MEDICAL TREATMENT AND DIAGNOSIS USING 160 MEV PROTONS*

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ABSTRACT

The 160 MeV proton synchro-cyclotron at Harvard University, abandoned for nuclear physics research in 1967, has been operating for 4.5 years on a part-time basis for the treatment of patients and for other investigations, several of which are medically oriented. The cost of operation is met entirely from users' fees of about $1200 per 24-hour day. In the current clinical program, initiated in 1961, the pituitary gland is the usual target and some 540 patients have been treated, the current case load being 55 to 60 new patients per year. The proton beam also offers advantages in terms of physical dose distribution for larger targets more typical of cancer therapy. Apparatus is being modified to test these advantages experimentally with the expectation that limited clinical trials might be undertaken later.

The use of protons for diagnostic purposes is also being investigated. Proton radiography shows some promise in visualizing soft tissue structures and abnormalities. Tumors, cerebral infarctions, hemorrhages and aneurisms have been visualized in brain specimens. In the human breast, malignant carcinoma has shown useful contrast. Clinical value of the technique remains to be explored.

As medical applications of protons in the 150 to 200 MeV energy range become better understood, the question arises whether a suitable accelerator could be designed within the budget, staff and space limitations of major cancer treatment centers. A synchro-cyclotron design concept is proposed which might prove suitable.

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OPERATING EXPERIENCE WITH THE HARVARD CYCLOTRON

The Harvard cyclotron was supported by the U.S. Office of Naval Research for full time operation, primarily for nuclear physics research, until the end of 1967. The annual budget in this period was approximately $200,000 and on-time of the machine, averaged over 365 days per year, was about 20 hours per day. Since then both budget and running time have fluctuated considerably in response to the requirements of users, as indicated in Table I.

Table I. Cyclotron use and gross budget by fiscal year

	1968-69	1969-70	1970-71	1971-72
Total paid use (days)	31.7	41.2	20.9	26.5
Clinical use (days)	14.5	19.5	12.5	14.0
Non-clinical use (days)	17.2	21.7	8.4	12.5
Gross budget ($1000's)	31.6	41.4	22.2	29.6

Despite these fluctuations it now appears that there is sufficient demand for proton irradiations to permit an indefinite continuation at this level of activity and of funding, provided that no major equipment failures occur. Since much of the equipment is very old, this possibility is ever present, yet the number of equipment faults causing a delay in operation of more than one hour has remained between one and two per year.

Although some degree of financial stability has been achieved, the budget is necessarily tight, as indicated in Table II, which presents approximate figures for the fiscal year 1971-72. Because of the budgetary constraint replacement of obsolescent equipment has been repeatedly deferred. In the new year some replacements will be made.

Table II. Approximate operating expense and income, 1971-72

Amount in reserve, 1 July 1971		- $ 2,030
Expenses, 1 July 1971 - 30 June 1972		
Salaries and benefits	$ 9620	
Electric power	4060	
Supplies and misc. exp.	750	
Services purchased	880	
Indirect costs (building+services)	8080	
Total		23,390
Income (from users' fees)		29,620
Amount in reserve, 1 July 1972		+ 4,200

Although detailed budgets make dull reading, the questions of cost and of overall reliability of operation are of great importance when routine medical applications are being considered. The experience gained at Harvard may serve as a reference point when making estimates for other installations.

CURRENT CLINICAL PROGRAM

Patients are irradiated at the Harvard cyclotron at the direction of Dr. R. N. Kjellberg of the Massachusetts General Hospital (MGH) and Harvard Medical School. Patients are referred to MGH from a number of medical centers throughout the United States and Canada and occasionally from other countries. All of the detailed examinations and tests which have been incorporated into the protocol since our first patient was treated in 1961 are carried out at the MGH over several days prior to the scheduled day of treatment. Four patients are usually scheduled for one day, although five have been accommodated without difficulty on several occasions. The patients are brought from the hospital to the cyclotron and returned after treatment in an ambulance. The entire procedure at the cyclotron, not counting waiting time, requires 1.5 to 2 hours per patient. However, extensive alignment and calibration of the beam are required prior to treatment, often requiring an equal amount of cyclotron time. Consequently a full 24-hour day is usually used to treat four patients, resulting in a cost to the patient in the vicinity of $400 for the irradiation. Since only the one treatment is required, the cost is quite favorable compared either to a course of conventional radiation therapy or to surgery. Furthermore, in the latter case, the short hospitalization and absence of any recuperative requirement favors the proton treatment substantially.

Approximately 550 patients have been treated during the past 11 years, and in every instance the Bragg peak of the proton beam has been used. The target in all but 20 or so cases has been the pituitary gland, and the objective has been to destroy completely a substantial portion of the tissues in the anterior lobe of the pituitary, while minimizing damage to other more sensitive structures nearby. To do this, the patient is rotated after each brief exposure, with the pituitary exactly at the center of rotation, so that the cumulative effect is that of twelve beams converging on the pituitary, six from either side of the head. In addition, the depth of penetration is adjusted by absorbers so that each time the Bragg peak falls within the pituitary. This procedure has been undertaken to reduce the hyperfunction of an abnormal gland, as in acromegaly or Cushing's disease, or to shut off as well as possible the secretions of a normal gland in order to deal with hormone-sensitive diseases such as the retinopathy arising from diabetes and some metastatic lesions of carcinoma of breast or prostate. The distribution of diseases treated over the last five years is given in Table III. Clearly the acromegalics and patients with Cushing's disease or the closely related Nelson's syndrome are the most important numerically.

Table III. Distribution of patients treated with the Harvard Cyclotron in the past five years according to radiation target and disease.

Target and Disease	67-68	68-69	69-70	70-71	71-72	5 YRS
1. Abnormal pituitary target:						
Acromegaly	46	33	52	32	21	184
Cushing's disease	7	9	8	4	12	40
Nelson's syndrome	1	2	1	0	1	5
Chromophobe adenoma	1	1	3	10	13	28
2. Normal pituitary target:						
Ca. of breast, prostate	1	1	1	1	1	5
Diab. retinopathy	12	6	5	0	0	23
3. Misc. intracranial targets:						
Tumor	0	0	1	2	5	8
AV malformation	0	0	0	0	2	2
Total	68	52	71	49	55	295

A recent review of the clinical results of this method of pituitary suppression shows an overall success rate exceeding 80 percent in the treatment of acromegaly and Cushing's disease, while about 50 percent of the cases showed remission to normal endocrine status[1]. (See table IV) About 15 percent failed to show any significant reduction in pituitary output although in some of these there may have been an arrest of progressive disease. The principal complication associated with the treatment is a transient disturbance of the function of the oculomotor nerves resulting usually in a mild diplopia observed for several months. In one case the episodes of diplopia seem to be permanent. The incidence of oculomotor problems has been decreasing as more refinements are made in delimiting the pituitary target radiographically and in tailoring the dose-distribution to fit each patient's anatomy. Visual field defects have also been measured in some patients, but interpretation is confused by a fairly high incidence of this problem before treatment.

Two complications have been noted which presumably result from nearly complete destruction of the pituitary when only partial destruction was intended. Thus about 14 percent of the patients have required routine hormonal supplements, and 2 percent have developed temporary diabetes insipidus as a result of damage to the <u>posterior</u> lobe of the pituitary, which is normally spared. All of these observations have been summarized in Table IV.

Table IV. Clinical observations on patients treated for acromegaly and for Cushing's disease.

	Acromegaly	Cushing's Disease
1. Cases available for study	118 cases	36 cases
2. Response:		
Remission	48%	58%
Improvement	36%	27%
No improvement	16%	14%
3. Complications:		
Oculomotor difficulties[a]	29 cases[b]	1 case
Visual field defects	10 cases[c]	3 cases
Hormonal insufficiency	16 cases	5 cases[d]
Diabetes insipidus	3 cases	

a) Transient except for one case
b) 7 cases before treatment
c) 6 cases before treatment
d) All had surgical adrenalectomy prior to treatment

The progressive loss of vision characteristic of diabetic retinopathy has also been treated by irradiating the pituitary with the Bragg peak in a total of 183 patients. The results have been extensively analyzed and compared with the results of other methods of treatment[2,3]. Briefly, we found that in about 70 percent of cases, vision was sustained for a year, but by 4 years the percentage had dropped to 50. The outcome seems to be strongly dependent on the extent to which vision has already deteriorated at the time of treatment. Since the proton beam cases were predominantly those whose general debility excluded them from surgical hypophysectomy, it is not surprising that, as a group, they showed severe deterioration of vision before treatment. When we compared the results of several different methods of treatment, we took this factor into account, and found that there was no significant difference in success rate for similarly advanced stages of visual deterioration[3]. One of these methods of treatment, retinal photo-coagulation, is especially appropriate to the early stages of deterioration and involves even less stress to the patient than the proton beam irradiation. Prompt treatment of diabetic retinopathy by photo-coagulation seems the wisest course.

APPLICABILITY TO IRRADIATION OF LARGER TUMORS

In the clinical work described above, the Bragg peak of the proton beam is used to destroy completely a selected volume of tissue, a result quite comparable to surgery. In radiation-therapy of maglignant tumors a more subtle effect is desired resulting in the death of all malignant cells but leaving essential normal tissue intact, even when it must be given the same radiation dose as the tumor. Since the difference between the dose required to sterilize the tumor and the dose that will ultimately cause unacceptable damage to the associated normal tissues is likely to be small, a highly uniform dose is needed throughout the tumor-bearing region. A rapid and substantial reduction of dose beyond the boundaries of the target volume is also desirable to avoid damage to neighboring structures. It has long been known that a beam of heavy charged particles offers, in principle, some advantage in dose distributions attainable[4]. Comparisons have been made between dose distributions attainable with protons, photons and electrons using rather idealized geometries[5,6,16]. Some results are presented in Table V and Figure 1.

Table V. Calculated doses along the axis when two opposed fields are used to irradiate a target in a slab of tissue. Dose in percent of target dose.

	Cobalt 60	20 or 22 MeV X rays	Protons
1. 10 cm target centered in 22 cm slab:			
Skin dose (0.5 cm avg)	~90	~54	45
Off-target (6 cm avg)	127	94	51
Overall (22 cm avg)	105	97	73
2. 6 cm target centered in 20 cm slab:			
Skin dose (0.5 cm avg)	~90	~56	32
Off-target (7 cm avg)	105	92	40
Overall (20 cm avg)	104	95	59
3. 6 cm target centered in 30 cm slab:			
Skin dose (0.5 cm avg)	~110	~53	28
Off-target (12 cm avg)	133	99	36
Overall (30 cm avg)	117	99	49

A number of problems appear when one departs from idealized geometries and considers actual cases. The target volume and the patient's anatomy are irregular;

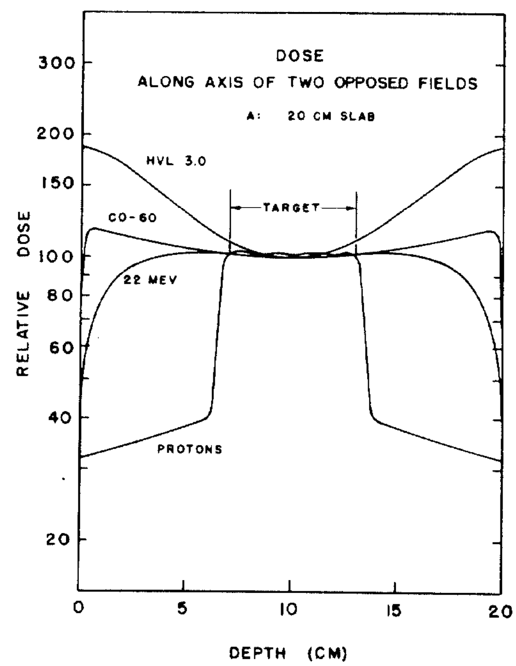

Fig. 1 Comparison of calculated dose distributions obtained with 250 KV (HVL 3.0), Cobal-60, and 22 MeV photons, and protons. A 6 cm target is irradiated by two parallel opposed fields in each instance, and the dose along the common axis is shown, relative to the target dose.

density anomalies must be taken into account due to bone, lung tissue, sinuses and so on; different tissues are more or less sensitive to radiation; and there are distinct limitations on the ways in which a patient may be positioned for irradiation. With the help of radiation therapy staff at the New England Deaconess Hospital and the Massachusetts General Hospital we are learning how to deal with these problems. Treatment plans for actual patients are being made to compare with the plan for conventional therapy actually given. The calculated dose distributions will be checked experimentally in suitable phantoms, and specific measurements made on bone and air cavities as well. It appears now that a vertical beam, and possibly an inclined beam, may be essential for even a limited clinical trial to be acceptable. A sketch showing how these might be provided is shown in Fig. 2.

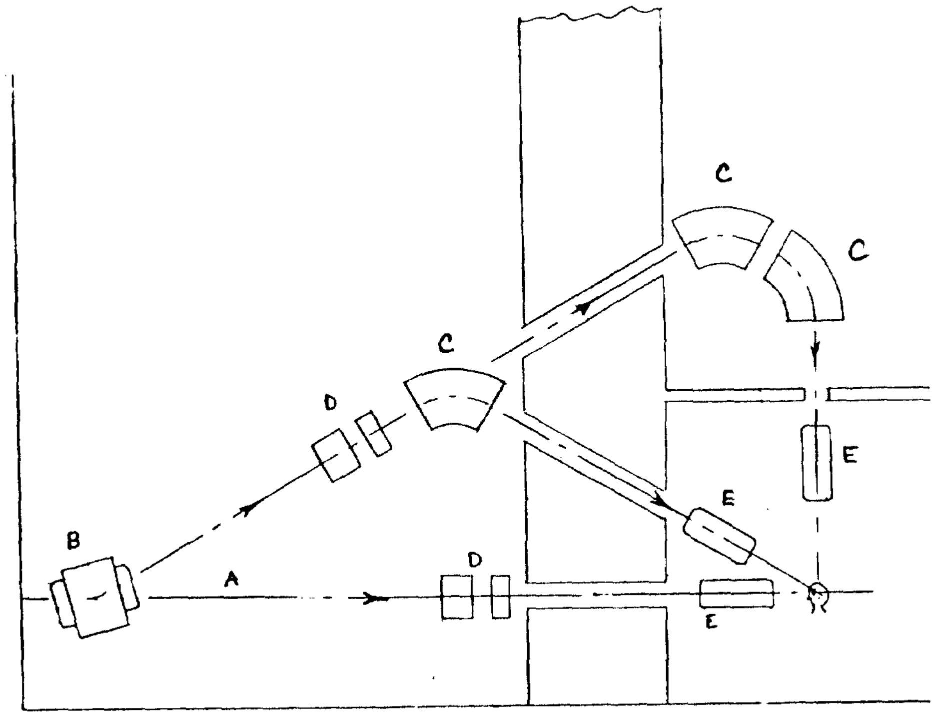

Fig. 2 Side view of a magnet system to deliver horizontal, vertical or inclined proton beams to a patient. A = present beam line, B = 30 degree bend, C = 60 degree bend, D = quadrupoles, E = collimators.

PROTON RADIOGRAPHY

The possibility of using a proton beam to make radiographs of unusually high contrast but relatively poor spatial resolution was pointed out some years ago[7], and some additional work on radiographic use of protons has appeared subsequently[8,9,10]. High contrast is available when photographic film is used to record the rapid attenuation of proton flux near the end of range of a nearly monoenergetic proton beam. Small angle multiple scattering of the protons is responsible for the poor spatial resolution. Figure 3 shows a proton radiograph of a cylindrical target of graphite (Grade AUC) 7.62 cm in diameter and 9.2 gm/cm^2 thick, and beside if a portion of an aluminum absorber 10.42 gm/cm^2 thick with a step-wedge added having steps of 0.05 gm (Al)/cm^2 thickness providing calibration. Optical densitometry of the radiograph showed extreme variations of about 3 percent peak to peak in the apparent thickness of the graphite

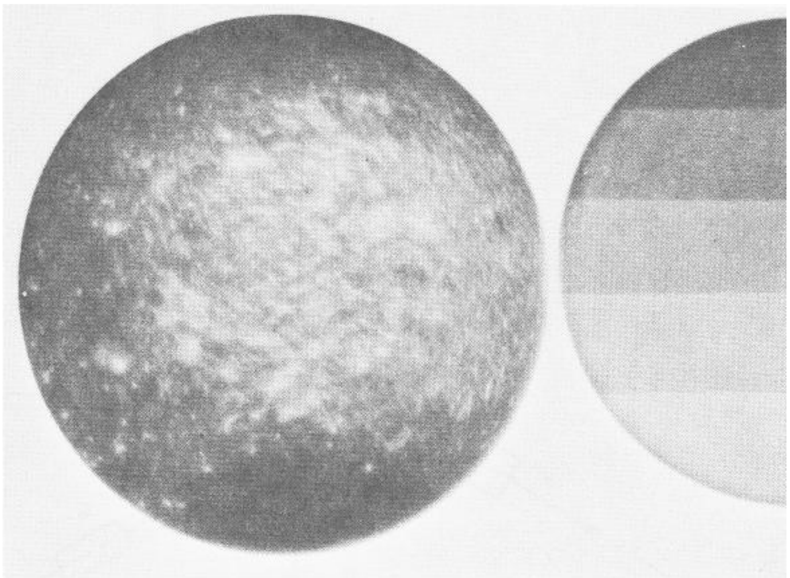

Fig. 3 Proton radiograph of Grade AUC graphite 7.62 cm diameter, 9.2 gm/cm^2 thick. Portion of aluminum stepwedge, having steps of 0.05 gm/cm^2, provides calibration. Variation of graphite density is about 3 percent peak to peak.

target which were not revealed on x-ray examination. Pyrolitic graphite proved to be much more uniform[11].

For the proton beam used in these experiments the flux at the end of range drops by a factor 10^3 over an increment in absorber thickness of 1 gm/cm^2. Outside this region flux is relatively constant. Furthermore, most photographic materials pass through the range of optical densities useful for direct viewing within an exposure range of 10 to 1, so that the dynamic range of a single proton radiograph of this sort is limited to about 0.3 gm/cm^2 (see Figure 3 for example). An object having surface irregularities greater than this can be inspected for small internal variations in density by immersion in a fluid having approximately equal density and similar chemical composition contained in a tank with parallel faces. This technique is illustrated in Figure 4 which shows a 1 cm lamb chop immersed in 12 cm of water and radiographed using 30 KVp x-rays (above) and protons (below). The enhanced contrast of the proton technique is self-evident.

In collaboration with V. W. Steward (University of Chicago) we are using this technique to examine human

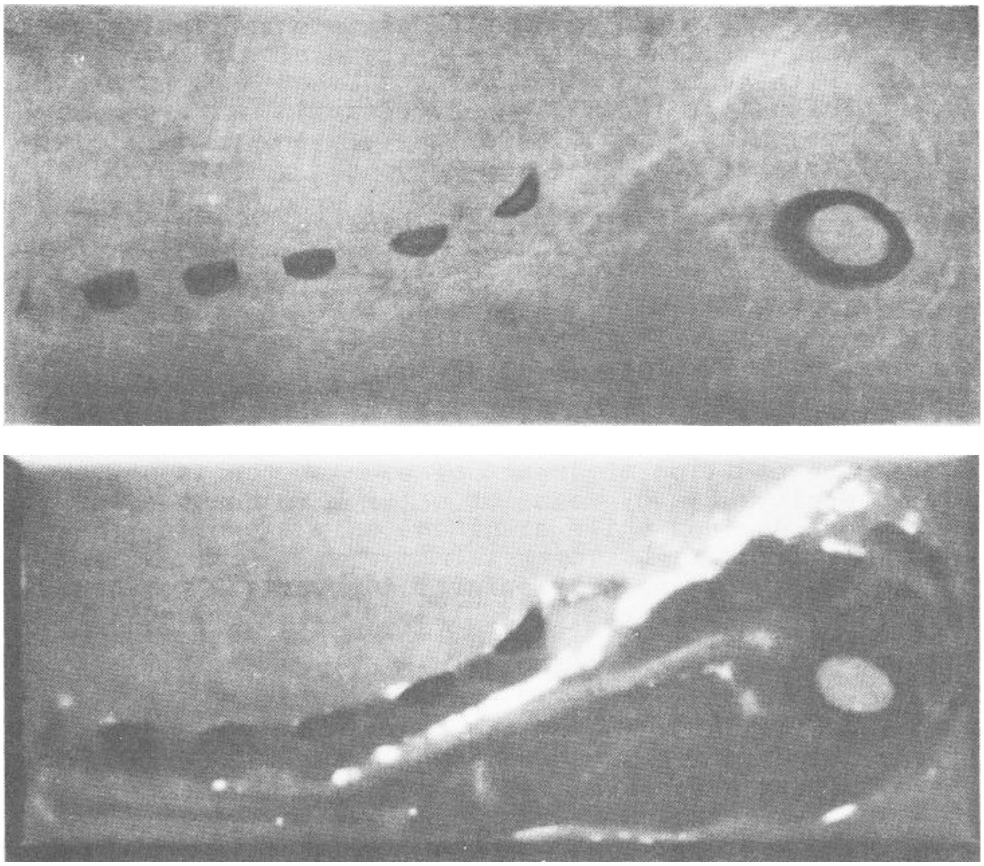

Fig. 4 X-ray photograph (above) and proton radiograph (below) of a lamb chop 1 cm thick immersed in a water phantom 12.5 cm thick. Note that the x-ray shows much less contrast for fat and essentially no contrast for lean meat (muscle), but has much better spatial resolution.

tissue specimens and (as conditions permit) living patients with the object of correlating features of the radiographic image with anatomic structures and pathologic conditions. Work with prepared specimens indicates that under favorable conditions cerebral white and gray matter can be distinguished as well as abnormalities such as tumors, cerebral infarctions, hemorrhages and aneurisms. We have also found that confusing artifacts are easily introduced which make it highly desirable to examine living patients, but the dose required for a good exposure using photographic film directly (typically 30 to 100 rads) is too high. Using an intensifying screen (DuPont Hi Speed MA) we have made several exposures of a patient with acute carcinoma of the breast and have been able to visualize the malignancy clearly, using a dose of a fraction of a rad. Unfortunately the picture quality suffers for reasons which we do not yet understand completely.

The details of film response and the optimization of intensifying screen design for proton exposure are being pursued. There is evidence that a fluorescent screen combined with television apparatus will provide a better solution[10], but all of these will still be restricted in the maximum variation of object thickness which can be recorded. This restriction can be removed by using a small collimated beam to scan the object while measuring the average transmitted proton energy, or else by measuring the position of impact of each proton in a broad low-intensity beam by means of multi-wire chambers or equivalent devices while simultaneously measuring the proton's energy as it emerges from the object[12]. Both of these methods are particularly appropriate for computer data analysis, which is likely to be essential.

A MEDICAL PROTON FACILITY

The clinical value of the proton beam has been proven only for treatment of some unusual disorders of the pituitary affecting at most a few hundred patients in North America each year. Its value for general radiation therapy seems plausible but has certainly not been demonstrated. Yet it is not premature to consider the design of a medical proton beam facility for several interrelated reasons:

1. One should expect only a modest improvement in outcome of radiation therapy as a result of using protons instead of the best photon or electron therapy now available. Consequently a large number of patients treated in a well-controlled study will be required to lend statistical validity to the result, a requirement virtually impossible to satisfy with existing physics installations[14,15].
2. Proton beam diagnostic techniques will be of little practical value unless they are conveniently available even for the critically ill.
3. For the reasons above as well as the equally valid limitations of available time, radiologists are reluctant to "commute" to existing accelerators for research work unless there is a reasonable possibility that a hospital-based facility can be built later.

Assuming an extracted beam of 10^{11} protons/sec and an efficient beam-spreading system, one should be able to get an average flux of 7 x 10^7 protons cm^{-2} sec^{-1} with good uniformity over a 30 cm diameter field. At the Bragg peak in water, the flux will have been attenuated to about 5 x 10^7, the mean stopping power per proton will be about 35 MeV gm^{-1} cm^{-2}, so the doserate will be 1700 rads/min. If the Bragg peak is spread over 10 cm in depth by means of a ridge-filter[6] or other range-modulating device, the average doserate over the target volume will still be 600 rads/min, a value consistent with current therapy practice. Much higher doserates are available for smaller fields if desired.

Assuming 10 percent extraction efficiency, an internal beam of 10^{12} protons sec^{-1} would be required, or about 0.2 x 10^{-6} A. Most synchro-cyclotrons run at 1 to 10 x 10^{-6} A, whereas isochronous machines develop 10^{-4} A, hence the former seems the better choice. In addition, the synchro-cyclotron has proven to be very reliable and simple to operate.

Since the output current required is so low, it should be possible to use a magnet-gap much smaller than in existing synchro-cyclotrons, resulting in smaller coils and less power dissipation as well as some reduction in the amount of iron required. A small gap also means reduced dee aperture which will be reflected in the reduced beam current, and increased dee to ground capacitance which increases the radio-frequency (RF) power requirement. An economic balance between magnet and RF power should be found taking account of the intermittent requirement for beam in clinical work.

More accelerated beam is lost than is extracted, hence effective shielding of the accelerator itself is important. The iron of the magnet structure can serve as the primary shield by wrapping it closely around the gap on all sides. This also provides an excellent magnetic circuit but makes access to the inside of the machine more difficult. However, if the accelerator is reliable enough for routine clinical work, the need for access should be very infrequent. On such rare occasions the magnet can be separated to expose the dee and other internal structures. Electrical connection to the dee can be made by lines penetrating through openings in the iron so that the modulating capacitor will be outside the iron in a region of nearly zero magnetic field.

To make best use of a small magnet gap, the dee should be designed with minimum skin thickness. If the orbit plane is made vertical the dee can hang from the transmission lines so that very little cantilever

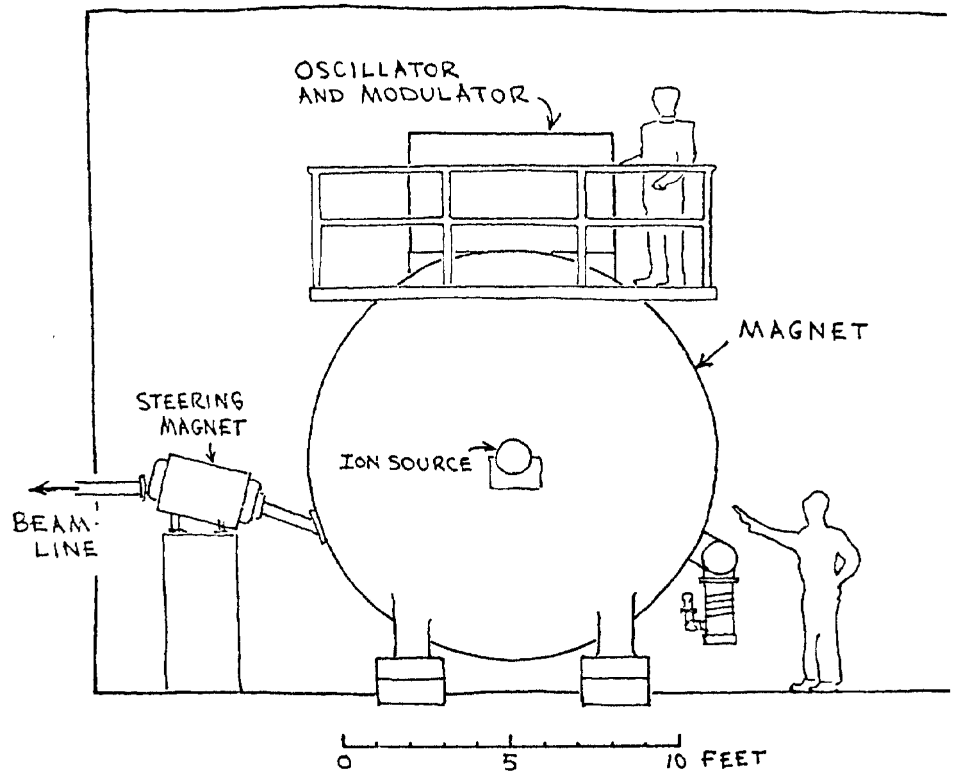

Fig. 5 Sketch of a suggested design for a synchro-cyclotron for medical applications of proton beams. See text for description.

strength is required. Thus a skin consisting of thin sheet held in tension by a semicircular peripheral frame might be adequate. Cooling of the skin would be limited to radiation and conduction to the periphery, hence it must be designed to operate at high temperature with proper allowance for thermal expansion. Transmission lines and peripheral frame would be water-cooled.

The optimum proton energy needs to be established with the help of detailed treatment - planning mentioned earlier. For pituitary irradiations 125 MeV would suffice but for more general radiotherapy 155 MeV would be minimal (16 cm penetration) and 180 MeV much more desirable (21 cm penetration). Proton radiography through the thicker sections of the human body would require about 220 MeV (31 cm). Figure 4 and Table VI suggest a design for 155 MeV. The cost of purchasing the various parts of this accelerator (magnet iron, coils, power supplies, etc.) has been roughly estimated at $0.2 million. Assuming the finished cost to be 3 times the component cost, such a machine might thus be duplicated for $0.6 million, assuming that the design had been perfected on the first model. This figure may be compared to a purchase price of $0.8 million for the largest therapy machines now on the market.

Table VI Condensed specifications for a medical cyclotron

Class of accelerator	Synchro-cyclotron
Proton energy	150 MeV
Extracted beam current	0.02 μA
Maximum field size	30 cm
Doserate for 30 cm field	600 rads/min
Total weight	95 tons
Weight of iron	92 tons
Weight of copper	1.6 tons
Coil power	110 KW
RF system power	39 KW

CONCLUSIONS

Both here and abroad proton beams and helium ion beams from existing accelerators are being increasingly considered for therapy. Clinical results are encouraging and in some situations this form of treatment has already gained widespread acceptance. Experience shows that good reliability can be maintained at an acceptable operating cost. If such medical applications are to be extended to a greater variety of problems, including promising diagnostic possibilities as well as larger numbers of patients requiring therapy, then careful, detailed, but imaginative design of accelerators and facilities specifically for this kind of work will be required.

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DISCUSSION

URTASUN: In the acramegalic patient how do your results compare--using the growth hormone radio-immuno assay--with patients treated with more conventional means such as Cobalt-60, as reported in the NIH series of two years ago?

KOEHLER: That question is a little outside my province, I am not a medical man. It is my understanding that the conventional radiotherapy has been rather unsuccessful in reducing growth hormone levels to the normal range. In fact, I believe a relatively small percentage show any significant reduction in growth hormone. Now this does not necessarily mean that there is not a clinical response. The correlation between chemical tests and the symptomatic relief that the patient feels is not as good as one might like.

HARPER: I would like to respond to the comment that was made to Dr. Wilson about the cyclotron down the street that we didn't use. It was a 450 MeV proton synchrocyclotron, and it wasn't really designed for making radioisotopes, which is our principal interest. I think it has now gone out to the National Accelerator Laboratory, and has become a bending magnet!

MORRISON: Can you tell me what kind of radiation doses were delivered by the proton radiography?

KOEHLER: Yes, the patient that you saw received a dose of 600 mrad. We are working currently with standard x-ray intensifying screens, which are rotten for protons. We hope that we will be able to develop screens or, if that fails, other appropriate methods for recording the information from proton beams. In principle, we should be able to get one or two orders of magnitude improvement in dose.

MORGAN: You showed the very superb advantage of geometric precision in hitting small targets. This is a precision which one could take over into ordinary conventional radiotherapy for malignant disease. I would like to pose you the question whether it is really worth it, in the sense that protons have, in fact, a geometric advantage which is unsurpassed but they haven't any biological advantage as far as malignant tumours are concerned. Any comment on that?

KOEHLER: I think my first comment is essentially the same as something that you said earlier: that is, there is a great lack of hard information on what makes radiotherapy work. And in particular there is a virtually complete lack of information about what effect, if any, a variation in physical dose distribution may have. I am familiar with only one actual comparison study of patients having supposedly the same kinds of disease being treated with two different types of radiation and efforts being made to change nothing except the physical dose distribution, and this is the paper by Ault. He showed that indeed there was a considerable improvement just on the basis of improving the physical dose distribution. My feeling is that we cannot generally expect any great improvement in cure rate using protons. I do think that we can reduce the discomfort and other more serious effects of complications due to injury to normal tissue which just happens to get in the way of treatment.

MICHAELIS: Am I right in thinking that your proton radiography is in fact a mass measurement via average measurement?

KOEHLER: That is correct.

MICHAELIS: Therefore, you could presumably replace those present detection methods by a beam of variable energy, by a wedge absorber of sufficiently small dimensions, or anything of this kind?

KOEHLER: That is right. In fact, I have been working on that.

MORGAN: Can I say that I agree with you 100% about the fact that you don't know what happens when you alter the distribution in tumours. But wouldn't you have thought that perhaps the geometric advantages may not be sufficient grounds for so vast an expense?

KOEHLER: Yes, if the expense were in fact vast I would agree with you. But the current operating cost of the 160 MeV machine that we are using is apparently about the same as that of a conventional therapy machine--about $50 an hour. The construction cost of a machine designed specifically for this kind of work I believe would be comparable with the costs of conventional therapy machines.