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# CLINICAL EXPERIENCE WITH PROTON BEAMS

by

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At Uppsala the work with fast protons in radiobiology and experimental radiotherapy could start in 1956 when the external 185 MeV proton beam was extracted from the Uppsala synchrocyclotron . (Fig. 1) At that time the radiophysical properties of high energy protons were well known in principle both theoretically[1] and practically[2] due to the early work at Berkeley. Inspired by that research we decided to explore in more detail the possible values of proton beams in radiotherapy and brain surgery. In the present context I limit myself to the theme radiotherapy referring to earlier papers for references to the surgical applications.[3,4,5,6,7,8,9,10,11,12]

In 1956-1959 we investigated the effects of high energy protons on rabbit skin[13,14], on small intestines[15] and rectal mucosa of rat[16] and on V x 2-carcinoma[14,17]. The ability of protons to induce chromosome aberrations was studied in broad bean roots.[18] The induced changes were

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grossly and microscopically comparable to those created by numerically equivalent doses of roentgen rays. These investigations were made to test the hypothesis that protons which show ionization patterns typical for low LET-radiations, create the same changes in tissue as gamma radiation. As expected the gross and microscopical changes induced by high energy protons did not differ from the changes induced by X-rays. The results of our studies also indicated that the RBE of high energy protons with a LET of about 0.5 keV/micron was 0.7-0.8 as compared to X-rays, (Table I) i.e. they were almost equivalent to cobalt gamma radiation. The estimated RBE values are in good conformity with the values found by others (Table II).[2,19,20,21,22,23,24,25] The RBE of Bragg-peak-protons (LET 30-50 keV/micron) was also studied and values of 3 - 8 were found in a narrow zone at the end of the range of penetration[18].

After this initial study we started to irradiate human carcinomas in 1957.[26,27] (Table III) The patients of the first three series had uterine or ovarian carcinomas and most of them had earlier received radiation therapy or been operated upon. The proton irradiation was given palliatively and for practical reasons in one sitting. The greatest diameter of the beam was 14 cm and the depth of penetration in tissue could be varied at will up to 23 cm. The Bragg peak, which is too narrow for practical use in tumour therapy was transformed into plateaux of variable length by means of filters.[8,9,35] By varying the range of protons in the body during irradiation it was possible to deliver an almost uniform dose to the tumour-involved tissue. Ridge filters are now normally used for this transformation of the Bragg peak.

The situation shown in Fig. 2 is typical for all therapeutical procedures considered in patients with genital carcinomas.

The first series included ten cases of microscopically verified recurrences of earlier irradiated genital carcinomas. The main aim of the investigation was to study the effects of protons on healthy and malignant tissues. Six of the patients had squamous cell carcinomas and four adenocarcinomas. Irradiation was given in single doses of 3000 rad over a perineal field. The results of the animal experiments had indicated that this very simple type of treatment could be tolerated. In all cases the irradiated tumour mass decreased grossly after irradiation and histological examination showed regressive changes in the malignant cells. These early results in a very inhomogeneous material did not permit any conclusions but for the general observation that the reaction of the normal tissues was comparatively slight. No acute reaction such as fever, nausea or fatigue due to the treatment was observed. All the patients had erythema of the irradiated skin two weeks after irradiation and seven of them a moist skin reaction which healed within 5 - 6 weeks leaving a pigmentation of the kind sometimes seen after X-ray treatment. No patient showed any urinary symptoms but all had rectal reactions, transient tenesmus and diarrhoea. A recto-vaginal fistula was found at autopsy in two cases. This complication may be explained as an effect of superimposition of protons and the earlier X-rays.

The second series included five cases with cervical adenocarcinomas or squamous cell carcinomas. These patients had not received earlier radiation therapy. A single dose of 2500 - 3000 rad protons was given to four very advanced cases. These patients all died within six months from wide-spread cancer. The reactions of the healthy and malignant tissues were the same as in the first series. At autopsy a rectal perforation was found in one patient and microscopic examination revealed cancer growth in the walls of the fistula which may have caused the perforation. One of these patients received a single dose of 3000 rad for a stage II cervical carcinoma of squamous cell type. This woman is alive and apparently cured 9 years after treatment without any permanent reaction from the skin, bladder or the intestine. At gynaecological examination this year only some fibrosis of the paracervical tissues was found and a slight pigmentation is present in the irradiated skin.

A third series of patients was now given fractionated treatment. Six patients got 500 rad twice a week up to a total dose of 4000 - 6000 rad for advanced genital carcinomas which earlier had been X-irradiated. In most cases a small volume containing node-metastases on the pelvic wall was treated. In one case all tissues in the abdomen caudal from the umbilicus were irradiated. The tumours all decreased in size after treatment and microscopic examination showed regressive changes or no cancer cells. As expected, the reactions of the skin after fractionation were less marked than after single irradiation. The treatment was also in these cases palliative and the patients all died from their carcinomas within 2 years.

At this time we felt a certain confidence in our technique and the equivalence of the protons to gamma radiation from biological point of view seemed fairly well established. From now on treatment was therefore planned in accord with normal clinical practice. The further work was concentrated on cases in which the geometrical advantages of the proton-dose-distribution could be exploited to maximum advantage. Graffman and Jung[31] for example, gave fractionated total doses of 2000 - 5000 rad to 10 patients with nasopharyngeal malignancies of different histologic types. Only the primary lesion was irradiated, local metastases were treated with X-rays or surgery. The proton irradiation was performed with two opposing, circular fields centered on the tumour region. The tumour dose was given in fractions of 1000 - 1500 rad, twice a week, alternatively from the left and from the right side. The beam penetrated to a depth of 2.5 cm beyond the midline of the skull and the two fields overlapped in a 5 cm wide zone around the midline. In this zone the dose was 3 times that at the skin. Seven of the patients had already at irradiation distant metastases and died from their disease. Three patients however had no sign of metastases at irradiation and two of them are living symptomfree more than 5 years after treatment. During the last 2 years another series of 10 patients[32] with nasopharyngeal carcinomas has been treated exclusively with protons. The irradiated volume has been larger but otherwise the treatment has been similar. The primary results are encouraging and no untoward side-effects were seen.

During the last two years a number of patients with various types of carcinomas in the head-and-neck region have been treated with comparatively large proton fields[32]. The doses have been 5000 - 6000 rad given in 5 - 6 fractions over that many weeks. No other form of treatment is given. The results are reported good but studies have not proceeded long enough.

Graffman and Jung [33] have also treated 7 patients with brain tumours, astrocytomas grade III-IV with doses of 3900 - 5200 rad over 4 to 8 weeks. A single field technique was used and the treatment was given postoperatively. The border of the tumour being marked with silver clips for orientation. One patient is alive more than 5 years after treatment. Beside epilation of the irradiated area no side-effects were seen.

As seen, the number of patients treated in the different series at Uppsala is small, and the material diverse. Any decision as to the therapeutic value of the treatment has to be based on a much larger material preferably studied under the conditions of a clinical trial permitting statistical analysis. There is thus a strong need for evaluating the role of protons in the development of modern radiotherapy but still we can base our considerations on the physical properties of the beam, which allows uniform and selected treatment of the carcinomas permitting at the same time the smallest possible radiation dose in the surrounding healthy tissues. This situation has been the dream of radiotherapists since the beginning of radiotherapy.

At present we feel that the properties of the proton beam are of special value for radiation therapy in 3 regions:[34]

1) the head-and-neck region where the eyes and the spinal chord must be avoided at irradiation.

2) the mediastinum where carcinomas of the oesophagus, for example,

can be treated with therapeutic doses while the integral dose can be kept low as well as protection of the spinal cord.

3) the pelvic region where for example malignancies of the bladder and the uterus can be treated with high doses without damaging the radiosensitive mucous membrane of the rectum.

It seems now worth while to scrutinize further practical aspects of large scale use of protons or other light ions in clinical practice. Within a larger group of experts from various fields, including accelerator technology and hospital organization, we are presently trying this approach. One important pre-requisite is beam-splitting so as to deliver, simultaneously, several beams of varying directions, vertically, oblique and horizontally. A lay-out for proton therapy in a larger hospital is being worked out.

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## REFERENCES


1. Wilson, R.: Radiological use of fast protons. Radiology 47 (1946), 487.

2. Tobias, C.A., Anger H. and Lawrence, J.: Radiological use of high energy deuterons and alpha particles. Am.J. Roentgenol. Rad. Therapy and Nuclear Med. 67 (1952), 1.

3. Larsson, B., Leksell, L., Rexed, B., Sourander, P., Mair, W. and Andersson, B.: The high-energy proton beam as a neurosurgical tool. Nature 182 (1958), 1222.

4. Larsson, B., Leksell, L., Rexed, B. and Sourander, P.: Effect of high energy protons on the spinal cord. Acta Radiol. 51 (1959), 52.

5. Rexed, B., Mair, W., Sourander, P., Larsson, B. and Leksell, L.: Effect of high energy protons on the brain of the rabbit. Acta Radiol. 53 (1960), 289.

6. Larsson, B.: Blood vessel changes following local irradiation of the brain with high-energy protons. Acta Soc. med. upsalien. 65 (1960), 61.

7. Leksell, L., Larsson, B., Andersson, B., Rexed, B., Sourander, P. and Mair, W.: Lesions in the depth of brain produced by a beam of high energy protons. Acta Radiol. 54 (1960), 251.

8. Larsson, B.: Pre-therapeutic physical experiments with high-energy protons. Brit. J. Radiol. 34 (1961), 143.

9. Larsson, B.: On the application of a 185 MeV proton beam to experimental cancer therapy and neurosurgery. A biophysical study. Acta Univ. Upsaliensis 9 (1962).

10. Larsson, B., Leksell, L. and Rexed, B.: The use of high energy protons for cerebral surgery in man. Acta Chir. Scan. 125 (1963), 1.

11. Larsson, B.: Radiological properties of beams of high-energy protons. Radiat. Res. Suppl. 7 (1967), 304.

12. Andersson, B., Larsson, B., Leksell, L., Mair, B., Rexed, B., Sourander, P. and Wennerstrand, J.: Histopathology of late local radiolesions in the goat brain. Acta Radiol. Ther. Phys. Biol. 9 (1970), 385.

13. Sténson, S.: Högenergetiska protoners inverkan på V x 2 tumörer på kanin. Nord. Med. 59 (1958), 786.

14. Falkmer, S., Larsson, B. and Sténson, S.: Effects of single dose proton irradiation of normal skin and V x 2 carcinoma in rabbit ears. A comparative investigation with protons and roentgen rays. Acta Radiol. 52 (1959), 217.

15. Sténson, S.: Weight changes and mortality of rats after abdominal proton and roentgen irradiation. A comparative investigation. Acta Radiol. Ther. Phys. Biol. 8 (1969), 423.

16. Stenson, S.: Effects of proton and roentgen radiation on the rectum of the rat. Acta Radiol. Ther. Phys. Biol. 8 (1969), 263.

17. Naeslund, J., Sténson, S. and Larsson, B.: Results of proton

irradiation of V x 2 carcinoma in the uterus of rabbits. Acta Obstet. Gynec. Scand. 38 (1959), 563.

18. Larsson, B. and Khilman, B.: Chromosome aberrations following irradiation with high-energy protons and their secondary radiation. A study of dose distribution and biological efficiency using root-tips of Vicia faba and Allium cepa. Int. J. Biol. 2 (1960), 8.

19. Warshaw, S. and Oldfield, D.: Pretherapeutic studies with the Chicago synchrocyclotron. Am. J. Roentgenol. Rad. Therapy and Nuclear Med. 78 (1957), 876.

20. Bonnet-Maury, P., Deysine, A., Frilley, M. and Stefan, C.: Efficacité biologique relative des protons de 157 MeV. C.R. Acad. Sci. (Paris ) 251 (1960), 3087.

21. Kurlyandskaya, E., Avrunina, G., Ponomareva, V., Federova, V., Yanovskaya, B. and Yarmonenko, S.: Relative biological effectiveness (RBE) of 660 MeV protons, translated from Dokl. Akad. Nauk. SSSR 142 (1962), 702.

22. Dalrymple, G., Lindsay, I., Ghidoni, J., Hall, J., Mitchell, J., Kundel, H. and Morgan, I.: Some effects of 138 MeV protons on primates. Radiation Res. 28 (1966), 471.

23. Dalrymple, G., Lindsay, I., Hall, J., Mitchell, J., Ghidoni, J., Kundel, H. and Morgan, J.: The relative biological effectiveness of 138 MeV protons as compared to $Co^{60}$ gamma radiation. Radiation Res. 28 (1966), 489.

24. Lindsay, I., Dalrymple, G.: Acute somatic effects in primates of protons to 400 MeV. Radiation Res. (1967) Suppl. 7, 330.

25. Ashikawa, J., Sondhaus, C., Tobias, C., Greenfield, A. and Paschkes, V.: Acute effects of high-energy protons and alpha particles in mice. Radiation Res. (1967) Suppl. 7, 312.

26. Falkmer, S., Fors, B., Larsson, B., Lindell, A., Naeslund, J. and Sténson, S.: Pilot study on proton irradiation of human carcinoma. Acta Radiol. 58 (1962), 33.

27. Fors, B., Larsson, B., Lindell, A., Naeslund, J. and Sténson, S.: Effects of high energy protons on human genital carcinoma. Acta Radiol. Ther. Phys. Biol. 2 (1964), 384.

28. Lawrence, J., Tobias, C., Born, J., Gottschalk, A., Linfoot, J. and Kling, R.: Alpha particle and proton beams in therapy. JAMA 186 (1963), 156.

29. Kjellberg, R., Sweet, W., Preston, W. and Koehler, A.: The Bragg peak of a proton beam in intracranial therapy of tumours. Trans. Am. Neurolog. Ass. 87 (1962), 216.

30. Gottschalk, A., Lyman, J. and McDonald, L.: Use of the Bragg peak for brain-tumour therapy. Semiannual report. Biology and Medicine, Donner Laboratory, University of California UCRL 11184 (1963), 121.

31. Graffman, S., Jung, B., Nohrman, B. and Bergström, R.: Supplementary treatment of nasopharyngeal tumours with high energy pro-

tons. Acta Radiol. Ther. Phys. Biol. 6 (1967), 361.

32. Graffman, S.: Personal communication (1971).

33. Graffman, S., Hugosson, R., Jung, B. and Nohrman, B.: High-energy protons in the postoperative treatment of glioblastoma multiforme. Excerpta Medica International Congress Series No. 105 (1967), 1050.

34. Graffman, S. and Jung, B.: Clinical trials in radiotherapy and the merits of high energy protons. Acta Radiol. Ther. Phys. Biol. 9 (1970), 1.

35. Karlsson, B.: Methoden zur Berechnung und Erzielung einiger für die Tiefentherapie mit hochenergetischen Protonen günstiger Dosisverteilungen. Strahlentherapie 124 (1964), 481.

Table I

RBE values for proton exposure

| Reference | Protons and reference radiation | Criterion | RBE |
|---|---|---|---|
| Sténson[13], 1958 | 40 MeV protons 220 kV X-rays | Epilation, erythema desquamation, necrosis, in rabbit skin. | 0.6-0.7 |
| Sténson[15] 1959 (prel.report) 1969 | 185 MeV protons 220 kV X-rays | Intestinal tract, rats. Weight changes and mortality. | 0.77±0.18 |
| Sténson[16] 1959 (prel.report) 1969 | 185 MeV protons 220 kV X-rays | Rectal mucosa, rats Histo-pathologic changes. | 0.6-0.7 |
| Larsson and Kihlman[18] 1960 | 170 MeV protons 180 kV X-rays | Broad bean root chromosome abberration. | 0.70±0.05 |
| Falkmer et coll.[14] 1959 | 40 MeV protons 220 kV X-rays | V x 2 carcinoma in rabbit ears. Induced regression. | Approx. 1 |

Table II

RBE values for proton exposure

| Reference | Protons and reference radiation | Criterion | RBE |
|---|---|---|---|
| Tobias et coll.[2] 1952 | 315 MeV protons 200 kV X-rays | Whole body, mice LD 50/30 | Approx. 1 |
| Warshaw and Oldfield[19] 1957 | Protons LET 2 keV/µm 250 kV X-rays | Whole body, mice Weight changes of thymus and spleen | 1.7±0.2 2.1±0.1 |
| Bonet-Maury et coll.[20] 1960 | 157 MeV protons 250 kV X-rays | Whole body, mice LD 50/30 | 0.77±0.1 |
| Kurlyandskaya et coll.[21] 1962 | 660 MeV protons 180 kV X-rays | Whole body, mice LD 50/30 | 0.55 |
| Dalrymple et coll.[22] 1966 | 138 MeV protons 2 MeV X-rays | Whole body, macaca mulatta | 1.0 |
| Dalrymple et coll.[23] 1966 | 138 MeV protons $^{60}Co$ | Whole body, mice LD 50/6 LD 50/30 | 1.06±0.05 0.97±0.04 |
| Lindsay et coll.[24] 1967 | 138 and 400 MeV protons 2 MeV X-rays | Whole body, macaca mulatta LD 50/30 | 1.04-1.09 |
| Ashikawa et coll.[25] 1967 | 730 MeV protons 250 kV X-rays | Whole body, mice LD 50/30 | 0.75 |

Table III

Medical use of high-energy protons, deuterons and alpha particles in radiotherapy

| Reference | Irradiation for | Started in | Number of cases |
|---|---|---|---|
| Falkmer [26] et coll. 1962 | Genital carcinomas | 1957 | 7 |
| Lawrence et coll.[28] 1963 | Breast cancer metastasis | 1960 | 1 |
| Kjellberg et coll.[29] 1962 | Brain tumours | 1961 | 3 |
| Gottschalk et coll.[30] 1963 | Brain tumours | 1961 | 3 |
| Fors et coll.[27] 1964 | Genital carcinomas | 1959 | 10 |
| Graffman [31] et coll. 1967 | Nasopharyngeal malignancies | 1964 | 10 |
| Graffman et coll.[33] 1967 | Brain tumours | 1964 | 7 |
| Graffman et coll.[32] 1971 | Nasopharyngeal malignancies | 1968 | 10 |

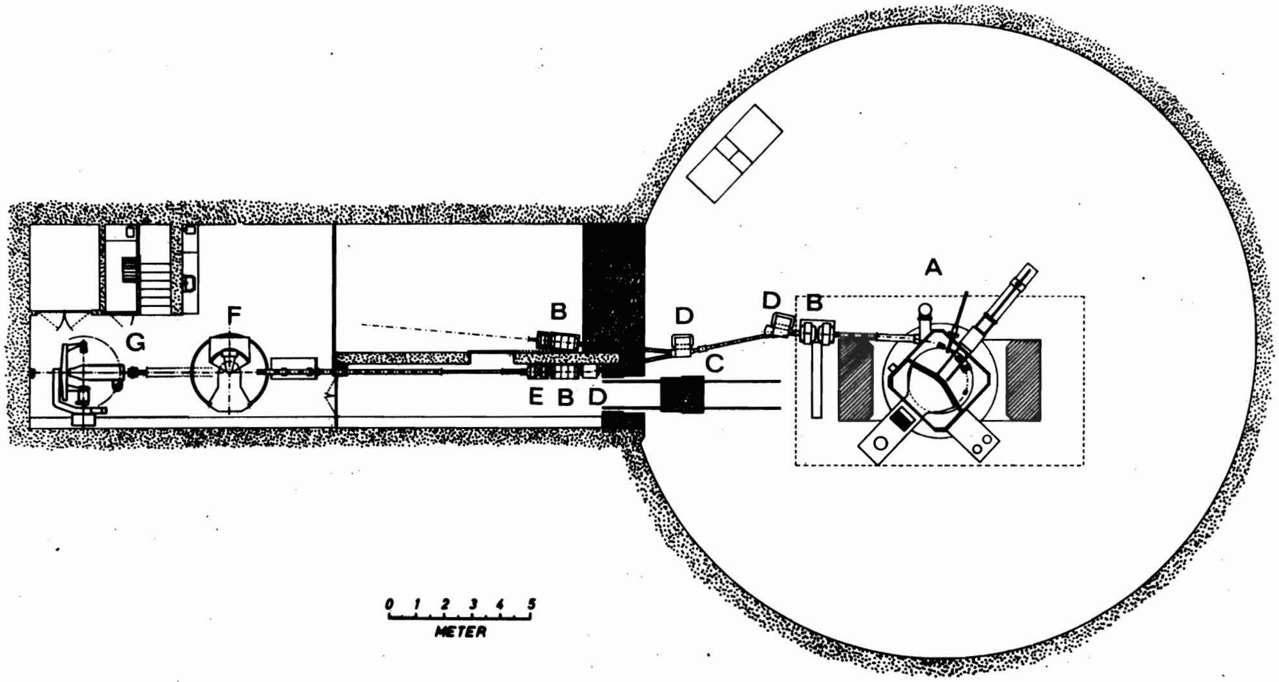


Fig. 1. Arrangements for biological experiments and therapy with beams of high-energy protons at the University of Uppsala. A) 230-cm synchrocyclotron. B) Strong-focusing magnets. C) Ion chambers and beam 'shutter'. D) Beam-deviating magnets. E) Magnetic sweeping coils for altering beam cross-section. F) Equipment for 'narrow beams'. G) Equipment for 'broad beams'.

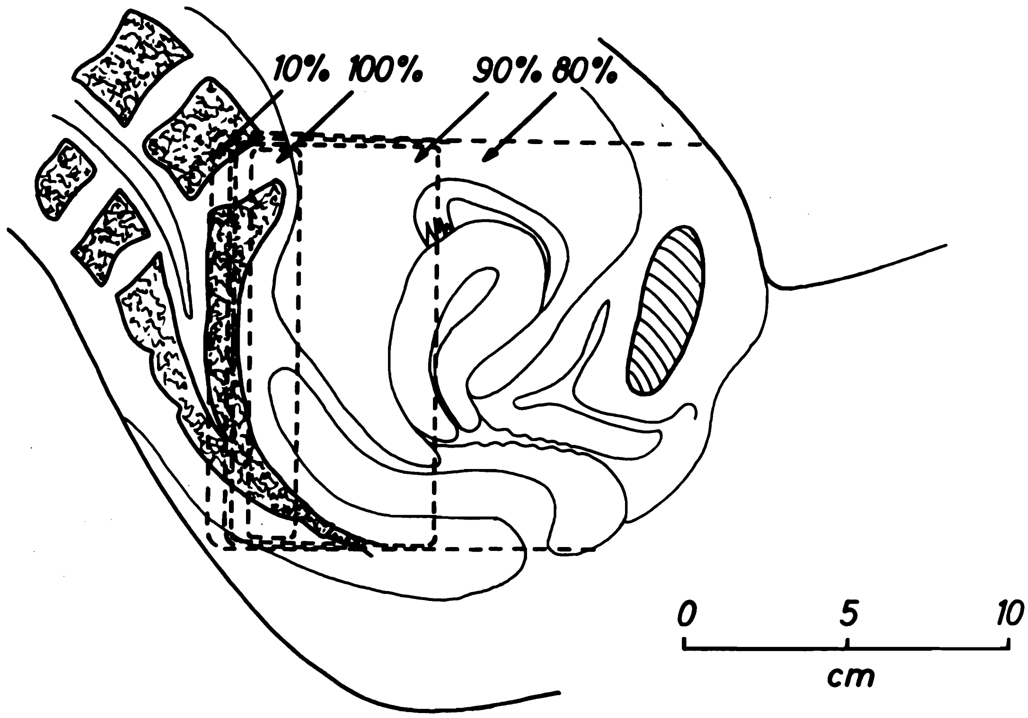


Fig. 2. Section through the pelvis. Distribution of the dose absorbed by the tissue on irradiation with a beam of 12.3 cm diameter.