FROM THE DEPARTMENTS OF RADIATION PHYSICS (DIRECTOR: PROF. G. HETTINGER) AND RADIATION THERAPY (DIRECTOR: PROF. L.-G. LARSSON), UNIVERSITY OF UMEÅ, S-901 85 UMEÅ, SWEDEN.

RADIATION-INDUCED LESIONS OF THE BRACHIAL PLEXUS CORRELATED TO THE DOSE-TIME-FRACTION SCHEDULE

H. SVENSSON, P. WESTLING and L.-G. LARSSON

Lesions of the brachial plexus have been reported by several authors (STOLL & ANDREWS 1966, WESTLING et coll. 1967, 1972, NOTTER et coll. 1970) to be a possible complication following post-operative radiation therapy of mammary carcinoma. WESTLING et coll. (1972) found a correlation between the frequency of these lesions and the cumulative absorbed dose according to the formula of STRANDQVIST (1944). Further analysis of this series is now presented, also considering the number of treatments and the dose per fraction. This analysis was based on Ellis' formula (ELLIS 1968) and the mathematical treatment made according to KIRK et coll. (1971). The radiation tolerance levels of the patients were expressed in a frequency distribution curve of the plexus lesions. Observations made by STOLL & ANDREWS and NOTTER et coll. also fitted well into this curve.

Material and Methods

The aim of the radiation treatment was to deliver a cancerocidal absorbed dose to the regional lymph node areas through one parasternal, one supraclavicular and one

Submitted for publication 7 January 1975.

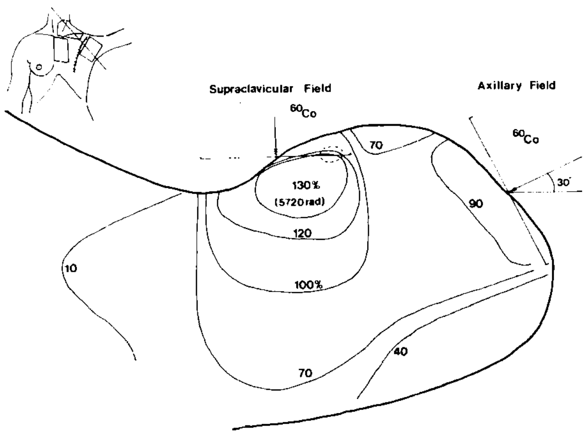

Fig. 1. A typical dose distribution through the centres of the axillary and supraclavicular fields. The treatment regime for this patient is given in Fig. 2.

axillary field. The treatment technique was standardized. Details of the technique were given by WESTLING et coll. (1972). All patients treated with this technique and at risk for radiation induced lesions during a period of 5 years or more following treatment were included, 130 patients in all.

The development of the lesions and their severity have been described in the previous report (WESTLING et coll.). In the present analysis no attempt was made to differentiate between different degrees of neurologic lesions. Thus, in addition to motor lesions, all types of sensory disturbances were regarded as lesions, i.e. symptoms varying from slight numbness of the fingers to total paresthesia of the arm.

The absorbed dose to the brachial plexus region was received from the axillary and supraclavicular irradiations. An isodose distribution for a typical treatment appears in Fig. 1. It was assumed that the affected part of the plexus was located at an average depth of 3 cm below the surface of the supraclavicular field. The plexus dose was for most cases approximately equal to the maximum absorbed dose. Injury to the connective tissue cells in the plexus region was thought to be the cause of the lesions (STOLL & ANDREWS 1966, WESTLING et coll. 1972). The Ellis formula is probably, within certain limits, valid for this tissue. The formula was rewritten according to KIRK et coll. and the Cumulative Radiation Effect, CRE, computed:

$$\mathrm{CRE} = d \cdot \varrho \cdot N^{0.65} (= D \cdot N^{-0.24} \cdot T^{-0.11}, \text{ Ellis' formula})$$

where d is the daily dose to plexus in rad, $\varrho = (T/N)^{-0.11}$ is the repetition parameter, T is the total time for the treatment in days, and D is the total absorbed dose to plexus for the whole course in rad.

The formula was assumed to be valid also for irregular treatment regimes. Fig. 2 illustrates the build-up of the CRE for a typical treatment course in which a total of 5 720 rad was given in 17 fractions over a period of 23 days.

The frequency of plexus lesions in patients grouped according to the CRE-values

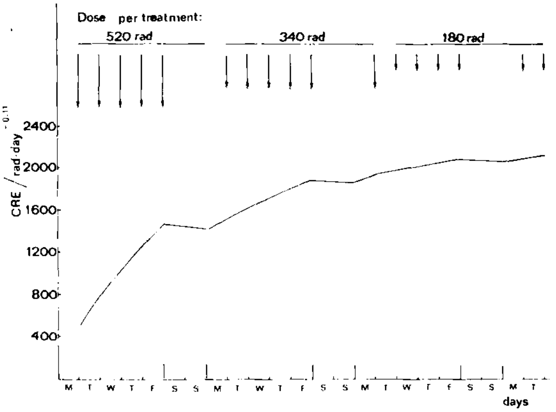

Fig. 2. The build-up of the CRE-value during the treatment course.

is given in Table 1. Group No. 1 was composed of patients irradiated with ^{60}Co through two fields with a treatment schedule similar to that in Fig. 2. The total dose for these patients varied only a few per cent. The overall time, T, varied somewhat between different patients which was the major reason for the spread of the CRE-values within this group.

Three patients received CRE-values lower than those mentioned above because a larger number of fractions were given. The treatment of the supraclavicular field in these cases was completed before the irradiation of the axillary field was started. These three patients together with one who received a somewhat lower total dose, D, were included in Group 2.

Groups 3, 4 and 5 were composed of patients who received 13 to 16 MeV electron radiation through the supraclavicular field and ^{60}Co radiation on the axillary field. Both the electron and the ^{60}Co fields were irradiated on each treatment day. As a rule, the two irradiations were made within 5 to 15 minutes and may thus be regarded as one dose fraction.

CRE-values were also calculated for data on the treatment schedules for series of patients from Stoll & Andrews, and Notter et coll. The frequencies of plexus lesions reported for these patients were related to the CRE-values (Table 2).

The patients in groups 6 and 7 were irradiated with 4 MV roentgen-rays through one supraclavicular-axillary field. The irradiated volume was approximately the same as in groups 1 and 2. Group 8 was also treated with 4 MV radiation but with a large, single, supraclavicular field, as large as 22 cm by 13 cm. The patients in group 9 received 200 kV roentgen treatment against one small field 4 cm by 6 cm, to the apical axillary region. The patients in these groups were followed for at least 30 months after the end of the irradiation period.

The patients in group 10 were irradiated through one supraclavicular-parasternal and one axillary field. The irradiated volume was approximately the same as in groups 1 and 2. Some patients were also treated through an electron field to the chest

Table 1

The frequency of plexus lesions as a function of the CRE-values from the authors' material. Patients irradiated on the supraclavicular field with electrons and with ^{60}Co are assigned to different groups. The confidence intervals have been calculated according to CLOPPER & PEARSON (*1934*)

Group No.	Irradiation fields		CRE-interval	Mean CRE in the interval	No. of lesions/ No. of patients	95 %-confidence interval
	Axillary	Supra-clavicular				
1	^{60}Co	^{60}Co	2 048–2 230	2 147	31/48 = 0.65	0.48–0.78
2	^{60}Co	^{60}Co	1 967–1 984	1 972	0/4 = 0	
3	^{60}Co	e^-	2 064–2 239	2 192	7/18 = 0.39	0.17–0.64
4	^{60}Co	e^-	1 851–2 037	1 921	5/30 = 0.17	0.05–0.22
5	^{60}Co	e^-	1 707–1 841	1 777	2/30 = 0.07	0.01–0.22

wall which, however, did not influence the brachial plexus dose. The patients were followed for at least two years.

Results

Radiation quality and volume effects. The frequency of plexus lesions of 0.65 (31/48) at CRE 2 147 (rad day$^{-0.11}$) of the pure ^{60}Co technique should be compared with 0.39 (=7/18) for CRE 2192 (rad day$^{-0.11}$) of the combined ^{60}Co and electron technique (Table 1). χ^2-test of this difference gave a p value of 0.08.

A somewhat higher effect from the pure ^{60}Co treatments could be expected as the irradiated volume was larger than that of the combined technique. This difference was due to the sharp dose fall-off at about 4 to 5 cm depth for the electron radiation which resulted in a high dose level within a relatively limited volume. It is well established that the tolerance dose level increases as the irradiation volume is decreased. The effect has been found empirically to be proportional to $(V/V_{ref})^{0.16}$ (RAGNHULT et coll. 1973) where V_{ref} was the reference volume, in this investigation defined as the volume irradiated through the two ^{60}Co fields (groups 1 and 2), and V was the volume irradiated with the combined electron and ^{60}Co fields (groups 3, 4 and 5). From the isodose distributions, V/V_{ref} was estimated to be 0.75. The correction for volume differences resulted in a decrease of the CRE-value for group 3 from 2 192 (Table 1) to 2 093 (CRE_{corr}) rad day$^{-0.11}$. The expected difference in the frequency of lesions corresponded to the difference actually found between group 1 (0.65) and group 3 (0.39).

Another possible reason for the difference between groups 1 and 3 may be a difference between the RBE-values for ^{60}Co and electron radiation. Some authors suggest a lower RBE for electron than for ^{60}Co radiation (LINDEN 1972). Such a difference, however, was not found during detailed RBE-investigations at our hospital (HETTINGER et coll. 1965).

Table 2

The CRE-values for groups 6, 7, 8 and 9 determined from information given by STOLL & ANDREWS *(1966). Group 6 was irradiated with a peak dose of 6 300 rad in 12 increments in 25 to 25 days, group 7 with a peak dose of 5 775 rad in 11 to 12 increments in 25 to 28 days, group 8 with a peak dose between 4 650 and 5 500 rad three times weekly with increments of 400–500 rad, and group 9 with a plexus dose of 4 300–5 300 rad three times weekly during 25 to 28 days. The relative depth dose values at 3 cm depth for 4 MV roentgen-rays were taken from HPA (the Hospital Physicists' Association) 1972. The data in group 10 were taken from* NOTTER *et coll. (1970) and were determined from a graph given by the authors. They have estimated the dose level for low frequency lesions (≈ 15 %) as a function of the over-all time for the treatment series. This curve passes 4 800 rad over 21 days. Each week 3 to 5 treatments were given which is the reason for the CRE-interval*

Reference	Group No.	Technique	CRE at plexus	Mean CRE in the interval	No. of lesions/ No. of patients	95 %-confidence level
STOLL & ANDREWS (1966)	6	4 MV, supra-clavicular field, moderate volume	2 350	2 350	24/33 = 0.73	0.55–0.87
	7	4 MV, supra-clavicular field, moderate volume	2 170	2 170	13/84 = 0.15	0.08–0.25
	8	4 MV, supra-clavicular field, large volume	1 870–2 130	1 900	4/25 = 0.16	0.04–0.37
	9	200 kV, field to apical axilla, small volume	1 767–2 030	1 898	14/139 = 0.10	0.05–0.16
NOTTER et coll. (1970)	10	^{60}Co supra-clavicular and axillary fields, moderate to large volume	1 800–2 030	1 915	≈0.15	

Uncertainty in dosimetry may also be of importance in comparing groups 1 and 3. The difference in the frequencies for the two groups corresponded to a change of approximately 5 per cent in the absorbed dose calibration. For both electron and photon radiation, the absorbed dose measurements were made with $FeSO_4$ dosimeters which were assumed to have equal sensitivity (G-value) for the two qualities. This assumption may be incorrect but the difference in sensitivity should certainly not be as great as 5 per cent. The largest error was probably due to variation in the anatomic

Table 3

The frequency for the same patient material as in Table 1. The groups of patients treated with electron- and ^{60}Co radiation on the supraclavicular fields have been combined in new groups according to CRE-values

CRE-interval	Mean CRE in the interval	No. of lesions/ No. of patients	95 %-confidence interval
1 707–1 800	1 770	2/26 = 0.08	0.02–0.27
1 800–1 900	1 857	2/20 = 0.10	0.02–0.33
1 900–2 000	1 950	2/11 = 0.18	0.02–0.55
2 000–2 100	2 048	4/12 = 0.33	0.09–0.67
2 100–2 230	2 166	35/61 = 0.57	0.43–0.70

position of the brachial plexus. The difference between groups 1 and 3 due to this variation cannot probably have exceeded a few percent.

A volume dependence was probably of importance also in groups 7 and 8. These groups had approximately the same frequency of lesions while the CRE-values were considerably lower for group 8 for which a large volume was irradiated.

It was more difficult to compare group 9 with the other groups as both the RBE and the technique differed from those of the remaining groups. However, the frequency would appear to be in agreement with the remainder of the results from STOLL & ANDREWS if corrections were made for both the RBE and the small volume.

Complications. The data in Table 1 were used in order to analyse the frequency distribution as a function of CRE-value (Table 3). No classification of patients in this analysis was made with regard to the irradiation technique. A possible volume or quality effect, discussed above, was thus not taken into consideration. The data from Table 3 and from groups 6 and 7 in Table 2 were plotted in Fig. 3. The two points in Fig. 3 from STOLL & ANDREWS have been displaced along the CRE-axis in order to make them coincide with the data from Table 3, a displacement which was equivalent to multiplying the CRE-values for the two groups by a factor of 0.93. This correction was thought to be justified by the fact that dosimetric differences of this order of magnitude between hospitals are not uncommon. The remaining groups in Table 2 were not included in the figure as they did not provide any further information on the shape of the curve, because groups 8 and 9 were irradiated using very different techniques compared with groups 6 and 7, and group 10 represented only a single data point from the patient material of NOTTER et coll.

The fitting of the curve to the observed points was made on the assumption that the tolerance level, or more exactly, the threshold for neurologic symptoms or signs expressed as a function of CRE followed a normal distribution curve. The statistical uncertainties of the different points were taken into account. The solid line represented the best fitting normal distribution. The curve revealed that the lesion

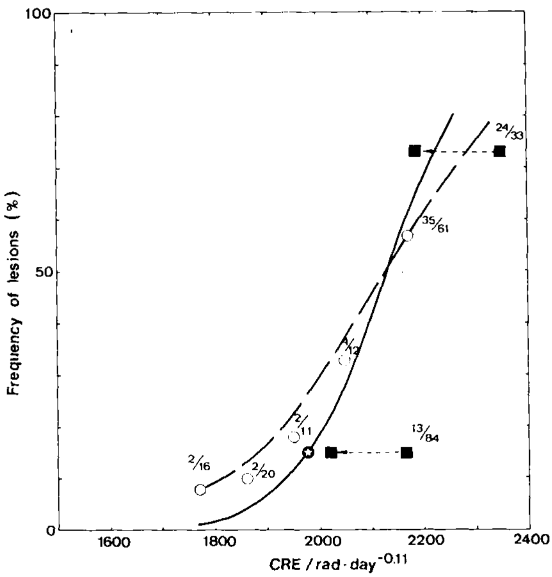

Fig. 3. The frequency of neurologic lesions as a function of the CRE. The open circles represent the authors' values from Table 3. The filled squares represent the data from STOLL & ANDREWS. The solid line represents the best fit taking the statistical uncertainties of the different points into consideration and assuming a normal distribution of the tolerance level. The solid curve is tied to a mean value from four groups of patients, indicated with a star. The broken line has been constructed to analyse the uncertainty, cf. text.

frequency increased very rapidly above a given CRE-value. An increase of 7 per cent for the CRE from 1 980 rad day$^{-0.11}$ in Fig. 3 thus caused an increase in the lesion frequency from 15 to 50 per cent.

Not only the relative but also the absolute relation between frequency of lesions and CRE could be estimated from the curve. The lesion frequencies for group 4, 7, 8 and 10 lay all between 15 and 17 %. The CRE-values in these groups, the means given in Tables 1 and 2, lay within the interval 1 900–2 170 with a mean value of 1 976 rad day$^{-0.11}$. The solid curve thus passed through CRE $\approx$ 1 976 rad day$^{-0.11}$ for a frequency of 15 %, i.e. the mean CRE for this frequency level for the four groups. The curve was therefore tied to a fairly well established point.

In comparing the three sets of data, no uniform definition of neurologic symptoms or signs was possible and the follow-up time varied considerably. Both these factors may have influenced the relation between the CRE-value and the frequency. The frequency of lesions for group 1 was 0.65 after 5 years and only 0.44 after 3 years. The lesions which appeared late were often mild which may explain why STOLL & ANDREWS did not observe initial symptoms later than 30 months after the irradiation. Differences between the series may also be due to dosimetrical, technical (e.g. irradiation volume and dose uniformity), biologic (RBE for group 9) and statistic factors. The width of the interval, 1 976 (-5, $+9$ %) rad day$^{-0.11}$ for groups 4, 7, 8 and 10, may seem small considering the number of factors which influenced the CRE-lesion frequency relation. One explanation of the narrow width might be the very rapid change of lesion frequency with the CRE-values. Different definitions of lesions and different lengths of observation time (time at risk) cause only a small

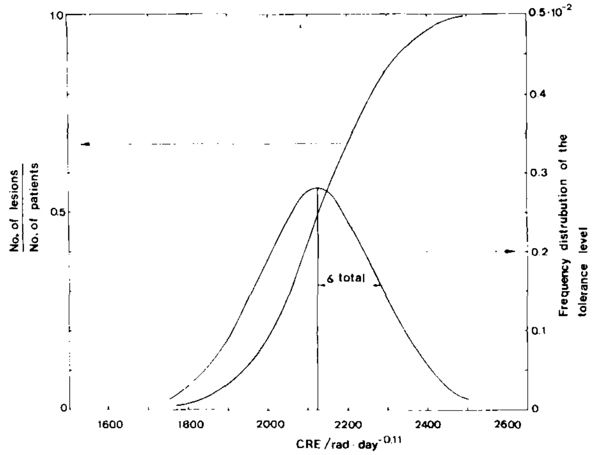

Fig. 4. The s-shaped curve is identical with the solid curve in Fig. 3. (The corresponding abscissa is given to the left in the figure.) This curve corresponds to a normal distribution of the dose tolerance level with $\sigma_{total} = 150$ rad days$^{-0.11}$. The area under this curve from a low CRE-value to some arbitrary CRE-value is equal to the numerical value found on the s-shaped curve. The area under the complete curve is unity.

displacement of the frequency curve along the CRE-scale. It was also significant that the maximum and minimum CRE-values came from the same hospital (groups 7 and 8) and that the difference between the frequencies for these two groups might be explained by the volume factor.

Discussion

The uncertainty of the shape of the frequency—CRE-curve is dependent on dosimetric, anatomic and statistic factors. The solid curve in Fig. 3 was redrawn in Fig. 4 to illustrate the influence of these factors. It was assumed in the fitting of the curve to the observed points that the tolerance level for neurologic lesions was normally distributed. The standard deviation of this best fitting normal distribution, σ_{total}, was 150 rad day$^{-0.11}$ (Fig. 4). The uncertainty of this value was evaluated. A standard deviation, σ_{total}, of 250 rad day$^{-0.11}$ meant that the corresponding curve (broken line, Fig. 3) passed just outside the 95 per cent confidence interval of two of the observed values (filled squares, Fig. 3). σ_{total} ought therefore to be less than this value.

The value of σ_{total} depended on the differing sensitivity to irradiation among the patients, and also on the relative dosimetric uncertainty. This may be realized from the fact that a presumed equal biologic sensitivity of all the patients, $\sigma_{biol} = 0$, also meant a standard deviation, that is $\sigma_{total} = \sigma_{dos}$. The pure biologic variation of the tolerance level for the patients can be evaluated if the precision of the dosimetry can be estimated. It is reasonable to assume that $\sigma_{dos} > 5\,\%$. The uncertainty due to anatomic, dosimetric and technical factors is included in this error. An error of 1 cm in the estimate of the site of the brachial plexus would alone cause an error of approximately 5 per cent. In addition there are uncertainties due to technical (e.g. placing the patient) and pure dosimetric factors. Furthermore, the numerical method used above to determine the curves in Fig. 3 probably implies an overestimate of σ_{total} and therefore also of σ_{biol} as no separation was made between the pure ^{60}Co- and the combined electron and ^{60}Co-method. An upper limit for σ_{biol} can be estimated from the relation

$$\sigma^2_{total} = \sigma^2_{biol} + \sigma^2_{dos}$$

For a σ_{total} of CRE 150 rad days$^{-0.11}$ $\sigma_{biol} < 5\,\%$. The extreme curve (broken line, Fig. 3) implies $\sigma_{biol} \leqslant 12\,\%$. Thus even with the larger of the two estimates of the biologic variation, which is not a very realistic estimate, the frequency of lesions increases very rapidly for small increases in the CRE above a threshold level.

It may be suggested that the special type of analysis, i.e. the use of Ellis' formula, which includes an exponential expression, may have caused the small standard deviation. However, this fact should be of minor importance, as the repetition number, ϱ, and the number of treatments, N, are nearly the same for the two sets of groups in Fig. 3. The main reason for the variation in the CRE-values in Table 3 was the variation in the daily dose, d, (cf. the equation page 3) among the patients (from 400 to 300 rad). A different treatment strategy for some of the patients had surely been chosen if the present knowledge of complication—dose level had been available. Difficulties in the transfer of experiences from one facility to another may however arise even with this knowledge, due to uncertainties in the dosimetry. HERRING & COMPTON (1970) concluded from the literature that, "since changes in the radiation dose of either plus or minus 10 per cent can give marked changes in the probability of necrosis or of local control, respectively, it is apparent that the therapist needs a system which will permit him to deliver the desired dose distribution to within ± 5 per cent or possibly even more accurately". One part of their conclusions is based on the correlation between dose and symptoms for such diverse complications as severe cases of laryngeal oedema and severe sigmoiditis. These observations are in agreement with the present results for brachial plexus lesions. In order to obtain a reasonably low risk for such lesions it is obvious that the CRE value should not exceed about 1 900 rad day$^{-0.11}$.

The need of this high accuracy for some situations in radiation therapy may to some extent be overcome if tables of numerical values for CRE at the tolerance level or NSD could be available (the NSD and CRE concepts have the same meaning at the tolerance level). New treatment techniques might thus be adopted more safely if the local NSD levels for some well-established techniques and the technique to be adopted could be compared. Some tables of this type have already been published (ELLIS 1971, RUBIN & CASARETT 1972) but more data are desirable.

SUMMARY

Radiation induced brachial plexus lesions were correlated to the dose–time–fraction schedule. Ellis' formula was used and the mathematical treatments were made according to

KIRK et coll. (1971). It was found that the frequency of lesions increases very rapidly for small increases of CRE over a certain level.

ZUSAMMENFASSUNG

Strahlenverursachte Läsionen des Plexus brachialis wurden zu dem Dosis–Zeit-Fraktionierungs-Schema korreliert. Es wurden die Ellis'sche Formel verwendet und die mathematische Bearbeitungen entsprechend KIRK et coll. (1971) vorgenommen. Es zeigte sich, dass die Frequenz von Schädigungen sehr rasch mit einem kleinen Anstieg der CRE über ein gewisses Niveau hinaus anstieg.

RÉSUMÉ

Les auteurs ont établi une relation entre les lésions du plexus brachial causées par l'irradiation et le schéma de fractionnement de la dose en fonction du temps. Ils ont utilisé la formule d'Ellis et le traitement mathématique a été fait suivant la méthode de KIRK et collaborateurs (1971). *Ils ont constaté que la fréquence des lésions augmente très rapidement* pour de petites augmentations de l'effet cumulatif des radiations au dessus d'un certain niveau.

REFERENCES

CLOPPER C. J. and PEARSON E. S.: The use of confidence and field limits illustrated in the case of binomial. Biometrika 26 (1934), 404.

ELLIS F.: Time fractionation and dose rate in radiotherapy. Front. Radiat. Ther. Onc. 3 (1968), 131.

— Nominal standard dose and the ret. Brit J. Radiol. 44 (1971), 101.

HERRING D. F. and COMPTON D. M. J.: The degree of precision required in the radiation dose delivered in cancer radiotherapy. *In:* Computors in radiotherapy, p. 51. Edited by A. S. Glicksman, M. Cohen and J. R. Cunningham. The British Institute of Radiology, London 1971.

HETTINGER G., BERGMAN S. and ÖSTERBERG S.: The relative biological efficiency (RBE) of 30 MeV electrons on haploid yeast. Biophysik 2 (1965), 276.

KIRK J., GRAY W. M. and WATSON E. R.: Cumulative radiation effect. Part I: Fractionated treatment regimes. Clin. Radiol. 22 (1971), 145.

LINDEN W. A.: Die relative biologische Wirksamkeit der Hochwoltstrahlen in der Strahlentherapie. Strahlentherapie 144 (1972), 679.

NOTTER G., HALLBERG O. and VIKTERLÖF K. J.: Strahlenschäden am Plexus Brachialis bei Patienten mit Mammakarzinom. Strahlentherapie 139 (1970), 538.

RAGNHULT I., NOTTER G. and TURESSON I.: Application of the CRE system in clinical radiotherapy. *In:* Proceedings of the Seventh Nordic Meeting on Clinical Physics, p. 115. Edited by R. Jahren, Department of Medical Physics, the Norwegian Radium Hospital, Montebello, Oslo 3.

RUBIN P. and CASARETT G.: A direction for clinical radiation pathology. The tolerance dose. Front. Radiat. Ther. Onc. 6 (1972), 1.

STOLL B. A. and ANDREWS J. T.: Radiation-induced peripheral neuropathy. Brit. med. J. 1 (1966), 834.

STRANDQVIST M.: Studien über die kumulative Wirkung der Röntgenstrahlen bei Fraktionierung. Acta radiol. (1944) Suppl. No. 55.

SVENSSON H.: Dosimetri measurements at the nordic medical accelerators. II. Absorbed dose measurements. Acta radiol. Ther. Phys. Biol. 10 (1971), 632.

WESTLING P. and NORDIN G.: Cervical plexus lesions following postoperative telecobalt therapy for carcinoma of the breast. (In Swedish.) 28th Congress of Scandinavian Society of Radiology 1967.

— and HELE P.: Cervikalplexusläsioner efter postoperativ strålbehandling vid cancer mammae. (In Swedish.) Nord. Med. 80 (1968), 1636.

— SVENSSON H. and HELE P.: Cervical plexus lesions following post-operative radiation therapy of mammary carcinoma. Acta radiol. Ther. Phys. Biol. 11 (1972), 209.