist desquamation). He also aimed for a high-grade mucosal reaction (COUTARD 1929). Coutard's guiding prin-

ciple was that the radiosensitivity of the cancer cells was the same as that of the regenerative cells of the tissue of origin (epithelium).

The swing toward fractionated treatments was also occurring in Zürich (SCHINZ 1930, 1937) and in Vienna, as evidenced by the complaints of FREUND (1927), who noted that Holzknecht, a user of single-dose treatments who had derided his fractionation method for many years, had suddenly switched because of the influence of Schwarz and since that time had been heralded as a pioneer in fractionation. For whatever reason, Holzknecht started a movement in 1921 in Austria against the methods of Seitz and Wintz. According to SCHWARZ (1937), Holzknecht was a gifted clinician to whom such concepts as 'carcinoma dose' and 'sarcoma dose' of Seitz and Wintz seemed too formalistic.

The conversion to fractionated treatments was widespread when Coutard reported his results at the American Congress of Roentgenology (COUTARD 1932). This was occasioned as much by evidence of comparative sparing of late complications as by cures of tumors previously thought incurable. JÜNGLING (1924) had reported a 23% incidence of severe edema and necrosis after the expedited, single-dose treatment of carcinoma of the larynx, as opposed to the low incidence of these complications in Coutard's material.

Simple vs. protracted fractionation. An interesting feature of the adoption of Coutard's technique was that many centers were obliged on economic grounds to discontinue the low-dose-rate in favor of high-dose-rate exposures. An example is provided by BORAK (1937) in his description of the adoption of Coutard's methods at Holzknecht's Institute in Vienna around 1930. Many conditions besides cancer were treated there, and this could not have been continued had they attempted to prolong treatments to 2 hours per sitting at a low-dose-rate. Therefore, Holzknecht decided to accept the fractionation technique, but not the low-dose-rate. This decision was justified by the results of later comparisons. PAPE (1933) showed that the effect of 4-fold increase in dose rate could be set aside by splitting the dose into halves separated by an interval 4 times as long as the exposure time at the lower dose rate. Similarly, MCWHIRTER (1935) of the Holt Radium Institute in Manchester showed that dose rate had no influence on the degree of erythema produced by fractionated treatment. BORAK (1937) found that 4400 R in 200 R (R = Roentgen) fractions caused the same skin reactions whatever the dose rate, i.e. the 1 : 4 change made no diffeence. The latter concluded that the important difference was in size of dose per fraction.

In the beginning Coutard gave large daily doses, especially to the smaller lesions, and it may have been necessary to deliver the large doses at low dose rates for tissue sparing. But this was thought no longer necessary when the daily dose was reduced, and this so-called *simple fractionation* with small fraction sizes was found to give results equivalent to those achieved by Coutard with the *protraction-fractionation* method ('protraction' at that time referred to low dose rate, i.e. protraction from a few minutes to an hour or two per sitting, and is not to be confused with its modern meaning of extended overall time). Indeed, Coutard used large daily doses only on the small tumors, reducing the daily dose and extending the overall time for large field sizes (COUTARD 1932, 1934).

Simple and protracted fractionation are compared with the older single-dose treatment and the 'saturation' method in Fig. 1 (SHINZ 1930). The size of dose per fraction is represented schematically by the height of the bars, which represent individual treatments. The view that simple fractionation was the treatment of choice was shared by BACLESSE, who had arrived at the Curie Institute in the late 1920's: 'We believe that dose rate plays a smaller role than has been maintained in the past. On the basis of our cures we can state that lowering the dose rate, even to values that threaten the functioning of the x-ray unit, in no way guarantees sparing of injury of skin, once a certain dose has been given. The influence of the daily dose is greater'. Beginning in 1928 Baclesse also extended the overall treatment time and developed a technique that avoided the skin and mucosal reactions that had been deliberately kept high with Coutard's method (BACLESSE 1949). The purpose was to spare severe reactions, particularly in old and feeble patients.

Coutard's technique was adopted throughout Europe and North America in the 1930's and 1940's. The low-dose-rate fractionation technique was maintained by SCHINZ & ZUPPINGER in Zürich, although as a mixture of simple fractionation and low-dose-rate fractionation (ZUPPINGER 1941). Simple fractionation (i.e. at high dose rate in each session) was employed in most other places (BORAK 1937); e.g. by CHAOUL in Berlin, MIESCHER in Bern, LENZ & MARTIN in New York, PATERSON in Manchester, and STRANDQVIST in Stockholm.

Paterson. Marked changes in treatment practice were brought about in Manchester by World War II, exemplified by the method of treatment of carcinoma of the cervix using radium. In 1932–33 (Christie Hospital 1939) the treatment was quoted as being an attempt at fusion of what seemed the best features of the two leading techniques of that time—the Paris technique of Regaud and the Stockholm technique of Heyman. The Manchester technique compromised between the two ideas, incorporating as far as practicable the low intensity factor from Paris and the divided but protracted overall period of treatment from Stockholm. In 1934–38 (PATERSON et al. 1945), treatments using radium alone were reduced to 2–3 weeks. If x-ray treatments were added, these were given over a 3-week period, making 5 to 6 weeks total. In 1939, even shorter treatments were introduced because of restrictions on the use of radium in wartime.

Radical small-field x-ray treatments were started in Manchester in 1935, and they increased in frequency,

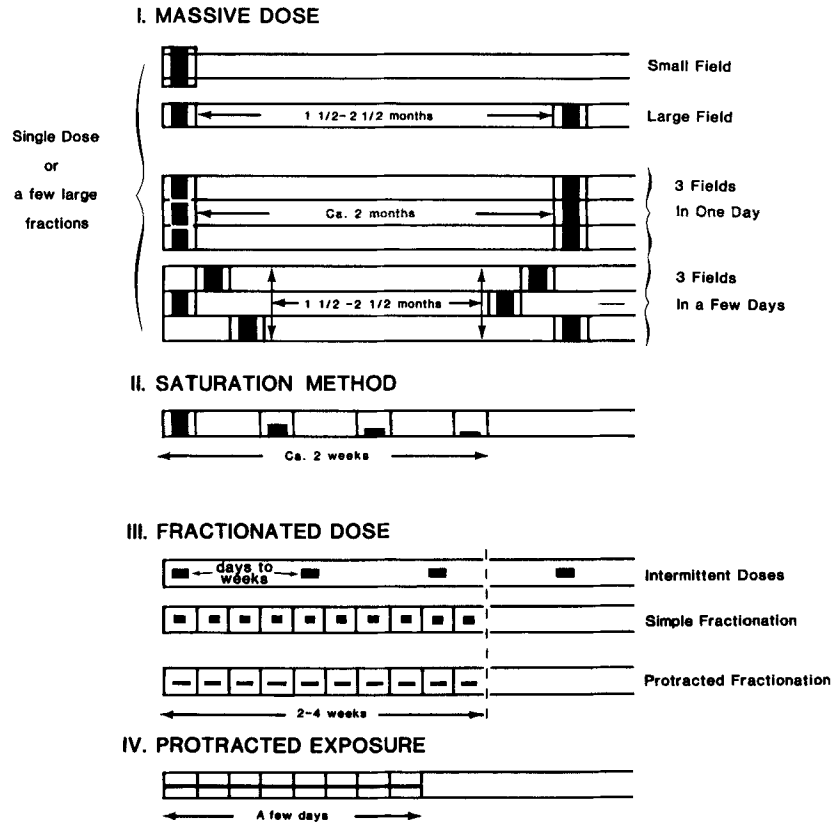

Fig. 1. Schematic representation of fractionation techniques used up to 1930. The relative heights of the bars indicate size of dose per fraction (adapted from Schinz 1930).

particularly during the war years. In most cases treatments were given 5 days a week over 5 weeks, with all fields being treated on each day (24 treatments were quoted for cancers of the posterior third of the oral cavity; 5500 R to 6000 R in 5 to 6 weeks was quoted for radical whole-neck treatments). With cancers of the mouth, 5-week treatments were used until 1944 (PATERSON et al. 1950). Then the pressure on beds and apparatus was so great that 3-week treatments were used, and doses were reduced by 500 R. The success of these treatments, and the increase in the patient load in postwar years, made this the standard schedule for radical treatments and it has remained so to the present day.

Nonstandard fractionation. What are today considered nonstandard fractionation techniques, such as multiple treatments per day, were used in the 1930's, as illustrated by the closing remarks of SCHWARZ (1937) before the first Congress of the Austrian Radiology Society. Based on his observation of recovery in skin after 2-h-fractionation intervals, he was led to the use of *superfractionation* (this may have occurred in the early 1930's depending on the meaning of the words '... seit einiger Zeit ...' spoken in September 1936). Appropriate cases were treated at 4-h intervals 3 times daily with doses per fraction of 70 R or 8-h intervals twice daily with doses per fraction of 100 R. This was not the only instance, as Coutard had often used 2 treatments daily, and ZUPPINGER (1960) reported fewer complications in the treatment of hypopharynx when he used 2 treatments per day 'as recommended originally by Coutard'.

In closing. The Baclesse technique was brought to the USA by his students, primarily Gilbert FLETCHER, and there fractionation practices include treatment in 6–7 weeks and differ from some parts of the UK and the Commonwealth Nations where treatment is usually with fewer, somewhat larger dose fractions in 3 to 5 weeks, as outlined above. However, clinical practice was influenced in both schools beginning in the 1950's by various concepts of the time factor in radiotherapy, the first being those based on power-low models, from STRANDQVIST (1944) to the NSD formula (1967). Much more recently time-factor concepts have been based on survival models (the LQ formalism).

The Time Factor

The importance of the time during which a dose is delivered in determining biological effect was recognized

in the first decade of this century when single-dose treatments began to replace fractionated treatments. In many cases severe complications might have been cases of overdosing, given the primitive techniques of dose measurement at that time. However, it was clear from clinical results that the effect of a dose was diminished by fractionation (KRÖNIG & FRIEDRICH 1918).

Recovery factors and the Schwarzschild law. In the 1920's and 1930's tabulated recovery factors for fractionated irradiation were published, especially those derived for equal daily treatments. Recovery factors multiplied by the biologically effective dose given in a single sitting gave the biologically equivalent dose for treatments given in a specified number of days. Many investigators showed the diminished effectiveness of a dose when it was fractionated (STENSTROM & MATTICK 1926, LIECHTI 1929), but usually with few patients. REISNER (1933) published the first systematic study, using as biological end-point a sharp degree of erythema.

Factors similar to the fractionation factor were derived to take account of the effect of changing the dose rate of single exposures. KRÖNIG & FRIEDRICH (1918) published findings indicative of stronger erythema when the dose rate was changed from 1.3 to 10.4 R/min. MIESCHER (1924) found weaker erythema with both 8- and 15-fold decreases of the dose rate. HOLTHUSEN & BRAUN (1933) found a much stronger dose-rate effect for threshold erythema than did MCWHIRTER (1935) for disappearance of skin tumors.

In any event, from early on many of the researchers (among others, LIECHTI 1929; SCHWARZ 1930; GLOCKER et al. 1931) attempted to link the time factor manifest with changing exposure time in a purely formal way to the Schwarzschild law of photochemistry, which states that the effect of a given exposure of light is proportional to the product of intensity (I) and time (T) raised to the power p, where p is less than 1 (STRANDQVIST 1944, p. 66):

$$I \times T^{p} = \text{Constant}. \quad (1)$$

This formula indicated that when the exposure time is increased, the effect of the light will be the same only if its amount (D = intensity × time) is increased, since the number p lay between 0 and 1 (LIECHTI 1929; GLOCKER et al. 1931). Therefore this relationship corresponds to a diminished effect with decreasing dose rate (I), suggesting some type of 'recovery' in the exposed material.

Eq. (1) can be rewritten in terms of 'dose', i.e. exposure rate × time, as

$$D = \text{Constant} \times T^{1-p} \quad (2)$$

and when logarithms are taken eq. (2) is transformed to

$$\log D = \log \text{Constant} + (1-p) \log T \quad (3)$$

Eq. (3) is a *power-law model* of the dose-rate effect, so called because it relates log isoeffect dose linearly to log exposure time. In the 1930's it was widely believed that power-law models were universally applicable in describing the dose-rate effect (e.g. HOLTHUSEN 1933). Values of p ranged from 0.8 to close to 1.0; there were indications that it increased with increasing dose rate for threshold erythema (HOLTHUSEN & BRAUN 1933), with the implication that the dose-rate effect gradually disappeared.

To summarize, power-law models were introduced because of the analogy between diminished effectiveness of a light exposure when intensity was decreased and diminished biological effectiveness of a radiation dose when dose rate was decreased. These models predicted a linear relationship between log isoeffect dose and log exposure time.

The Strandqvist monograph. Strandqvist's presentation of isoeffect data in double-log coordinates represented a departure from previous practice (WITTE 1942; WACHSMANN 1943), since he defined the abscissa in terms of *number of days after the first treatment*, rather than number of treatments. It is worthwhile to review his reasoning, since the change forced him to assign a time for a single treatment in a somewhat awkward way, and subsequent authors went back to the practice of plotting in terms of number of treatments when they assigned one day to the time for one treatment. This seemingly trivial matter will be seen to have had significant consequences.

STRANDQVIST (1944, p. 70) made an assumption fundamental to his analysis: '... if not completely definitive on the matter, nevertheless published reports suggest that, within certain bounds, radiation effect depends only on the total dose and overall time. If then the fractions are in the main separated by 24 h it is clear that it matters very little if the fractional doses are of variable size, or if somewhat longer intervals occur'. This assumption, in accord with the view of QUIMBY & MACCOMB (1937), was nevertheless inconsistent with evidence pointing toward the importance of size of dose per fraction: REISNER (1933) and HOLTHUSEN (1933) felt that, with the same total dose and overall time, lower reactions accompanied the use of smaller fraction sizes, as did ZUPPINGER (1941).

In addition to the importance this biological assumption had for his thinking, Strandqvist was influenced by the apparent theoretical value of power-law representations. When he analyzed the results of treatment of skin cancer at the Radiumhemmet from 1933 to 1937, in terms of recurrences and complications (skin necroses, not erythema), he found that a parabola could separate these successfully (Fig. 2). While admitting that recovery probably did not follow a simple curve, Strandqvist appealed to arguments justifying empirical approximations of complex phenomena. These rested on the observation that various pharmacological formulas relating dose and effect (Langmuir absorption formula, Weber-Fechner law, Freundlich formula), whose mathematical representations were respectively hyperbolic, exponential, and parabolic, all lay within 5% of each other over a wide range of

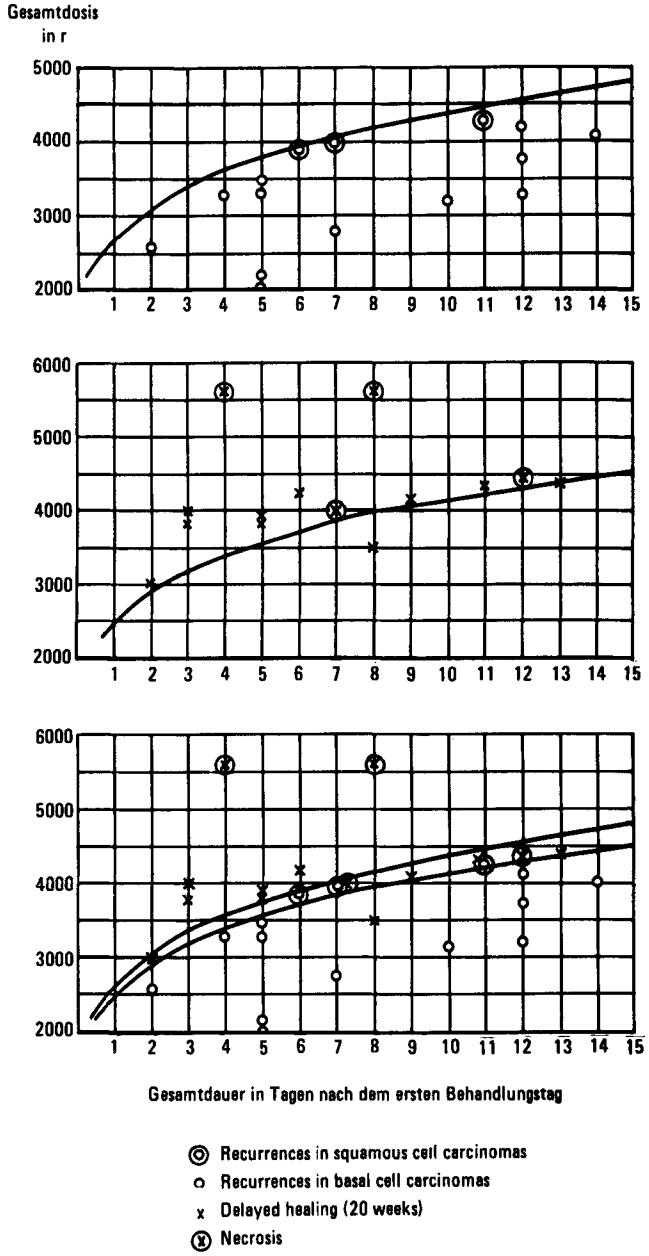

Fig. 2. Recurrences and complications at the Radiumhemmet, 1933–1937 (from Strandqvist (1944) and Fletcher (1980)). Total dose (Gesamtdosis) as a function of overall time in days after the first treatment day for recurrences within 1 year (circles) and complications (x's). (a) Curve lying above recurrences; (b) Curve lying below complications; (c) Boundary zone between the curves of (a) and (b) which separates recurrences and complications with the least possible admixture (reproduced with permission of Lea and Febiger and the author).

concentrations. Strandqvist applied this line of thinking in observing that the diminishing effect of dose with protraction, parabolic in linear-linear coordinates (Fig. 2), became linear in the double-log coordinates introduced by WITTE (1939, 1942). The same was true of the Schwarzschild law of photochemistry eq. (1), which had been applied to describe dose rate effects.

Strandqvist chose 0.35 day as the nominal time for treatments conducted in a single sitting based on the equivalent skin reactions after a single dose of 2250 R and 4200 R in 6 days: the line with slope 0.22 intersected the dose axis at a time 0.35 days. He also presented the following theoretical argument in favor of this choice (p. 225). He noted that, at moderately high dose rates, the overall time was roughly the sum of interfraction intervals. Therefore it was approximately zero for a single dose, and zero could not be placed on a logarithmic scale. But the single dose could be conceptualized as composed of two half doses, given with a pause short enough that negligible recovery took place during it. Strandqvist considered that the evidence favored an interval fulfilling this condition of as long as 8 hours. Therefore, the time for a single dose was taken as 1/3 day, i.e. approximately 0.35 day.

Fig. 3 shows the data for recurrences and complications from 1933 to 1937, as Strandqvist first presented them in double-log coordinates, with elapsed time since first treatment as the abscissa. He found the same slope applicable to both recurrences and necroses (0.22) on the double-log plots. Furthermore, he found that *the slope 0.22 resulted in good agreement with the data of* REISNER *(1933) as well as with those of* MACCOMB *and* QUIMBY *(1936)*. This agreement was surprising since the data of Reisner pertained to strong erythema, and those of MacComb and Quimby to threshold erythema, a reaction whose variability was known to change with its degree. For example, the variability in isoeffect doses was greatest for weak erythema (±40%, MIESCHER 1924; ±30%, HOLTHUSEN 1933). For strong erythema it was less (±15–20%, MIESCHER 1924), and smallest for moist desquamation (STRANDQVIST 1944, p. 47). In WACHSMANN's (1943) analysis, slopes were different for strong and weak erythema.

Also noteworthy is the paucity of data on which the slope was based. The data from the period 1933 to 1937 consisted of 15 recurrences and 14 complications, and *only one patient was treated in a time longer than 14 days*. Of the recurrences, about 25% were squamous cell carcinomas, and the remainder were basal cell carcinomas.

Thus in the 1930's and 1940's the time factor in radiotherapy was conceptualized in terms of the power-law model taken from the Schwarzschild law of photochemistry; quantitation of the time factor was provided by the slope of the isoeffect line relating log dose to log time. We turn next to the ways in which this slope was exploited in the 1950's and 1960's.

The NSD Concept

Normal tissues vs. tumors. COHEN (1949) compared data for normal skin response (single treatment = 1 day)

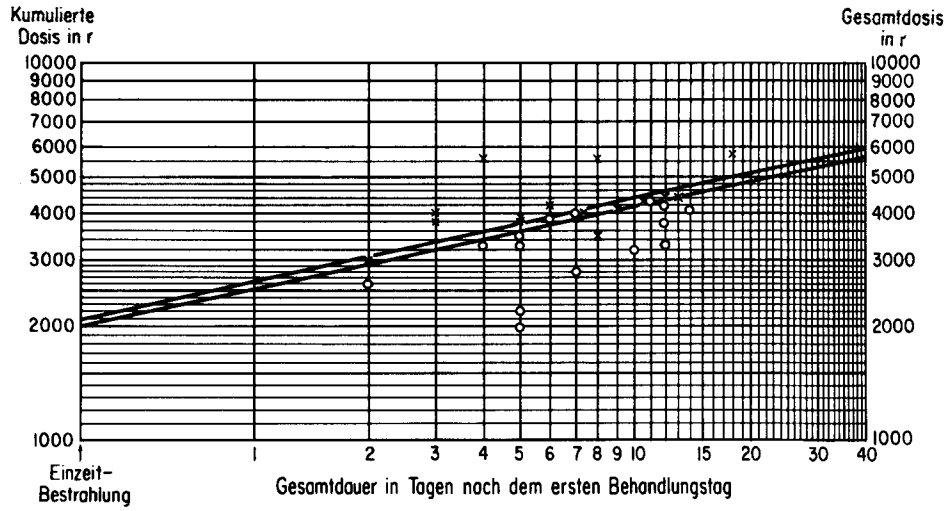

Fig. 3. Total dose in Röntgen units of exposure vs. overall time in days since the first treatment day (from Strandqvist (1944) and Fletcher (1980)). The same data are plotted as in Fig. 2, except that double-log coordinates have been used. Single-dose treatment (Einzeitbestrahlung) was placed at 0.35 days. Recurrences are indicated by circles, and complications by x's (reproduced with permission of Lea and Febiger and the author).

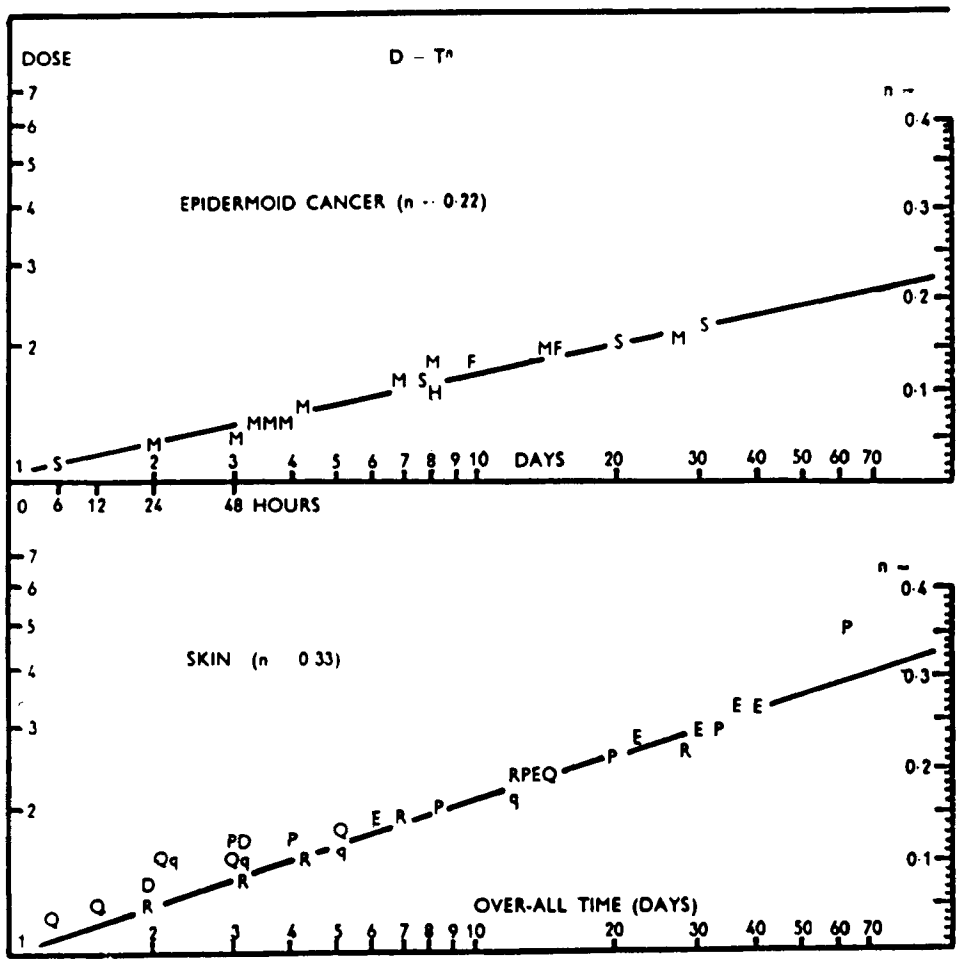

Fig. 4. Determination of the recovery exponent for skin and skin cancer (from Cohen 1949). Symbols refer to authors listed in Table 1 of Cohen (1949); M = McWhirter (1935); R = Reisner (1933); S = Strandqvist (1944). Note that Strandqvist's convention was followed for the tumors with the result that the recovery exponent was 0.22, while a time of 1 day was assigned for a single treatment for skin reactions (recovery exponent = 0.33). When these are plotted with the same convention for single doses, parallel lines cannot be ruled out (reproduced with permission of The British Institute of Radiology and the author).

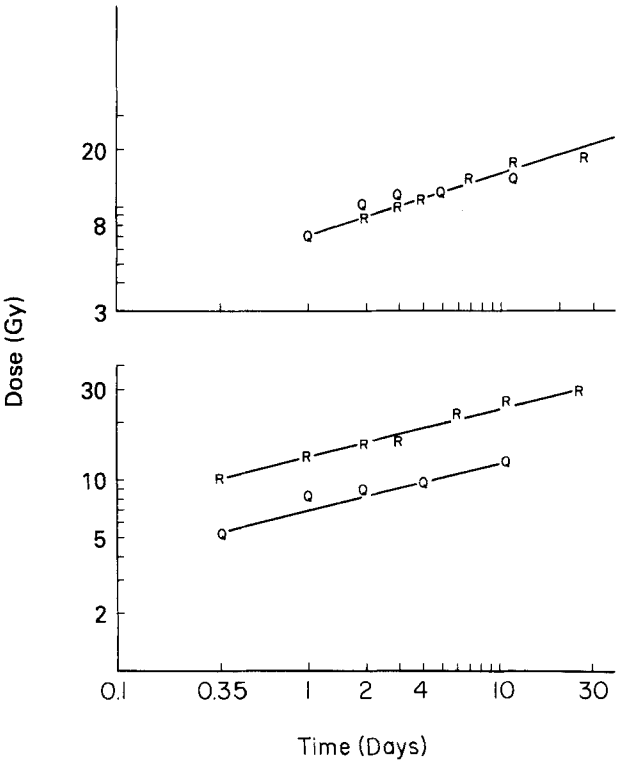

Fig. 5. Effect of definition of the time for a single dose on the isoeffect exponent (from Withers and Peters 1980). The data plotted are those of Quimby and MacComb (1937) for 'threshold erythema' in 70 cm^2 fields (Q), and of Reisner (1933) for strong erythema in 4 cm^2 fields (R). In the lower panel, the raw data are plotted as a function of the time *between* the first and the last doses, with the single dose points being plotted at T = 0.35 days, the convention used by Strandqvist. These isoeffect curves have an exponent of 0.22. In the upper panel, the data are plotted according to Cohen (1949), who normalized the doses to a 10-cm diameter field, and defined T (in days) as being numerically equal to the number of daily fractions, i.e., single doses are plotted at T = 1 day. This curve has an exponent of 0.33. This marked difference is a consequence of the use of a logarithmic scale for time in which the interval between 0.1 day and 1 day is the same as that between 1 and 10 days or 10 and 100 days, etc. (reproduced with permission of Lea and Febiger and the authors).

and recurrences of skin cancer (single treatment = '0' days) and deduced that Reisner's data for human skin (strong erythema), Quimby's data (weak erythema), and Ellis' tables (skin 'tolerances') were fitted by a line with slope 0.30. From this it was concluded that '... there can be no doubt that the difference between the Strandqvist exponent 0.22 for squamous carcinoma and the value of 0.30 for normal skin as obtained by three independent observers, is real and significant'. This analysis is illustrated in Fig. 4. It was inferred that recovery occurred more efficiently in normal skin than in squamous cell tumors, thus explaining the advantage of fractionated radiotherapy.

However, it is unlikely that a difference in fractionation sensitivity of squamous cell carcinoma and normal skin can be deduced in this way. First, there is the choice of time scale. Strandqvist took pains to point out (pp. 224, 271–272) that his use of 0.35 days for a single treatment represented a departure from the usual practice and that the slope was affected by this choice. Moreover, with the slope 0.22 there was good agreement between his isoeffect data for skin necrosis, those of REISNER (1933) for strong erythema, and those of MACCOMB & QUIMBY (1936) for threshold erythema. As pointed out by FLETCHER & BARKLEY (1974, Table II), choice of the time for a single dose has a strong effect on the estimated slope. This is illustrated in Fig. 5, where the data are plotted with 2 conventions used for the time assigned to a single treatment: 0.35 days and 1 day. When the same convention is applied, there is no significant difference between the slopes for normal tissues and tumors (BARKLEY & FLETCHER 1975).

Second, the majority of Strandqvist's patients had basal cell carcinomas, not squamous cell carcinoma. Out of a total of 32 recurrences (15 during the initial time period 1933–37, during which 91 patients constituted the data base for the first isoeffect curves separating recurrences and complications), 8 were squamous cell tumors (including lip carcinoma).

Third, some of the sources have been questioned, and probable bias has been pointed out (BARKLEY & FLETCHER 1975). The vast majority of cases was treated between 1 and 15 days (16 were treated in more than 15 days, from a total of several hundred), and the patients with larger lesions were treated in longer times.

Similar time-dose formulae were applied to different sets of clinical data by various authors in the 1940's and 1950's (JOLLES & MITCHELL 1947; COHEN & KERRICH 1951; COHEN 1952; ANDREWS & MOODY 1956; DUSAULT 1956; VON ESSEN 1960). Noteworthy for its effect on subsequent clinical practice was Cohen's (1952) finding that the recovery exponent for breast cancer treated with daily fractions was at least as great as that of normal skin (0.33). He concluded that 'whether there is any advantage, therefore, in prolonged fractionation for this tumor is open to doubt'. This principle, when put into practice, led to severe late complications after treatment of breast cancer (ATKINS 1964; MONTAGUE 1968).

The difficulty of assigning appropriate time exponents to clinical data was illustrated by VON ESSEN's (1960) study of the complications attending treatment of skin cancers. He attempted to determine the position and slope of a line that would separate the majority of successfully treated lesions from necroses. Following Strandqvist, he assigned 0.35 days as the time for a single treatment. He found that a number of slopes and intercepts appeared to achieve equivalent separation for small fields, from $D = 2500 \times T^{0.20}$ to $D = 1400 \times T^{0.34}$; the best separation was found for $D = 1950 \times T^{0.27}$. The small number of necroses resulting from treatment of large fields made it impossible to estimate a slope. This large range of possibilities for slope reflects the considerable scatter in the data, scatter that was typical of most clinical studies.

Thus the time-dose formula, an edifice whose foundations rested on different time scales, few patients, and the concept that overall time but not dose per fraction was important grew to include the concept that normal-tissue recovery differed from that of tumors.

Number of fractions vs. overall time. In all this work, the crucial assumption that varying the number of fractions for the same total dose in the same overall time did not appreciably affect the degree of reaction (REISNER 1933; QUIMBY & MACCOMB 1937) was rarely challenged. This changed with the publications of FOWLER et al. (1963) of results of experiments on pigskin and by DUTREIX et al. (1973) of experiments on human skin. Fowler and colleagues were motivated by a theoretical analysis (later published as FOWLER & STERN 1960) using 'slow repair' (repopulation) and 'fast repair', which at the time had not been identified. Fast repair was characterized by the experiments of ELKIND & SUTTON (1959, 1960), which offered a different explanation for *the way in which total isoeffect dose increased with overall time* (or number of fractions), namely the rapid restoration of the original shape of the dose-effect curve ('Elkind recovery', as distinguished from slower tissue repair and repopulation processes).

FOWLER et al. (1963) designed experiments on pigskin to distinguish between two competing explanations of recovery: Elkind recovery and slow tissue repair, or repopulation. The results showed that 5 fractions over 28 days gave the same skin effect with total doses of about 42 Gy, leading the authors to conclude that overall time was relatively unimportant between 5 and 28 days and that the main effect determining the increase in dose with extended fractionation was the size and number of the individual fractions. The effect of overall time was not negligible, however, as it contributed about one third of the increase in total dose. The main conclusion was that the use of fewer and larger fractions required a reduction in total dose, in contrast to QUIMBY & MACCOMB's (1937) finding.

The Ellis NSD formula. At least 2 key factors influenced the development of the NSD formula of ELLIS (1967, 1968, 1969): first, the perception from the papers of COHEN (1949, 1952, 1966) that the recovery exponents for squamous cell carcinoma and acute skin reactions were different; and second, the animal experiments of Fowler and colleagues, which demonstrated that for skin reactions the number of fractions was of greater importance in determining isoeffect doses than time, at least up to 28 days. Ellis interpreted the difference between recovery exponents, 0.33–0.22 = 0.11, as the appropriate time coefficient, on grounds that it was justifiable to assume that squamous cell carcinoma was not subject to homeostatic control. Since it could safely be assumed that normal skin was subject to such control, the ground was laid for separation of fractionation and time factors, i.e. the difference between the slopes for normal skin and squamous cell carcinoma, 0.11, could be taken as a 'regression' coefficient with time for normal tissue recovery, while the coefficient 0.22 represented the effect of fractionation. The latter was corrected by R. OLIVER for 5-times-weekly treatment to 0.24, and the NSD formula (ELLIS 1967, 1969) resulted:

$$\text{Total Dose} = \text{NSD}\ N^{0.24}T^{0.11}$$

wherein NSD stood for nominal standard dose.

The NSD formula seemed to work well enough for acute reactions when relatively small changes in overall time (T) or fraction number (N) were involved. In fact, Ellis realized that it could not be applied too far outside the values of N and T from the skin data on which it was based. It seemed not to work well for late reactions, however (e.g. BERRY et al. 1974).

Nevertheless, the NSD equation has had a significant impact on clinical practice. The most important reason was that it established a method for giving fewer than 5 treatments per week, with obvious potential for reducing the cost and time consumed by treatment. Two-fractions-per-week treatment is still in use in the UK (BATES 1975); but the possibility of reducing the number of treatments to 1 per week has had perhaps its greatest impact in third-world countries, sometimes with adverse consequences (SINGH 1978). Another reason for the success of the NSD concept was that it allowed for routine adjustments of dosage in the clinic, and the calculation of putatively isoeffective treatment regimens with different numbers of fractions, overall times; etc.

Various extensions of the formula have been developed. KIRK et al. (1971) developed the CRE (cumulative radiation effect) system to account for the effect on normal tissues of 'subtolerance' doses. They proposed that for different levels of injury in skin,

$$D = \text{CRE}\ N^{0.24}T^{0.11}$$

At full tolerance, CRE = NSD, while at lower levels of reaction, families of isoeffect curves could be generated, each with its own CRE. ORTON & ELLIS (1973) introduced the TDF (time, dose, and fractionation) factors, which had the advantage of additivity of partial tolerances (PT), defined (ELLIS 1969) as

$$PT = (n/N)\ \text{NSD}$$

where N = number of fractions of a chosen size to give full tolerance, and n = number of such fractions actually given. The PTs were additive, but very cumbersome for computations. Orton and Ellis noted that whenever the biological effect of alternative fractionation schemes was the same, the NSD canceled and played no further part in the calculations. Therefore, tables of the factor TDF:

$$TDF = n.d^{1.538} \times (T/N)^{-0.169} 10^{-3}$$

Table

Number-of-fractions exponents

Tissue	Reference	Conditions	Exponent
Early reacting			
Jejunum	Withers et al. (1975), Withers (1975 a)	1–10 fractions	0.32
		10–20 fractions	0.30
		1-h intervals: 1–10 fractions	0.27
		10–20 factions	0.08
Skin	Fowler et al. (1974)	3 fractions/wk	0.31
		2 to 18 days	
		5 fractions/wk	0.35
Lip mucosa	Xu et al. (1984)	1–4 fractions: 2 Gy/min	0.35
		0.33 Gy/min	0.29
Spleen colonies	Withers (1975 b)	1–4 fractions	0.24
		6–12 fractions	0.08
Colon	Withers and Mason (1974)	1–10 fractions	0.32
		10–22 fractions	0.22
Testis	Thames and Withers (1980)	1–4 fractions	0.29
		10–22 fractions	0.07
Late reacting			
Cervical cord	van der Kogel (1979)	White-matter necrosis	0.46
		Vascular damage	0.42
Kidney	Stewart et al. (1984 a)	1–16 fractions	0.43
		16–64 fractions	0.24
Lung	Wara et al. (1973)	Mice (350 kV x-rays)	0.38
		Humans (Co, 1 or 4 MV X rays)	0.41
	Field et al. (1976)	1 to 8 fractions	0.39
		8 to 30 fractions	0.25
	Travis et al. (1987)	1–4 fractions	0.36
		6–10 fractions	0.33
Bladder	Stewart et al. (1984 b)	1–2 fractions	0.50
		10–20 fractions	0.24

From Thames and Hendry (1987).

wherein d = dose per fraction, could be prepared that were independent of any specific NSD value.

Generalizations of these formulas were developed to account for split courses and continuous exposures. Similarities and differences in the approaches were discussed in the review by GOITEIN (1976).

Critique. The difficulties encountered in the use of the power-law model plague each of these formulas equally, since they all rest on Ellis' original NSD equation. A critique can be presented along three lines of argument. First, misconceptions connected with the origins of the power-law models, which have been discussed already, e.g. the idea that normal tissues, notably skin and squamous cell tumors, were characterized by different time factors, and the mixed conventions for the time scales. A second line of criticism is statistically oriented, i.e., given that the power-law models provide approximations to clinical experience over limited ranges of fraction number and time and that the techniques by which the exponents were arrived at were primitive at best, more appropriate methods should produce more reliable estimates (HERBERT 1986). The possibility of deriving more reliable exponents for clinical use, however, is opposed by the third line of criticism, based on biological reasoning, which suggests that power-law models are inappropriate over any range of time and over extended ranges of number of fractions, particularly with different tissues characterized by different fractionation sensitivities.

The biological case is briefly as follows. First, the use of a power-law representation for the time factor implies that recovery is maximal in the first week or two of treatment and progressively decreases thereafter (WITHERS & PETERS 1980, Table 2–20). But this contradicts biological data, which indicate that proliferation begins only after a certain time lag, becomes rapid, and then gradually returns to equilibrium (or lower, if a large dose has been given). This effect has been demonstrated clinically by TURESSON & NOTTER (1984). Therefore, no matter how sophisticated the fitting techniques or careful the design of the experiment, no power-law representation of proliferative response can be expected to describe the data adequately.

Second, in connection with the number-of-fractions exponent, it is known that tissues differ in their fractionation sensitivity (Table). Therefore, no single exponent can describe 'connective tissue tolerance', especially when this has been derived from acute skin reactions. While account could conceivably be taken of these differing

fractionation sensitivities by applying different number-of-fractions exponents, there is the added difficulty that these should depend on fraction size (Table 1). Thus, the steepness of the fractionation response should be greatest for the large dose fractions and gradually decrease with decreasing dose per fraction. This has been confirmed experimentally for functional changes in various organs and tissues and clinically for human skin by DUTREIX et al. (1973).

Epilogue: The LQ Formalism

The development of technology that permitted the evaluation of the proliferative capacity of individual mammalian cells after their exposure to ionizing radiation (PUCK & MARCUS 1956) introduced a completely new way of thinking about radiation isoeffect data, namely as manifestations of killing of target cells characterized by specific survival curves (ELKIND 1960; FOWLER & STERN 1960, 1963; MUNRO & GILBERT 1961; LAJTHA & OLIVER 1961). The concept 'isoeffect equals isosurvival' was applied using several types of survival models. DUTREIX et al. (1973) proposed a formulation based on the concept of increase in spared dose when the dose per fraction was halved. When interpreted in terms of survival curves, their results led to several important conclusions. First, little additional sparing in skin and gut could be achieved by further fractionation below 2 Gy per fraction. This result was incompatible with the NSD equation. Second, and as a consequence, the dependence of total isoeffect dose on number of fractions disappeared as the fraction size was decreased (or fraction number increased as shown in Table 1). Reactions in skin and gut thus seemed dependent on fraction size up to about 15 fractions, after which protraction resulted in an increased isoeffect dose mainly by virtue of cellular repopulation, amounting to over 1 Gy per day (see also DENEKAMP 1973).

A different survival model was employed by DOUGLAS & FOWLER (1976) for interpretation of skin isoeffect doses for fractionated radiation, namely the so-called linear-quadratic (LQ) model. In the 10 years following publication of Douglas and Fowler's work, the LQ isoeffect model has grown in influence, perhaps because of the discovery that the fractionation sensitivity of tissues may be classified according to the ratio α/β, which can be derived from tissue-isoeffect doses (THAMES et al. 1982).

There are indications of at least 2 difficulties associated with the use of the LQ model. First, studies of paralysis in the rat spinal cord (ANG et al. 1985) suggest that isoeffect doses may be overestimated when dose per fraction is less than 2 Gy. The same finding was made for kidney by STEWART et al. (1987). This could be interpreted as the manifestation of an initial linear part of the survival curve of the target cells, not well approximated by the LQ model at very low doses per fraction, or by incomplete repair during the short intervals that were used (THAMES et al. 1987).

Second, there is the possibility that repair kinetics in tissues may have several components, and moreover may not always be first-order, i.e. that repair rate may depend on size of dose per fraction. Such a difference, if it indeed existed, would have important therapeutic implications since complete repair in late-effect tissues might be possible in shorter interfraction intervals than the relatively long ones predicted from first-order repair kinetics (THAMES et al. 1984).

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