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MAGNUS STRANDQVIST: 50TH ANNIVERSARY OF HIS DOCTORAL THESIS

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This article is dedicated to Magnus Strandqvist's famous doctoral thesis "Studien über die kumulative Wirkung der Röntgenstrahlen bei Fraktionierung. Erfahrungen aus dem Radiumhemmet an 280 Haut- und Lippenkarzinomen" published in Acta Radiologica in 1944. After a short biography of Strandquist some central points of his work and their influence on future development of modern radiotherapy are presented.

Magnus Strandqvist was born on December 29th, 1904, in Skövde, Sweden. Following graduation from high school in Skövde in 1923, he registered at Tekniska Högskolan in Stockholm, intending to study architecture. However, he soon changed his mind and instead enrolled the Karolinska Institute where he passed his final examination as a physician in 1931. As a young undergraduate physician he practiced under, among others, Professor Gösta Forssell (1876–1950), who was the founder and first director of Radiumhemmet, who ignited Strandqvist's interest in radiotherapy (1).

In 1932, Strandqvist was enrolled as an assistent physician at Radiumhemmet in Stockholm (1). There his head was Elis Berven (1885–1966), who was Gösta Forssell's first assistant and successor as director of the institution. Berven's main interest dealt with cancer of the head and neck region and skin. James Heyman (1882–1956) head of the gynaecological department at Radiumhemmet, introduced Strandqvist to intracavitary radiotherapy. Before his disputation Strandqvist wrote papers on a direction indicator for x-ray tubes (2), a circular slide rule for calculating time of irradiation (3), a dosage system for radium surface application (4, 5) and external 200 kV in roentgen treatment of oesophageal cancer by a cross-fire technique (6).

In May 1944, under the supervision of Professor Elis Berven, Strandqvist published his doctoral thesis 'Studien über die kumulative Wirkung der Röntgenstrahlen bei Fraktionierung. Erfahrungen aus dem Radiumhemmet an 280 Haut- und Lippenkarzinomen' (7). This study was carried out at Radiumhemmet during the years 1934–1942. This work is one of the most outstanding and cited publications in modern clinical radiobiology. In 1946, it was presented in English by Hugo Ahlbom, Berven's successor as director of the Radiumhemmet (8).

In 1942 Strandqvist became head of King Gustaf V's Jubilee Clinic in Gothenburg and in 1953, he was given a personal chair as professor of radiotherapy at the Medical Faculty in Gothenburg. In 1964, he experienced the first symptoms of Parkinsons's disease, which caused his premature retirement. Magnus Stradqvist died in March 1978.

In the following some central issues of Strandqvist's doctoral thesis are presented.

Purpose of the study and a historical survey

In the introduction, Strandqvist gives an account of the main purpose of his study: to analyse the relation between the temporal distribution of the dose and the biological effect. The difficulty to predetermine the biological effect of radiotherapy was well recognized during that time. Almost every department had its own fractionation method. Therefore, Strandqvist selected his patient material from one department only. The exposure capable of producing a visible erythematous skin reaction, the erythema dose, was chosen as the reference. All patients included in his study had superficial (skin and lip) tumours, either basal cell or squamous cell carcinomas.

The first three chapters of the book give an excellent review of the development of radiotherapy before World

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War II, including development of dosimetry and studies on factors, which influence the relationship between the physical dose and the biological effect. Special attention was paid to the time factor and the fractionation, and to the mathematical models developed to explain the relationship between treatment time, total dose and recovery of the tissues. At the end of this review Strandqvist stated that, although some essential progress had been made, the problems concerning the time factor and the fractionation were still far away from their solution. The purpose of the study was to contribute to this research.

Materials and Methods

Patients. The material consisted of totally 270 patients (148 males and 122 females) with 280 lesions: 183 basal cell and 74 squamous cell carcinomas of the skin of the face, and 23 carcinomas of the lower lip, all irradiated at Radiumhemmet. Strandqvist described carefully every lesion with an accurate drawing made by himself. The lesions were distributed in 7 groups according to the site in the face and detailed data for each lesion are given as, year of treatment, age and sex of patient, gross appearance of the tumour, size (in cm^2) and thickness of the lesion, histopathological diagnosis, field size, radiation quality, type of fractionation, dose per fraction, total dose, minimum tumour dose, overall treatment time, 'cumulative' dose, skin reaction, recovery time, time for appearance of recurrence, recurrence-free time, and condition of the skin at the end of the follow-up. All lesions were followed up for at least two years. The sizes of the tumours varied from 1 cm^2 to 150 cm^2; 170 tumours were less than 9 cm^2 and 110 were between 10 to 150 cm^2. The thickness of the tumours varied between 0 to 19 mm, being mostly (64%) less than 4 mm.

Radiotherapy. All lesions were treated with external roentgen therapy. The field sizes varied from 2 to 255 cm^2 (mostly between 5 to 36 cm^2, median 16.3 cm^2). The exposure rate was less than 100 R/min in 180 cases, and between 101 to 280 R/min in 100 cases. Twenty-nine lesions were treated with one fraction only. The fraction size in this group was between 1000 to 2700 R. Totally 251 lesions were treated with two or more fractions with total doses between 2000 and 6000 R. The dose per fraction was mostly 700 R (in 150 lesions), but varied between 240 to 1 700 R. The overall treatment time was counted from the second day after the start of the therapy, i.e. if the treatment started on Monday and ended on Friday the same week, the treatment time was decided as four days. In 179 cases the overall time was between 5 and 10 days, mostly between 6 and 7 days. In 39 cases the overall time was more than 10 days, and in four cases 21 days or more. A total dose of 4 200 R given in 6 fractions of 700 R was regarded as standard treatment.

The effect of irradiation

To demonstrate the effect of irradiation given by different treatment schedules Strandqvist published photographs (Tables 1–17 in the thesis) of the treated lesions. Strandqvist found that with one single tumour exposure between 2 000 and 2 500 R was usually curative, whereas at multifractionated therapy a total exposure between 4 200 and 4 500 R given in 6 or 7 days was needed. The skin reactions were fairly similar, independent of the dose per fraction. However, the biologic effect probably depended on so many factors, that Strandqvist refrained from stating that these two forms of fractionation had absolutely equal biological effect.

During one year follow-up, 13 patients died: 2 with recurrence, 2 with complications of irradiation and 9 due to intermittent diseases. During this time, there were totally 32 recurrences and 48 complications. The complications were primary or secondary skin necrosis (11 cases), pronounced atrophy of the skin (11 cases), or slow recovery of the acute radiation reaction which had lasted at least 24 weeks (26 cases). According to Strandqvist, these complications were related to high tumour doses which were partly related to the size of the tumour.

When the lesions were divided into different groups according to the overall treatment time, the recurrences in each group appeared after a lower total dose compared to those with local control. When the treatment results according to number of recurrences, complications and smooth skin recovery were further analysed in relation to histopathology, thickness and site of the tumours, age of the patients, quality of radiation, field size, intensity of irradiation and overall treatment time (0–6 vs. 7 days or more), no really significant differences were observed. According to Strandqvist, the material was, however, too small for adequate statistical analysis of the mentioned factors. It was obvious however, that small tumours were more easily cured without complications than more extensive tumours.

Relationship between total dose and overall treatment time and the biological effect

On the basis of the radiobiological analysis mentioned before, Strandqvist stated that it was impossible to set up a definite law or mathematical formula that exactly covered a certain radiobiologic course of events. The latter could be reproduced by several courses, e.g. a parabola, a hyperbola or an exponential curve. There was some reason to believe that the cumulative effect of various fractionated doses could be computed according to a law resembling Schwarzschild's law of photochemsitry, 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, i.e. $I = T^p = \text{constant}$. This law can be expressed by a parabola.

For his analysis Strandqvist included lesions treated with reliable dosimetry based on R-units from 1933–1937. He plotted the total doses (range 2 000–5 000 R) against the overall times counted in days after the first day from the start of the therapy (range 0–15 days).

When he plotted the data of the 15 recurrent lesions and 14 complications (skin necrosis) on this diagram, he could contruct two parabolic curves in such a way that all the recurrences fell below the lower curve and all the complications above the upper curve. Therefore, he concluded, that for uneventful curative treatment the dose should be situated between these two parabolic curves (p. 218, Fig. 5 in the thesis). These parabolas became straight lines in a system, where both coordinates were graded logarithmically (p. 224, Fig. 6 in the thesis). As point zero could not be placed on a logarithmic scale Strandqvist chose 0.35 day as the nominal time for treatments given with one fraction only. A certain endpoint for the biological effect was in this system represented by a straight line and two total doses, D and d, gave similar biological effect if: $D/d = (T/t)^{0.22}$ where T and t are number of days respectively, after the first day of treatment. Using the intensity instead of the total dose D, $I = D/T$, in R per day (24 h) the equation obtains the same appearance as the Schwarzschild's law:

$$\text{constant} = I \times T^{1-p}$$

On the basis of 95 comparable, healed basal cell carcinomas Strandqvist calculated the position and slope of the line according to the method of least squares. The biological effect of the equivalent total doses arrived at by the formula were compared with the effect after a massive dose at one sitting (Do). According to the formula $Do = D \times 10^{-0.1} \times T^{-0.22}$, where $10^{-0.1}$ is an approximation of 0.35, 6 000 R in 30 days and 4 200 R in 6 days thus both have a biological effect corresponding to the effect of a single dose of 2 250 R. The single dose which gave an equivalent biological response was by Strandqvist called the 'cumulative dose'.

Going further in his mathematical analysis, Strandqvist named the part of his formula $10^{0.1} \times T^{0.22}$ as the fractionation factor F. If $F = 10^{0.1} \times T^{0.22}$ then $\log F = 0.1 + 0.22 \log T$. The fractionation factors for 1, 2, 3, 4, 5, 6, 7 days, thus became: 1.26, 1.47, 1.6, 1.7, 1.87, 1.93, 1.99 respectively. These values could be read directly from a double logarithmic diagram. For example, if 2 250 R given in one fraction was optimal for cure of skin cancer, which total dose should be given in 6 days?. From the formula one receives $\log D = \log 2\,250 + 0.1 + 0.22 \log 6$ and D = 4 200 R, or by using only the fractionation factor 2 250 R × 1.87 = 4 200 R.

Studying radiation doses producing specific radiobiologic effects in normal skin as erythema, dry and exudative epidermitis and necrosis, he found that the doses producing these reactions also represented straight lines when plotted on a double logarithmic graph with the slope of 0.22. In addition, the fractionation factors were compared with values found by other authors, using normal skin reactions as biologic indicators, and were found to correspond satisfactorily.

Future development

With his work Strandqvist created a new basis for fractionation, for more accurate ratiotherapy and for future studies about time–dose effect relationship. The importance of this doctoral thesis for the modern radiotherapy and radiobiology has been reviewed by Fowler (9) and Thames (10)

Strandqvist's formula was based on observations on skin and lip carcinomas but was found useful, and during a period also widely used, for treatment of for instance squamous cell carcinomas in the head and neck region. One great limitation of the formula was, however, that it could only be used for comparison of treatments given with a certain type of fractionation, i.e. about 6 fractions per week.

Cohen (11) assumed the exponent for normal tissue response to be 0.33. This exponent was later on used also by Ellis (12). It was based on the definition of first treatment as day 1 but would have been 0.22 using the convention by Strandqvist, i.e. with the second treatment defined as time day 1. In 1963, Fowler irradiating pig skin, demonstrated, how the number of fractions greatly affects the biological response (13). Based on these results (11, 13) Ellis derived the NSD (Nominal Standard Dose) formula (12):

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

where N is the number of fractions and T the overall treatment time. Ellis (12) interpreted the difference between the recovery exponents for normal tissue response and for recurrence of skin cancer (0.33–0.22 = 0.11) as exponent for time (T). The exponent 0.24 of fraction number was obtained from Strandqvist's slope 0.22 by allowing for 5 instead of 6 treatments per week. Ellis' formula, which was partly based on Strandqvist's data, had a great importance for the understanding that the number of fractions was much more important than the total treatment time for the biological response.

To facilitate the use of the NSD formula, Orton & Ellis (14) in 1973 published TDF (time, dose, fractionation) tables and instructions for their use. However, today both Strandqvist's formula and formulas of Ellis' type are largely abandoned in clinical work and replaced by formulas based on the α/β formalism with trials to define adequate values for early and late reaction in different tissues (15). The relation between dose, fractionation, treatment time and biological response is still a field of extensive research. Strandqvist's thesis once represented an important milestone in this research.

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