July 1946

November 1946

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Radiological Use of Fast Protons

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EXCEPT FOR electrons, the particles which have been accelerated to high energies by machines such as cyclotrons or Van de Graaff generators have not been directly used therapeutically. Rather, the neutrons, gamma rays, or artificial radioactivities produced in various reactions of the primary particles have been applied to medical problems. This has, in large part, been due to the very short penetration in tissue of protons, deuterons, and alpha particles from present accelerators. Higher-energy machines are now under construction, however, and the ions from them will in general be energetic enough to have a range in tissue comparable to body dimensions. It must have occurred to many people that the particles themselves now become of considerable therapeutic interest. The object of this paper is to acquaint medical and biological workers with some of the physical properties and possibilities of such rays.

To be as simple as possible, let us consider only high-energy protons: later we can generalize to other particles. The accelerators now being constructed or planned will yield protons of energies above 125 Mev (million electron volts) and perhaps as high as 400 Mev. The range of a 125 Mev proton in tissue is 12 cm., while that of a 200 Mev proton is 27 cm. It is clear that such protons can penetrate to any part of the body.

The proton proceeds through the tissue in very nearly a straight line, and the tissue is ionized at the expense of the energy of the proton until the proton is stopped. The dosage is proportional to the ionization per centimeter of path, or specific ionization, and this varies almost inversely with the energy of the proton. Thus the specific ionization or dose is many times less where the proton enters the tissue at high energy than it is in the last centimeter of the path where the ion is brought to rest. Bragg Peak

These properties make it possible to irradiate intensely a strictly localized region within the body, with but little skin dose. It will be easy to produce well collimated narrow beams of fast protons, and since the range of the beam is easily controllable, precision exposure of well defined small volumes within the body will soon be feasible.

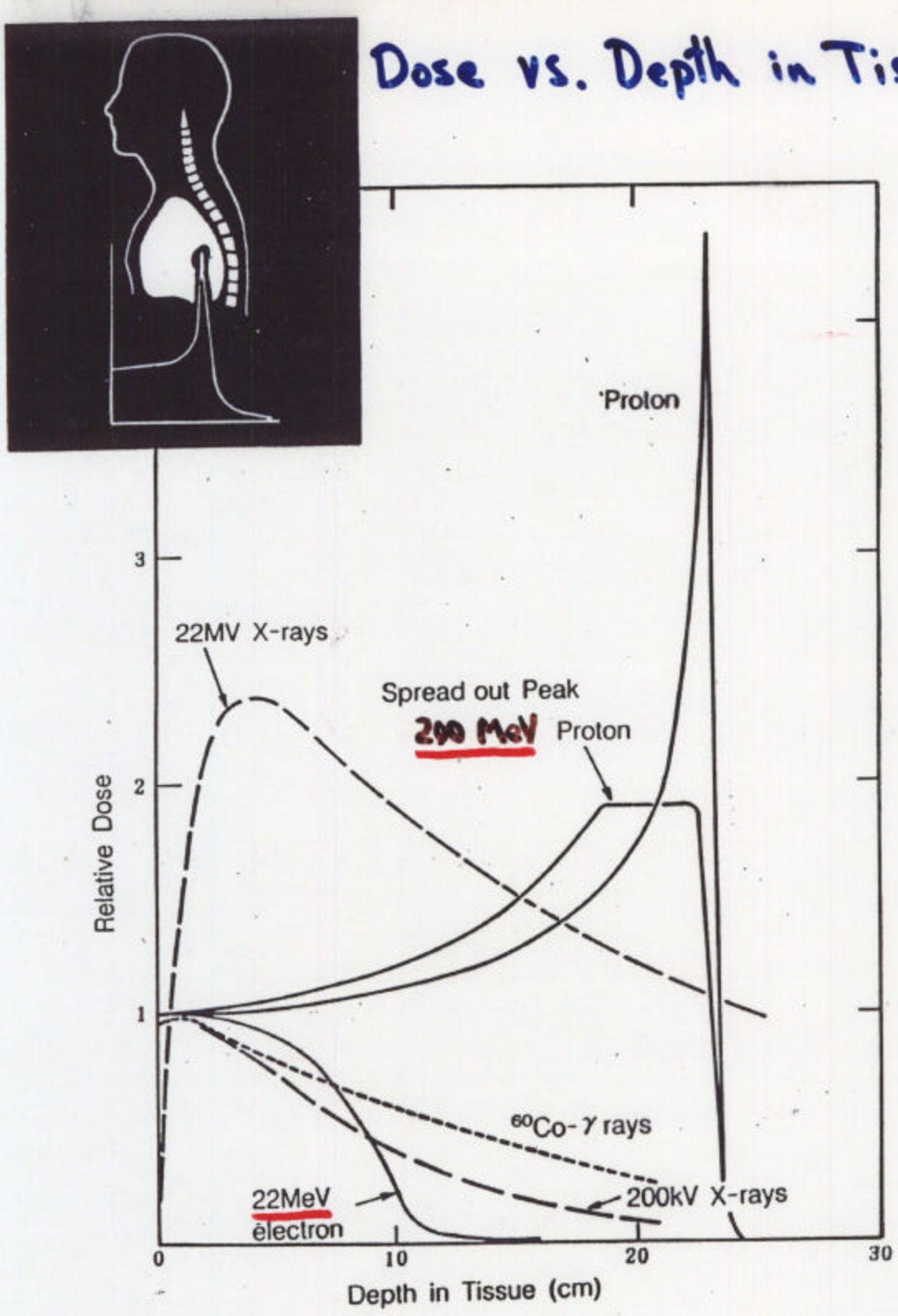
Let us examine the properties of fast protons somewhat more quantitatively. Perhaps the most important biological quantity is the specific ionization, or number of ions per centimeter of track. This quantity is not difficult to calculate. The results of such calculations are shown in Figure 1, where the range of protons in tissue is plotted for protons of various energies. In the same figure, the specific ionization is plotted as a function of the range in tissue. For purposes of calculation, tissue has been assumed to have the molecular formula (1): $C_{0.5}H_8O_{2.5}N_{0.14}$, and to be of unit density, *i.e.*, 15 per cent protein and 85 per cent water. The calculations can be easily extended to other materials and densities.[2] The accuracy is perhaps 5 per cent. However, exact values for various tissues can be quickly measured as soon as the fast protons are available.

Figure 1 shows, for example, that if we want to expose a region located 10 cm. be-

[1] Accepted for publication in July 1946.

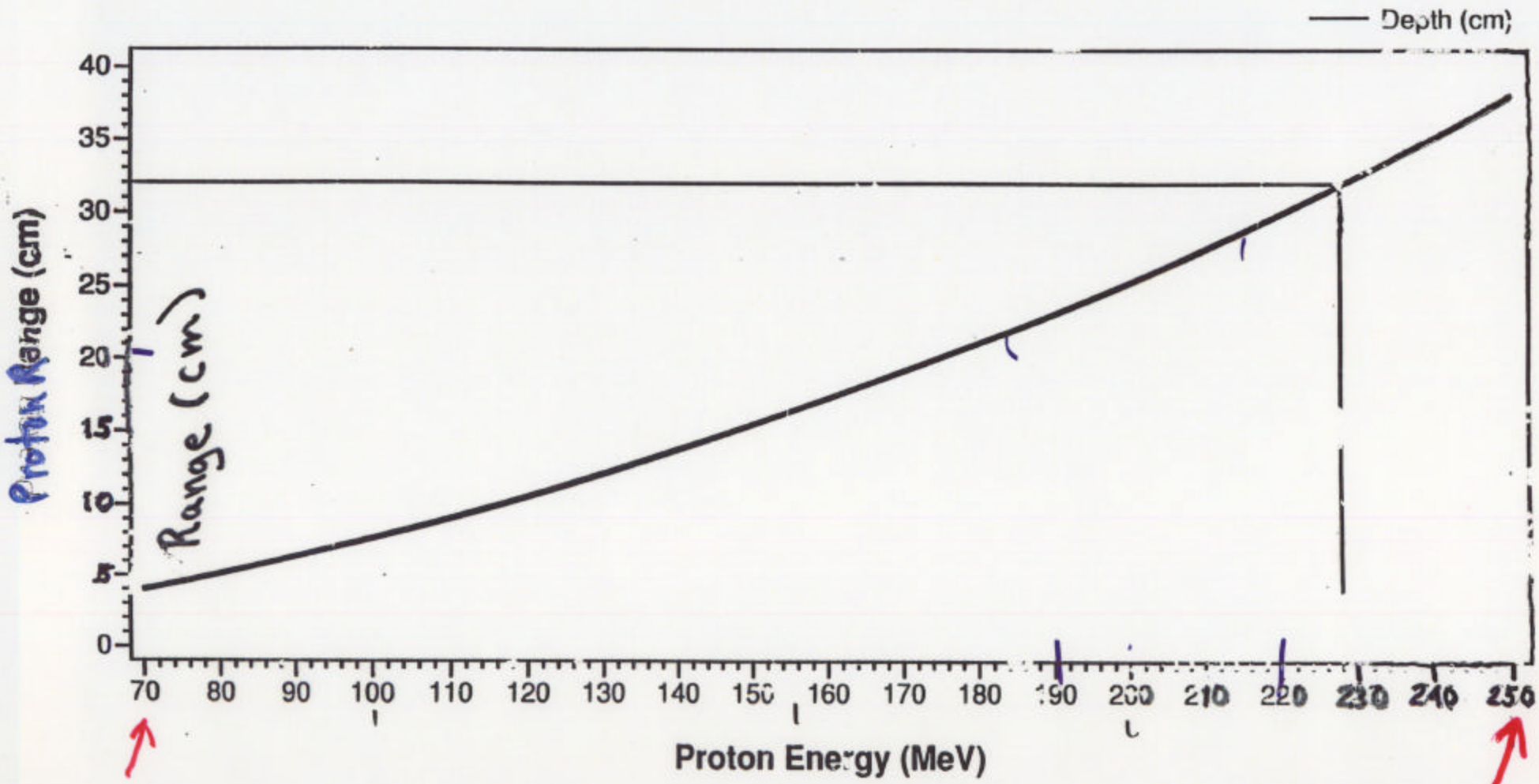
[2] The range of a proton in air in meters is given by the convenient formula $R = (E/9.29)^{1.8}$ where the energy is expressed in Mev. The range in tissue is 1.11×10^{-3} times the range in air. The stopping power of other substances may be found in Livingston and Bethe: Rev. Mod. Physics 9: 246, 1937. The physical calculations of this paper will be submitted to the *Physical Review* for publication.

Dose vs. Depth in Tissue



Comparison of depth dose distribution for X–, γ–ray and electron beam with proton beam

Maximum Depth Depends on Proton beam Energy



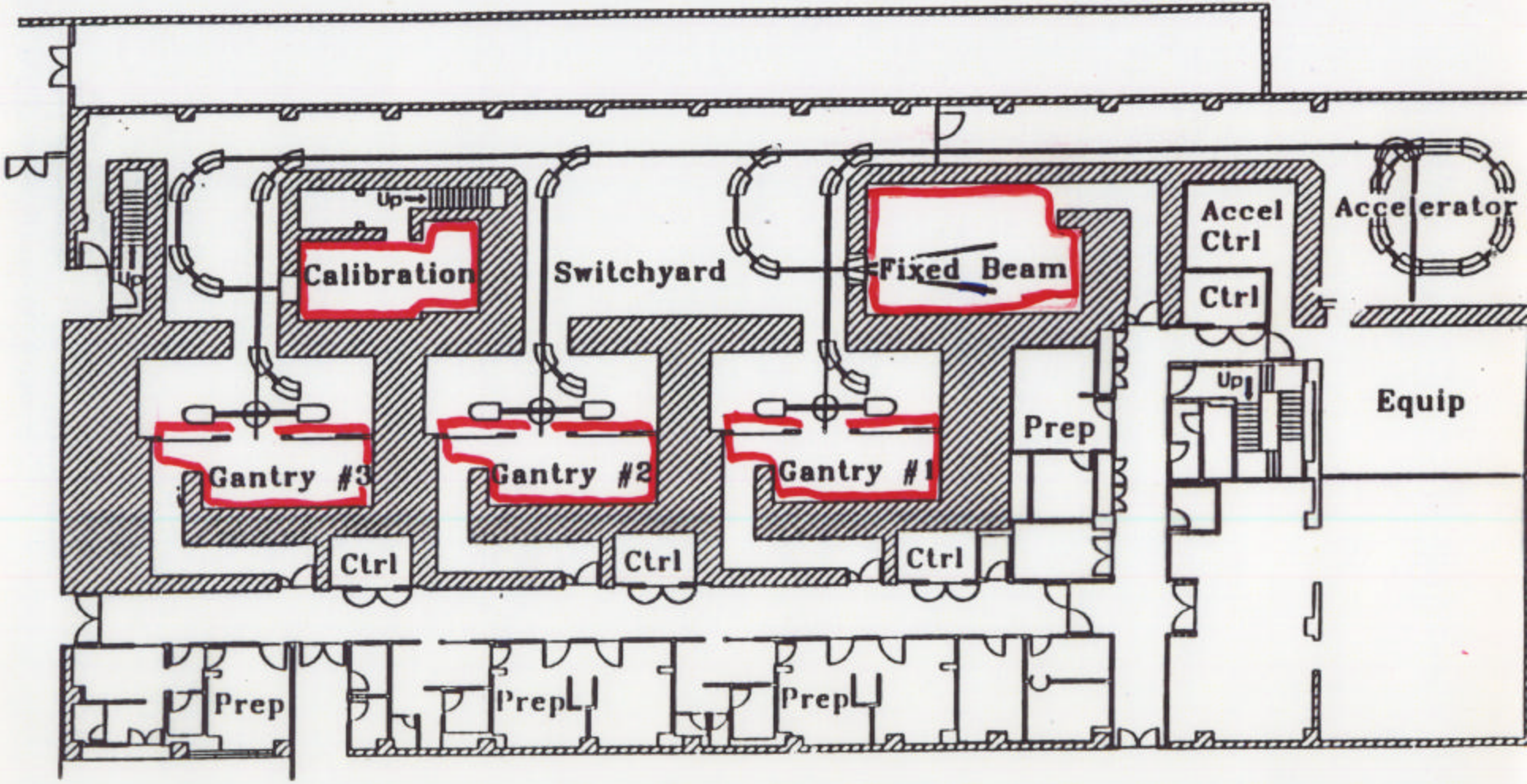
Velocity = .4c

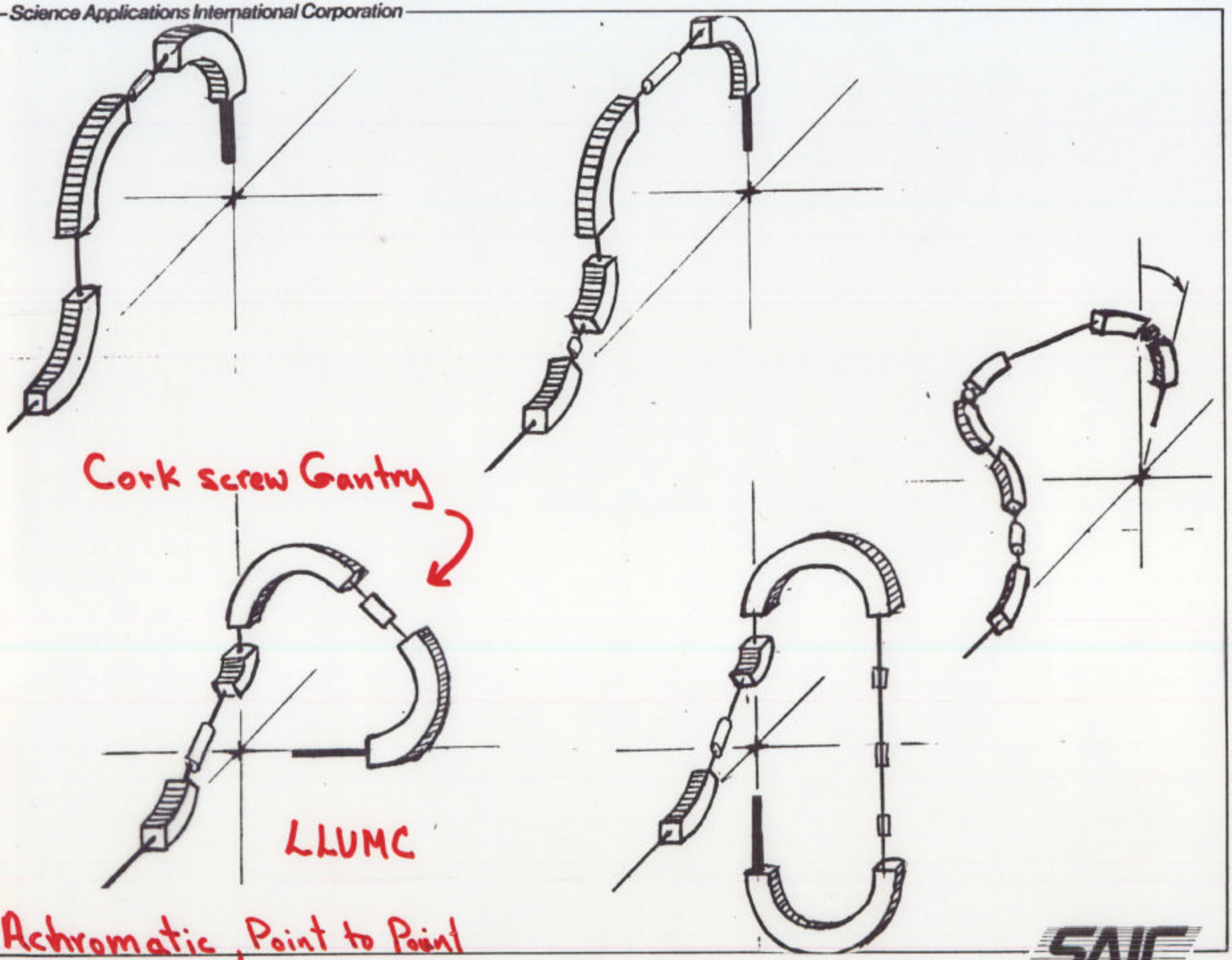
Velocity = .7c

Fig. 8 Proton range in water vs beam energy.

C = speed of light = 3×10^8 m/sec

Loma Linda Proton Therapy Facility





Achromatic, Point to Point Focussing

Accelerator Requirements For Proton Therapy

1. Sufficient Intensity

Rule of Thumb: 10^{12} protons/minute

$\Rightarrow$ 100 Rads/minute in 20 cm diameter using 50% of Protons

2. Variable Energy 70-250 MeV

3. Compact Size 20 to 40 meters o.k.

4. Cost - Low as possible

5. Low Transverse emittance - To minimize beam sizes in Transport + Gantry Magnets

6. Low $\frac{\Delta p}{p} \lesssim .25\%$

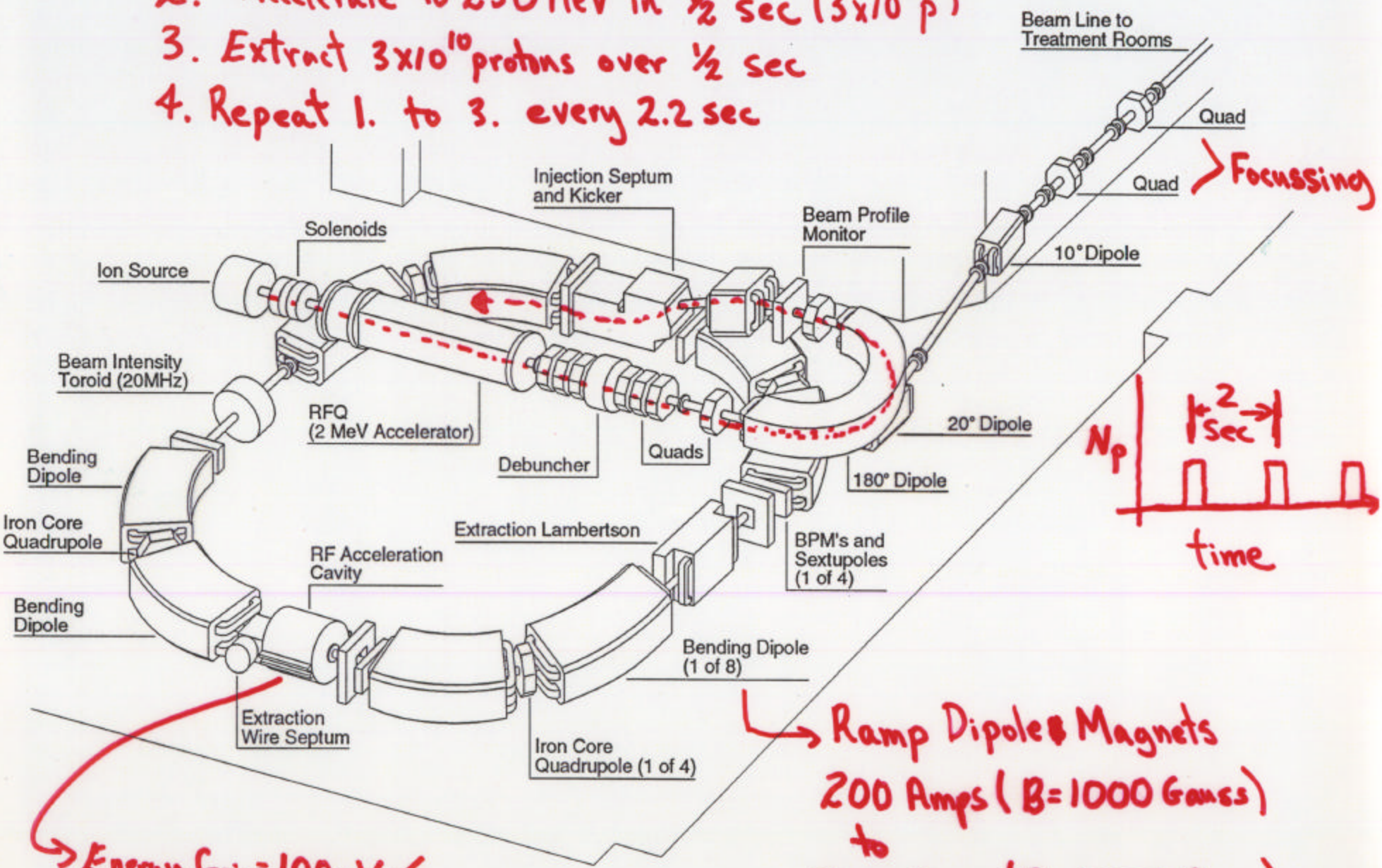
For Raster Scanning Beam with Synchrotron

1. Slow Uniform Extracted Beam

$\frac{\Delta I}{I} \leq 1\%$ in 1 msec time intervals

2. Spill by Spill Energy Variability

1. Inject 10^{11} protons in 1 μsec at 2 MeV (v=.06c)
2. Accelerate to 250 MeV in ½ sec (3×10^{10} p)
3. Extract 3×10^{10} protons over ½ sec
4. Repeat 1. to 3. every 2.2 sec



Ramp Dipole Magnets
200 Amps (B=1000 Gauss)
to
3000 Amps (B=15,000 Gauss)
in ½ sec (Earth's Field ½ Gauss)

Energy Gain = 100 eV/turn
for 2,500,000 turns in 0.5 seconds

Figure 1

The Loma Linda

ZGS chosen for the following

A. Simple Lattice - Focussing done by bending dipoles only.

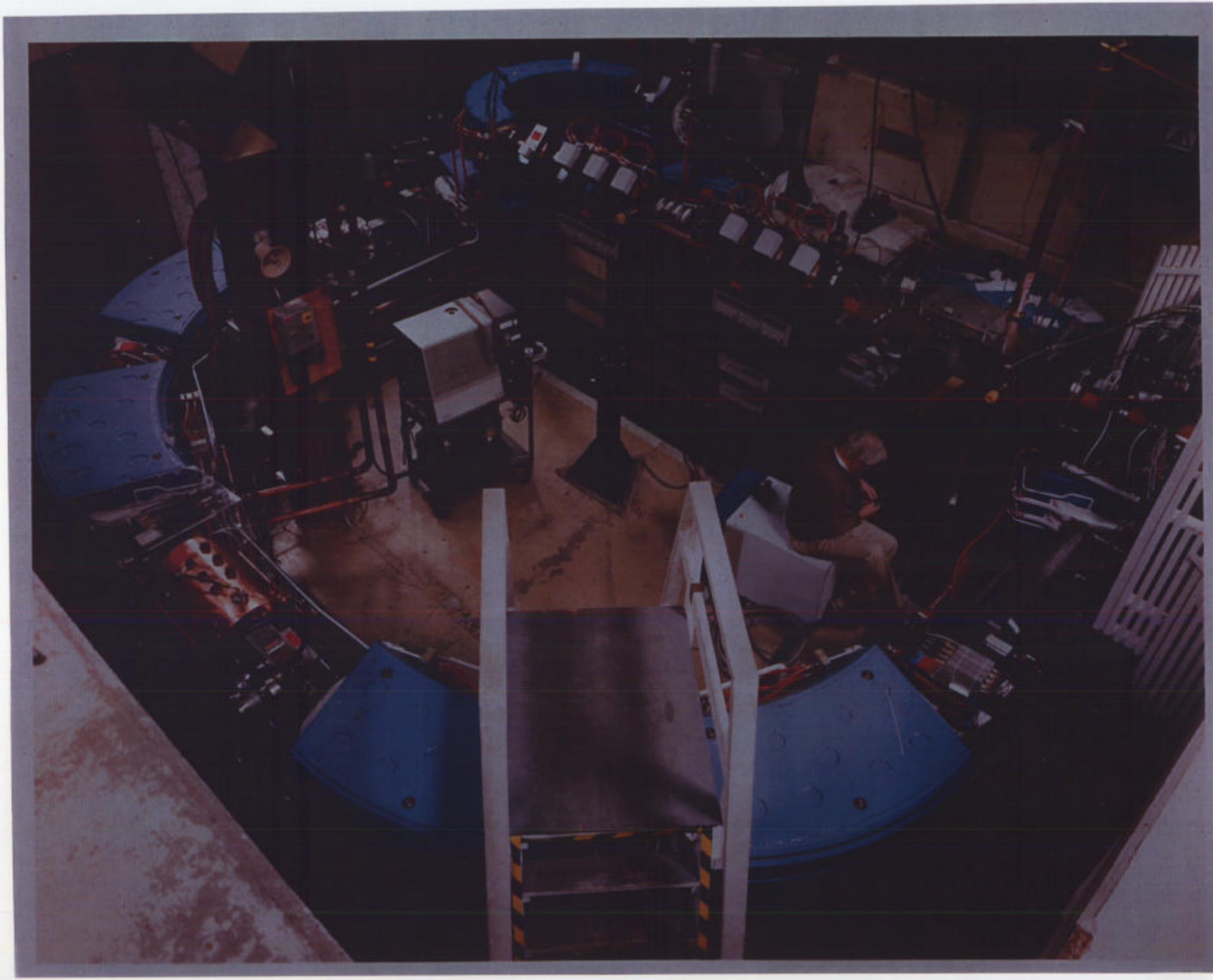
B. Compactness - 20 foot diameter fits well in hospital confines

C. Beam Stability - Large dispersion insures high space charge limit.

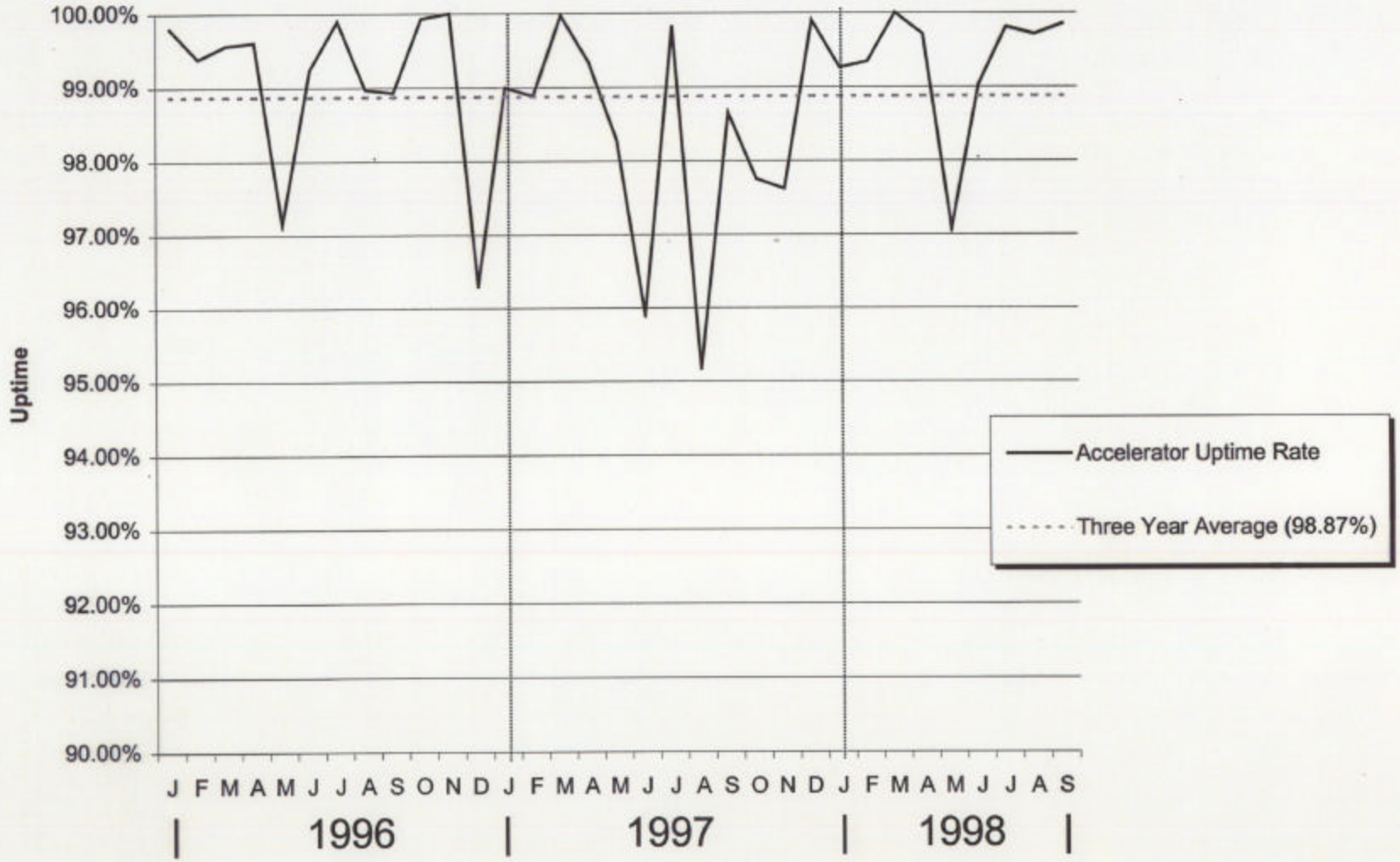
D. Injection energy is above "transition" energy <u>always</u>. ⇒ No longitudinal instabilities during acceleration

However, large dispersion limits momentum acceptance of machine $\Delta r = D \frac{\Delta p}{p}$.

$$\left.\begin{array}{l}\Delta r = 10\,\text{cm} \\ D = 10\,\text{meters}\end{array}\right\} \Rightarrow \frac{\Delta p}{p} \leq \pm 0.5\%$$



LLUMC Synchrotron Three Year Uptime Analysis



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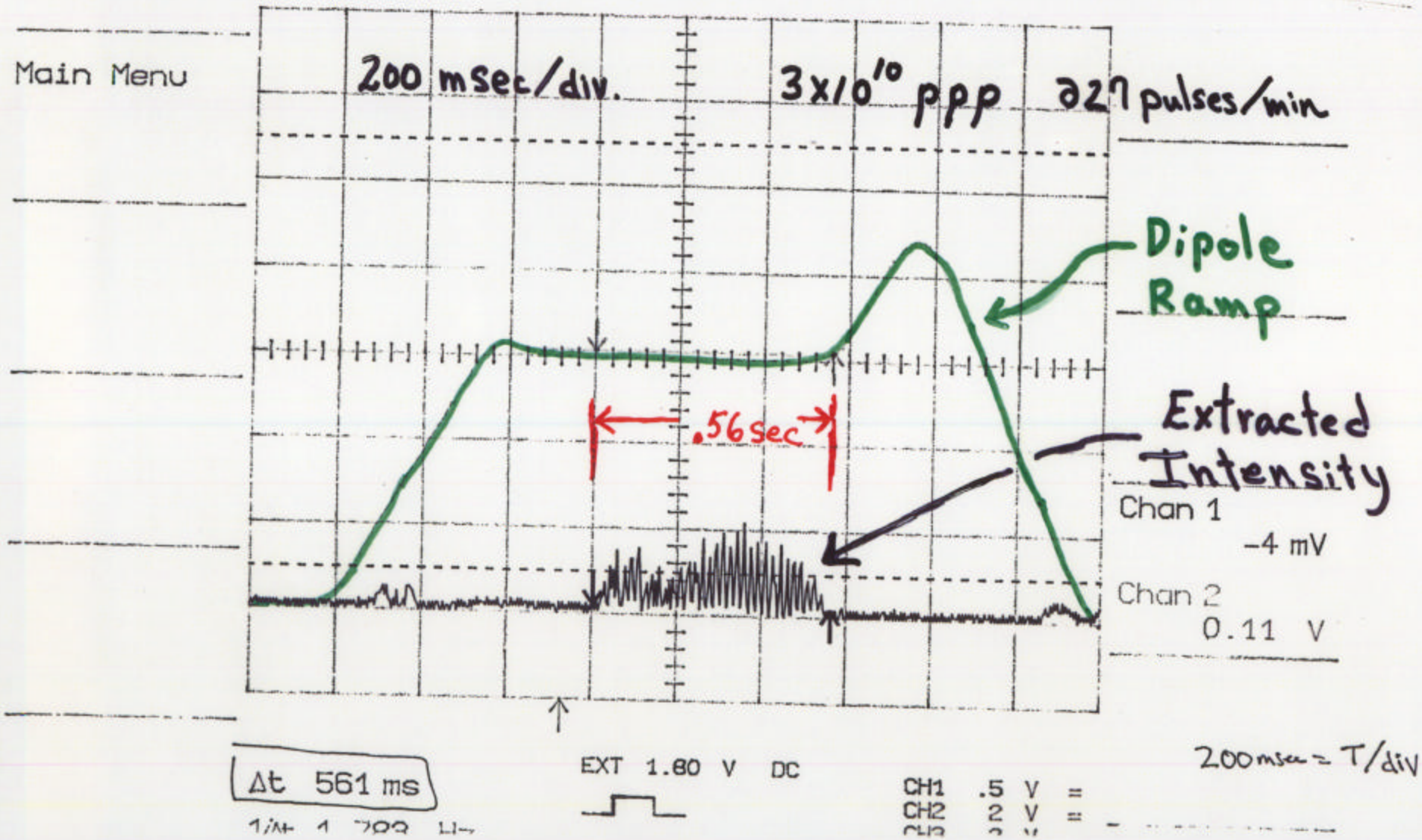
The 2 second Accelerator Cycle

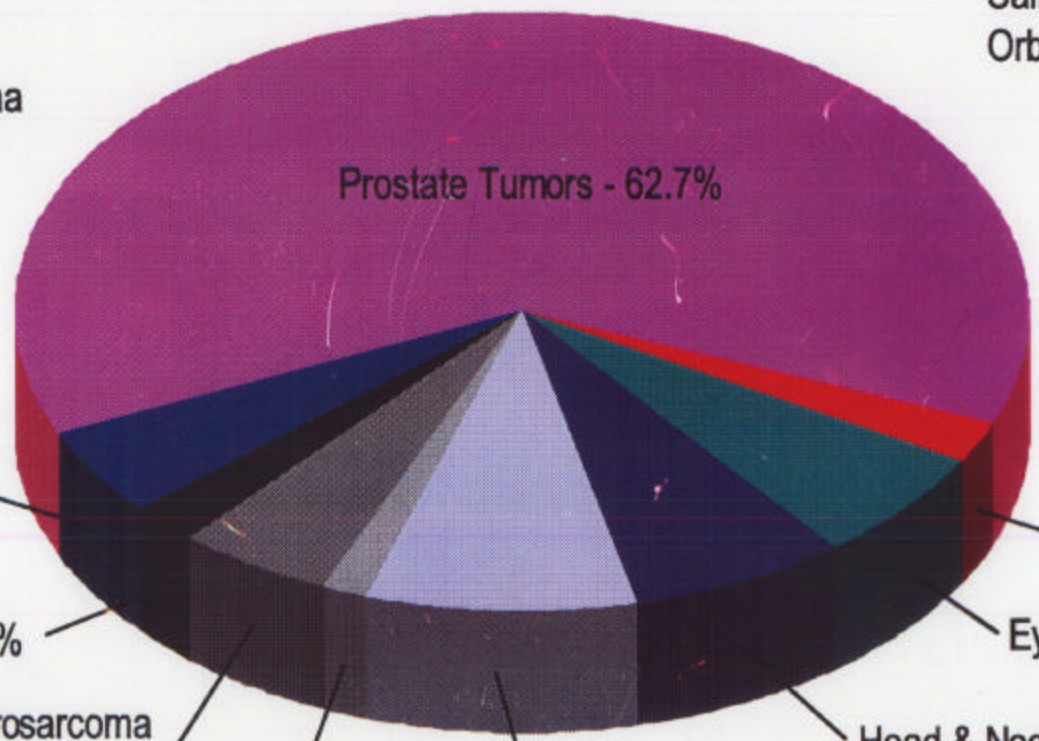


LLUMC Patient Treatments (1990-2000)

CNS/Intercranial
- Pituitary
- Acoustic Neuroma
- Meningioma
- Astrocytoma
- Craniopharyngioma

Eyes
- Ocular Melanoma
- Macular Degeneration

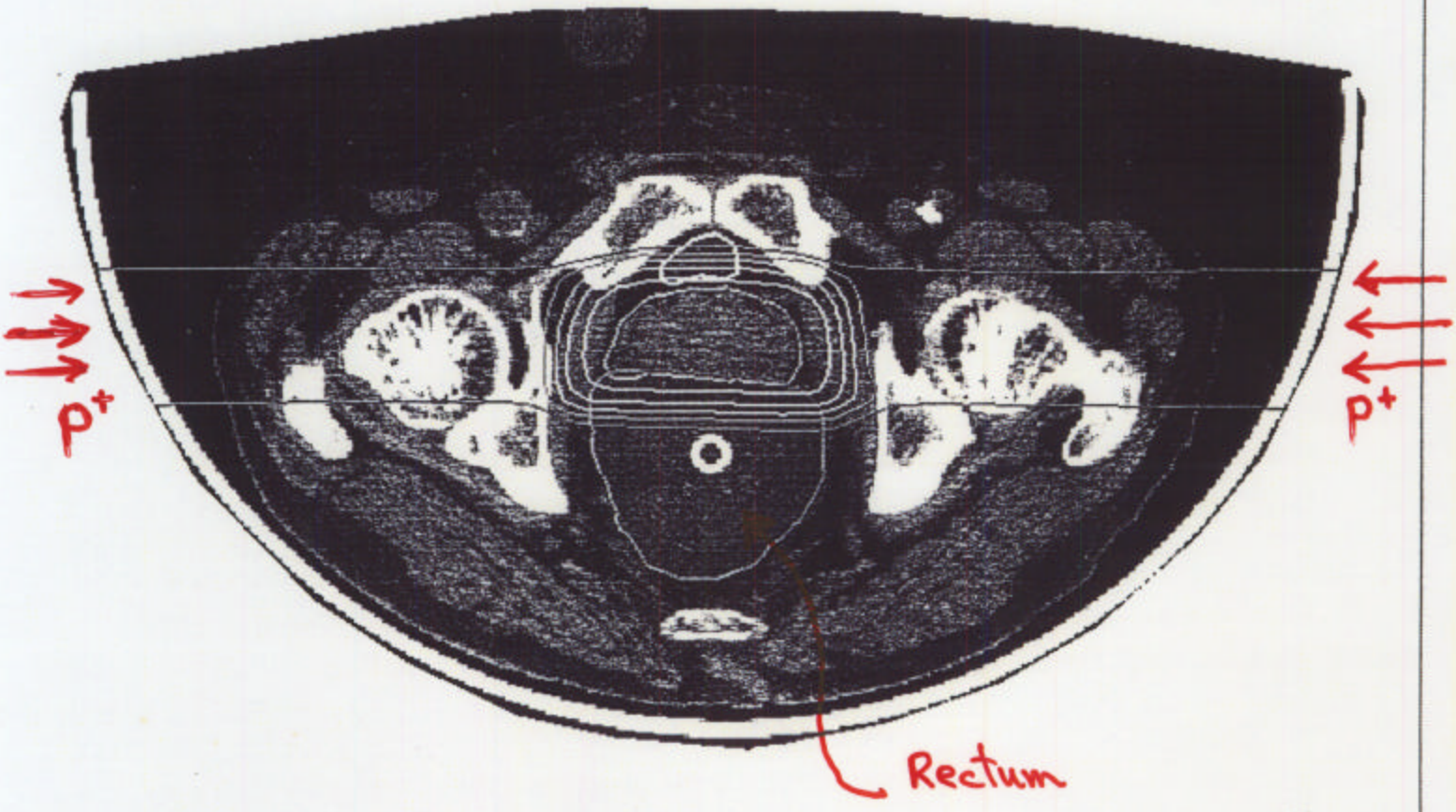
Head and Neck
- Nasal pharynx
- Parotid
- Salivary gland tumor
- Orbit of eye



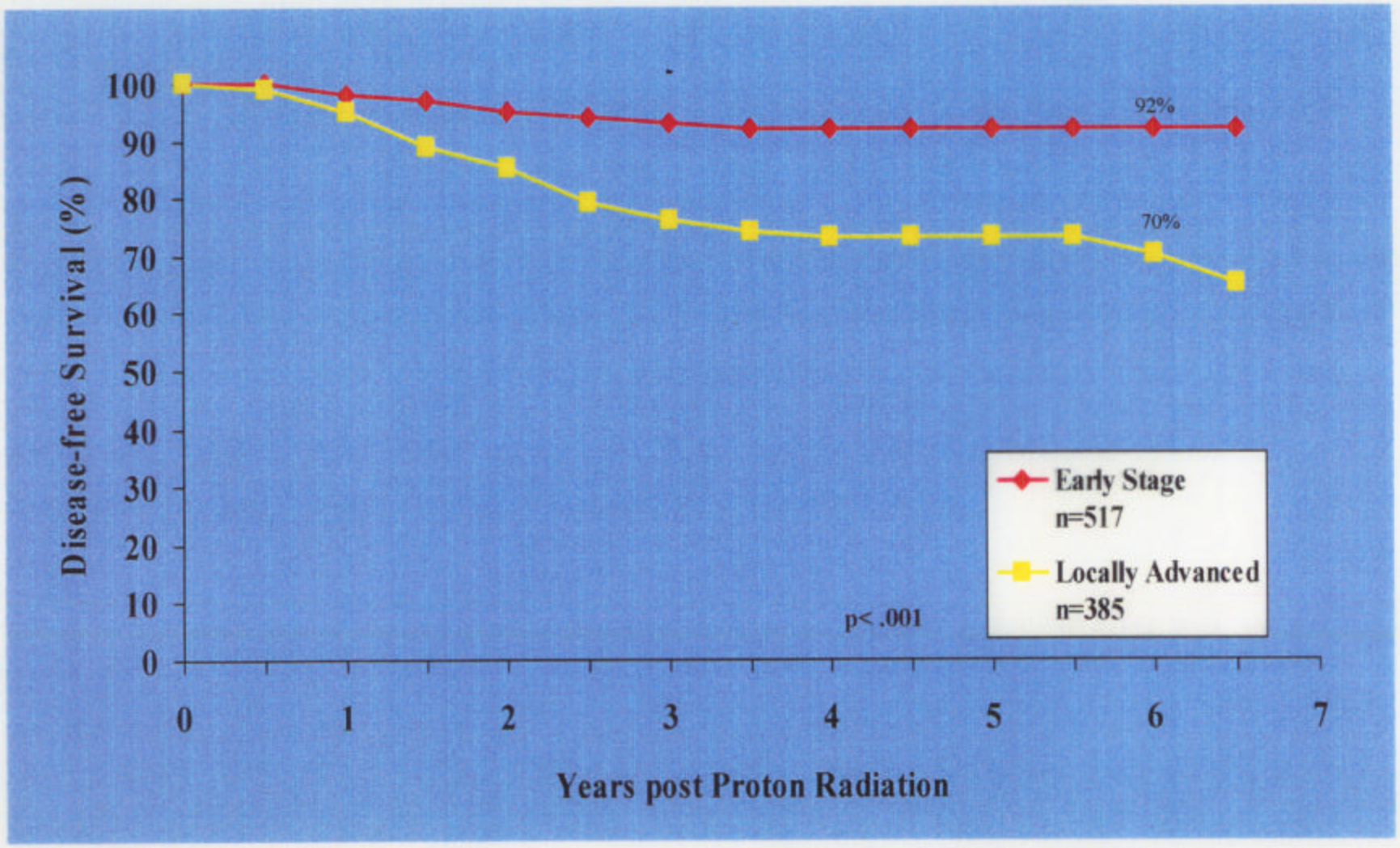
Test PLAN: plan1 Slice = 36

70.0 Gy
60.0 Gy
50.0 Gy
40.0 Gy
30.0 Gy

CT Slice of Prostate Target



Proton Prostate Patient Results



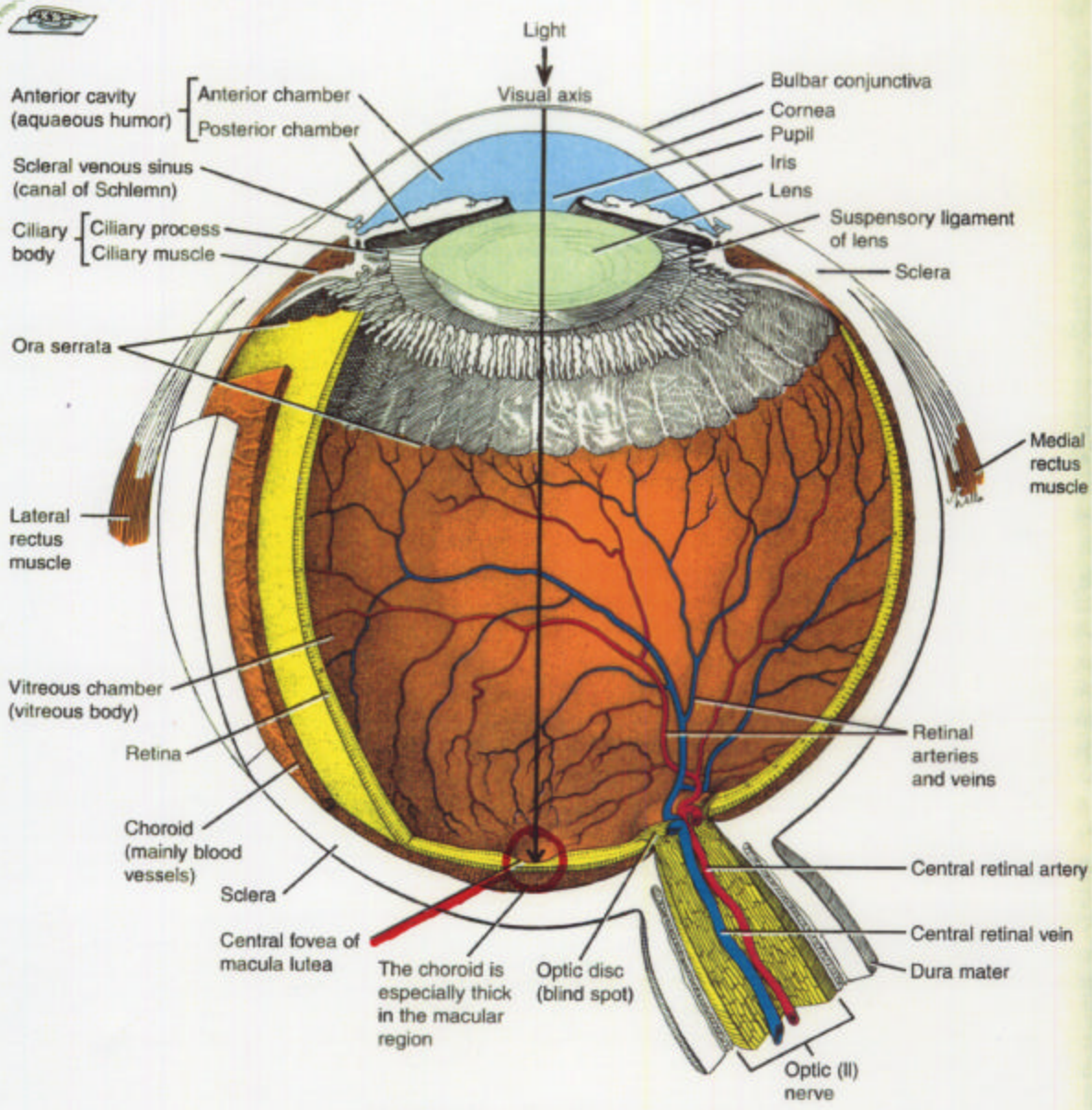
T1 - T2 Prostate Cancer

5-year Biochemical Disease-free Survival

Initial PSA	Radical Prostatectomy Johns Hopkins	Conventional Photons median 65 Gy MDACC	Protons median 75 CGE LLUMC
≤ 4.0	92% (284)	91% (117)	100% (47)
4.1 - 10.0	83% (237)	69% (169)	89% (265)
10.1 - 20.0	56% (105)	62% (118)	72% (157)
> 20.0	45% (40)	38% (57)	57% (73)

Macular Degeneration
(100,000 cases annually)

FIGURE 19.11 Gross structure of the eyeball.

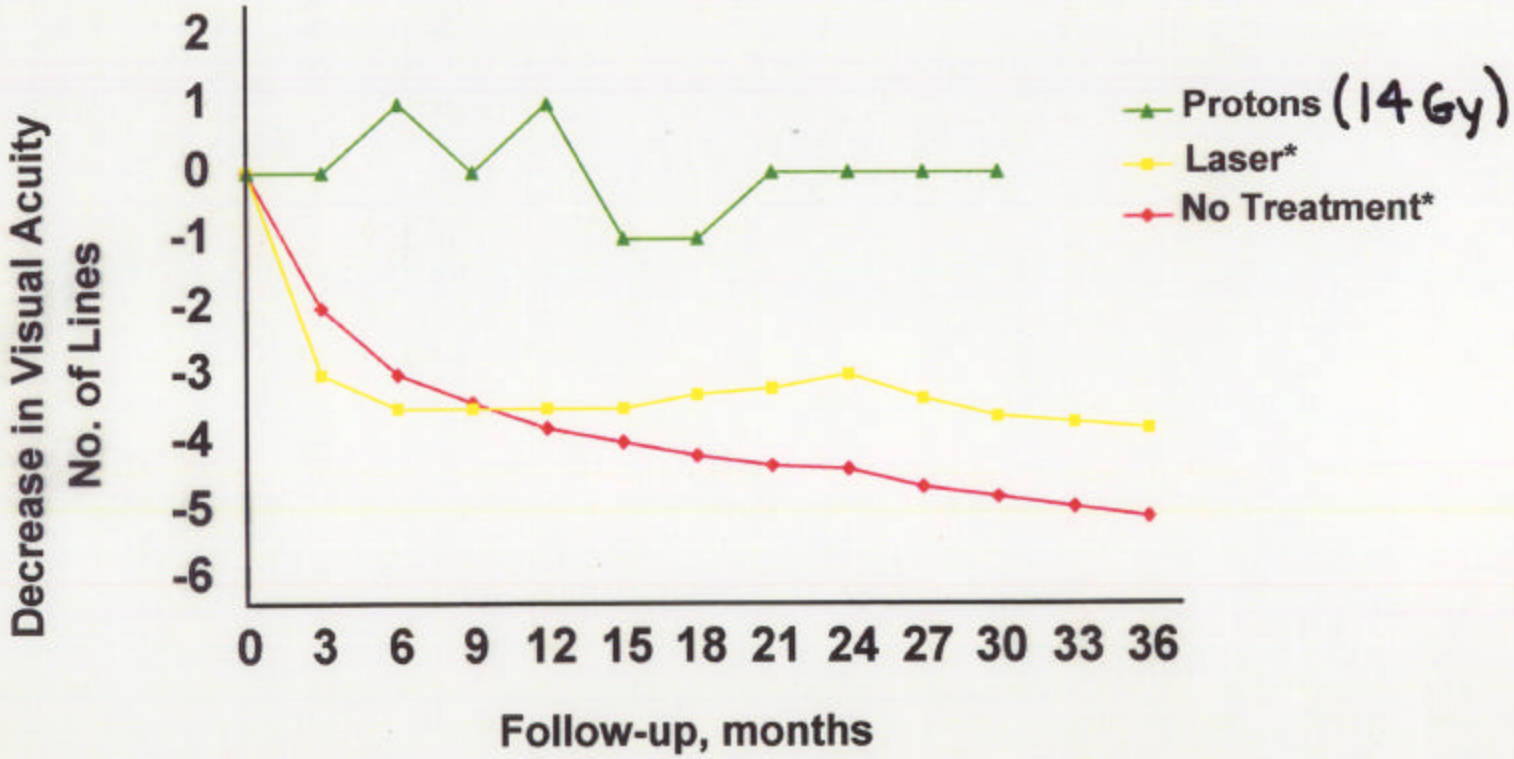


Transverse section of left eyeball (superior view)

▶ ***Which structures in the eye do not have their own blood supply and therefore rely on diffusion of oxygen and nutrients from adjacent tissues or fluid? What***

Macular Degeneration (50 patients)

Mean Decrease in Visual Acuity



*Arch Ophth. 109: 1220, 1991

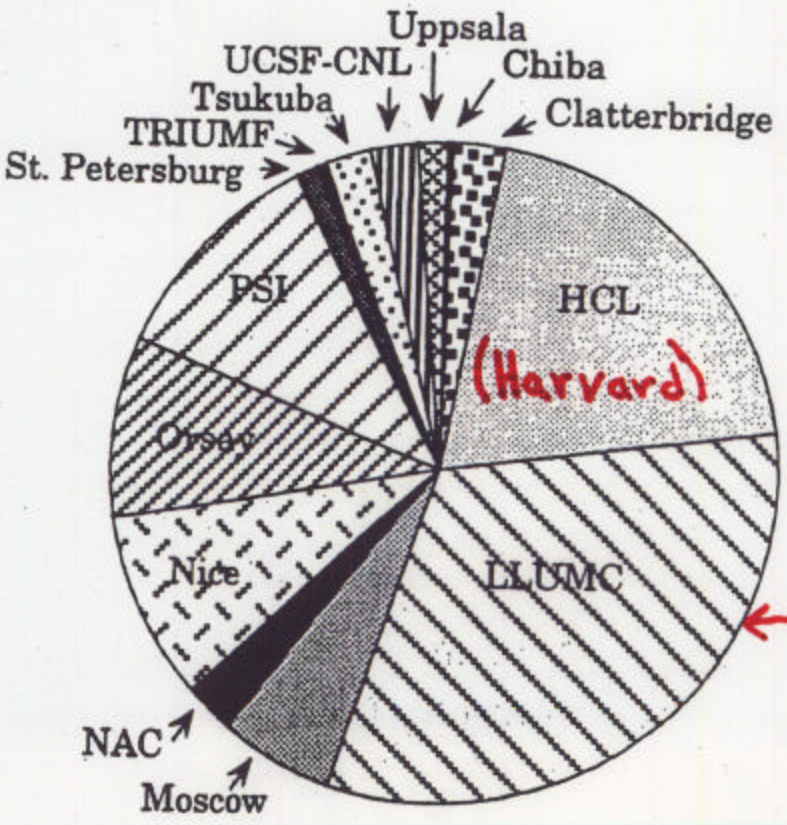
Charged Particle Therapy Facilities

Name	Location	Particle	Date Opened	Date Closed	Total Patients Through ~ 1996	1999
Berkeley 184	CA, USA	Protons	1954	1957	30	
Berkeley	CA, USA	Helium	1957	1992	2054	
Uppsala	Sweden	Protons	1957	1976	73	
Harvard	MA, USA	Protons	1961		6972	8500
Dubna	Russia	Protons	1967	1974	84	
Moscow	Russia	Protons	1969		2838	
Los Alamos	NM, USA	Pions	1974	1982	230	
St. Petersburg	Russia	Protons	1975		969	
Berkeley	CA, USA	Heavy ions	1975	1992	433	
Chiba	Japan	Protons	1979		96	
TRIUMF	Canada	Pions	1979	1994	367	
PSI	Switzerland	Pions	1980	1993	503	
PMRC, Tsukuba	Japan	Protons	1983		462	
PSI	Switzerland	Protons	1984		2261	
Dubna	Russia	Protons	1987		40	
Uppsala	Sweden	Protons	1989		81	
Clatterbridge	England	Protons	1989		698	
Loma Linda	CA, USA	Protons	1990		2500	5000
Louvain-la-neuve	Belgium	Protons	1991		21	
Nice	France	Protons	1991		636	
Orsay	France	Protons	1991		673	
N.A.C.	South Africa	Protons	1993		175	
IUCF	IN, USA	Protons	1993		1	
UCSF - CNL	CA, USA	Protons	1994		92	
HIMAC, Chiba	Japan	Heavy ions	1994		150	900
TRIUMF	Canada	Protons	1995		23	
PSI (200MeV)	Switzerland	Protons	1996		1	
GSI	Germany	Heavy Ions	1998	Total	Pions 1100 Ions 2637 Protons 18726	

TABLE 1. Proton therapy facilities

Year	1994[a]	1996	1997
Total number of proton therapy facilities	16	17	17
Number of operating facilities	14	15	14
Estimated Annual Patient Total	1711	2054	2321
Annual patient load/facility			
≤ 10 patients/year	2	2	1
11 - 100 patients/year	5	7	7
101 - 200 patients/year	4	3	1
201 - 300 patients/year	2	1	3
301 - 400 patients/year	1	1	
401 - 500 patients/year			1
501 - 600 patients/year			
601 - 700 patients/year		1	
701 - 800 patients/year			1
No. of centers using fractionated therapy	8	8	8
No. of centers treating eye tumors	9	10	10

[a]Revised from data presented in reference (7)



2321 patients for 1997

Loma Linda

Proton Therapy Accelerators in Construction or Completed

	Facility	Location	accelerator type	vendor	date of 1st Tx
a)	LLUMC	Loma Linda	270 MeV synchrotron	FNAL	1990
b)	HIMAC	Chiba	Heavy ion synchrotron	N/A	1995
c)	NCC	Kashiwa	230 MeV cyclotron	Sumitomo/IBA	1998
d)	NPTC	Boston	230 MeV cyclotron	IBA	1999
* e)	Tsukuba	Japan	270 MeV synchrotron	Hitachi	2001
* f)	Shizouka	Japan	250 MeV synchrotron	Mitsubishi	????
g)	IRE*	Rome	200 MeV LINAC	ENEA	2007?

* Instituto Regina Elena

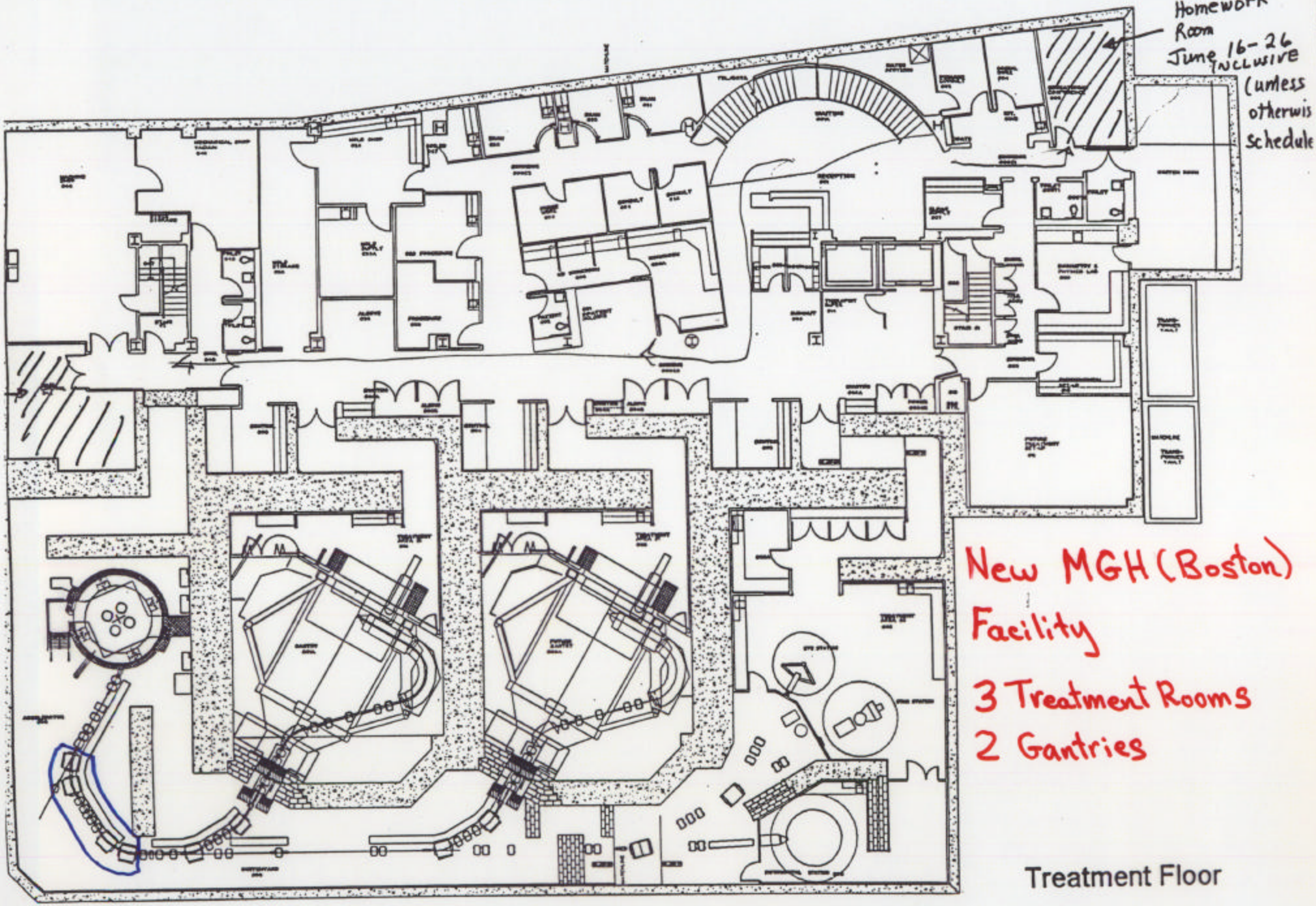
AccSys Technology of Pleasanton,CA is a subcontractor for all proton synchrotrons and LINACs

Two more proposed synchrotrons in Japan and one in Germany

* Hyogo, JP — 250 MeV p^+ Synchrotron (and Carbon Ions)

* Wakasa Bay, JP — p^+ Synchrotron

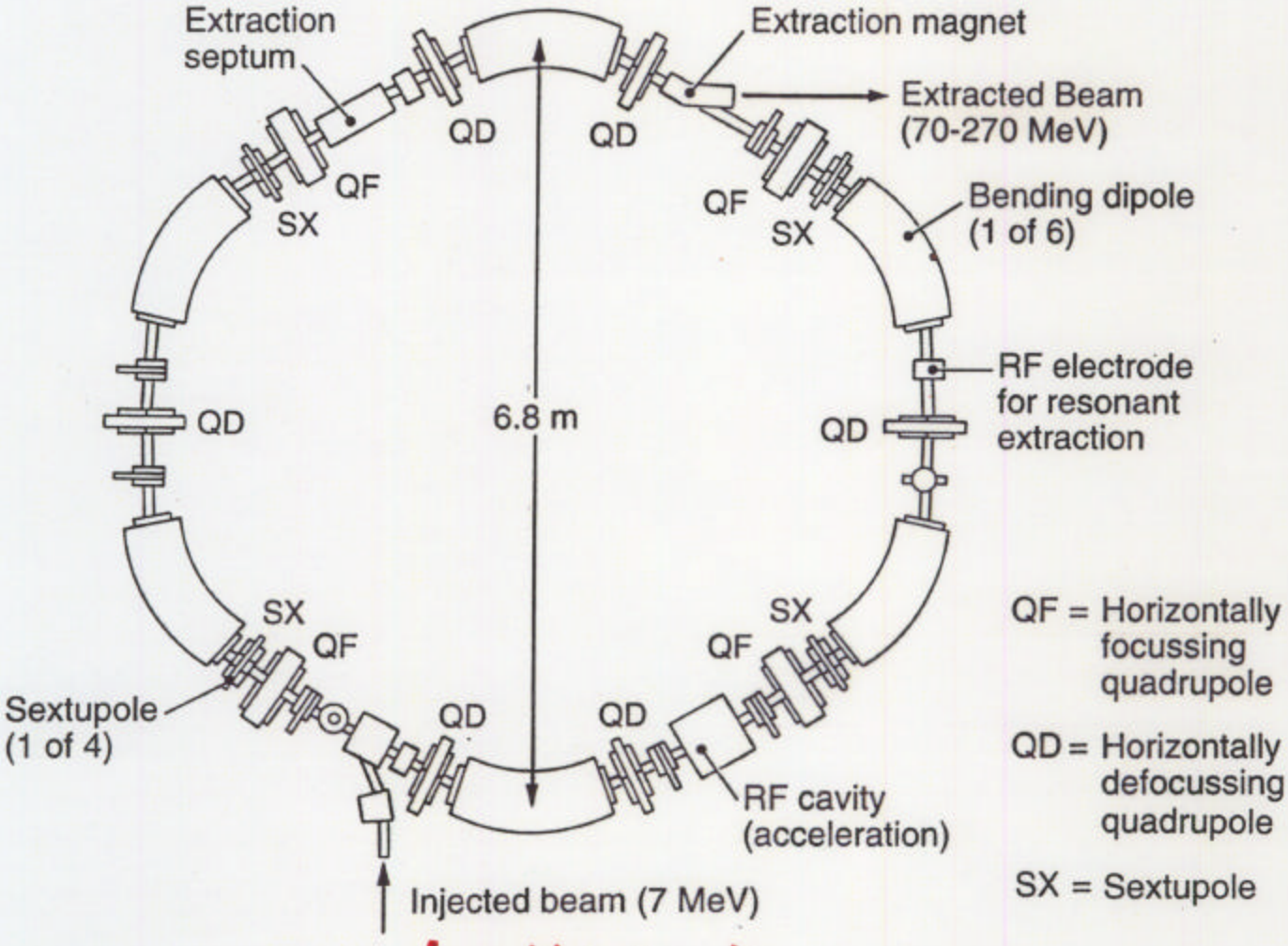
* – Beam Tests in Progress



Treatment Floor

Hitachi Synchrotron for Univ. of Tsukuba

7 MeV, multi-turn injection ⇒ 1.8×10^{11} ppp, 30 $\frac{\text{pulses}}{\text{minute}}$



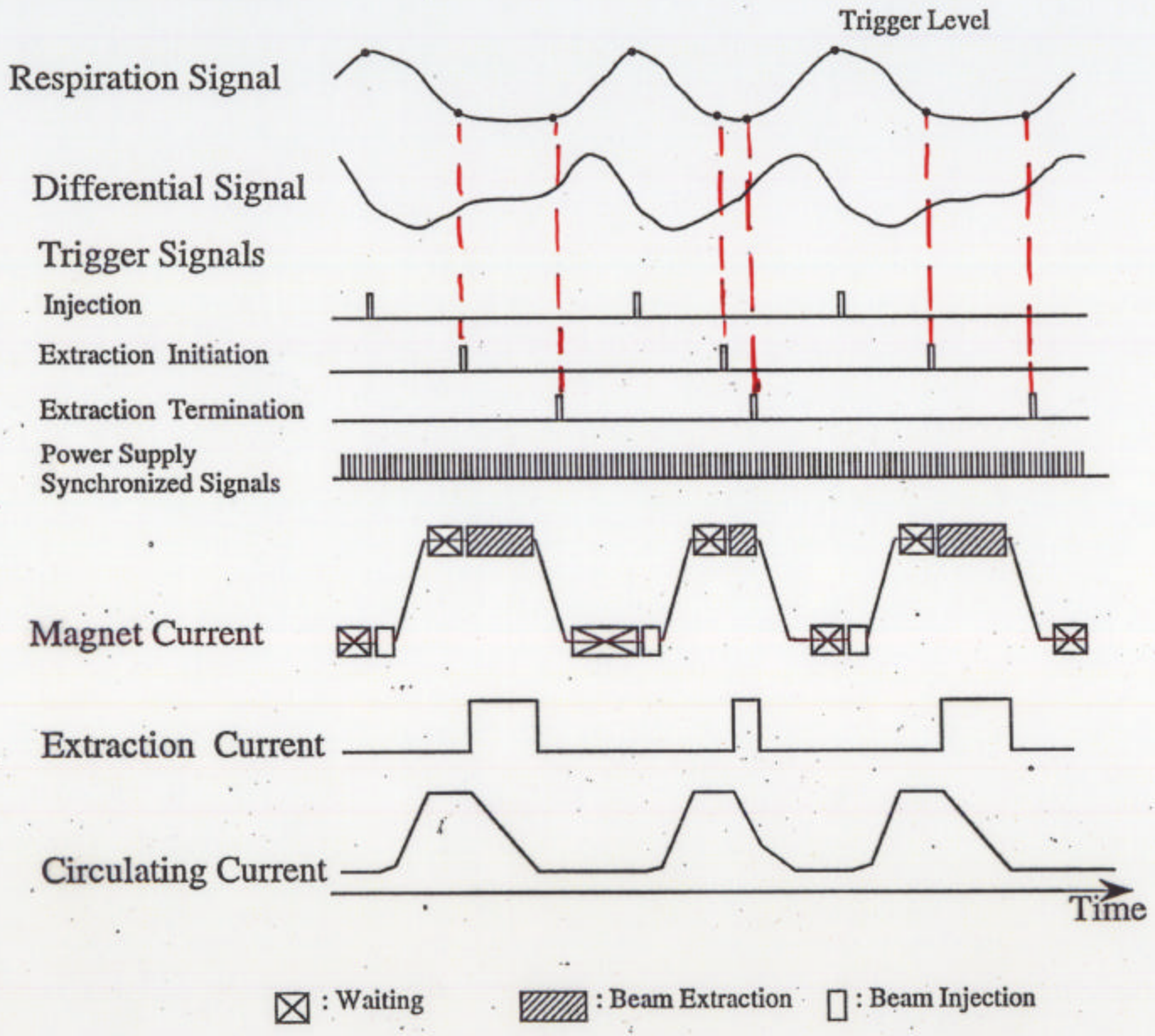
(multi-turn)

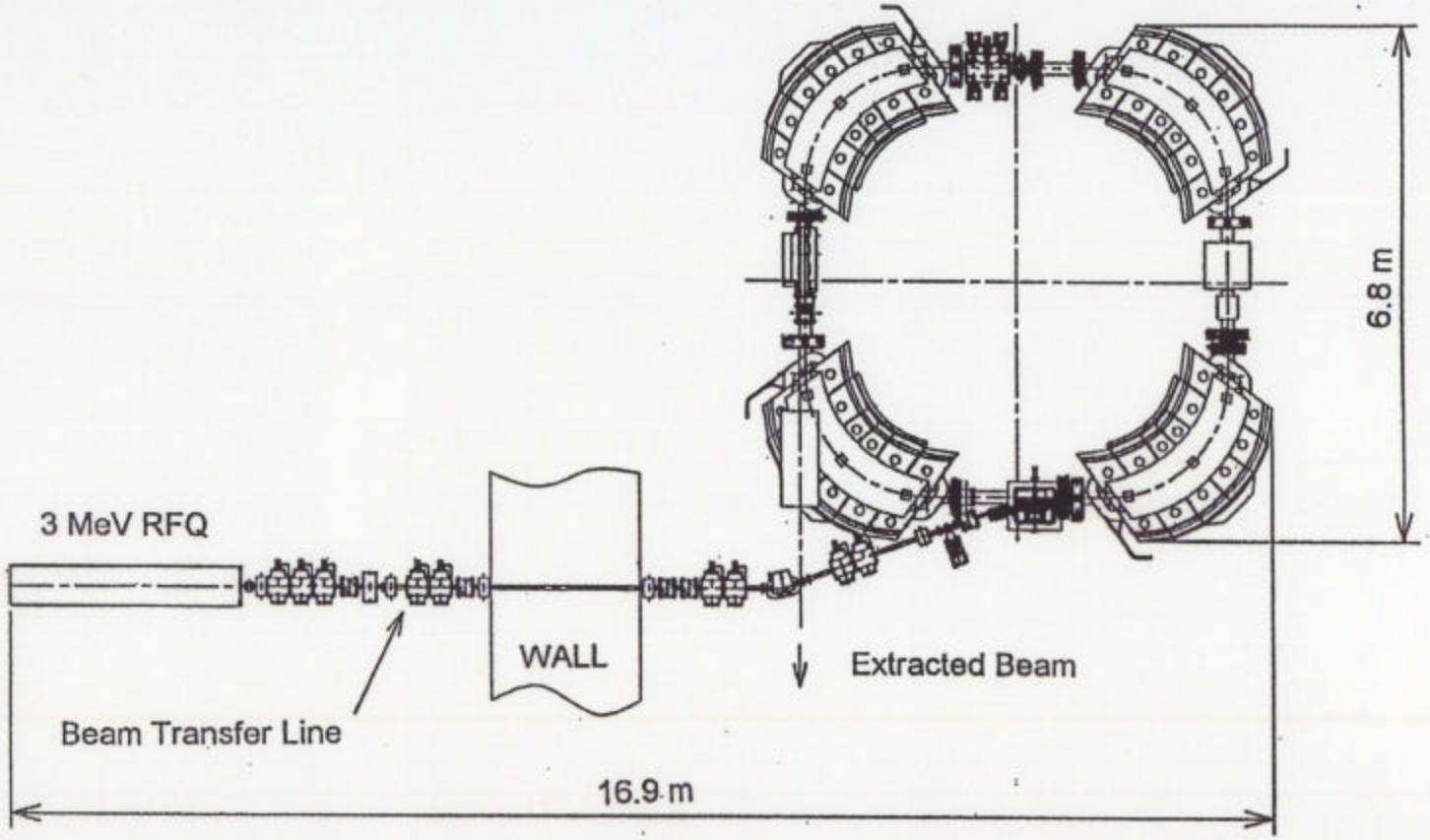
$\nu_x = 1.73$ Extract on $\nu_x = 5/3$; D = 1.75 meters

Hitachi Synchrotron

Hitachi

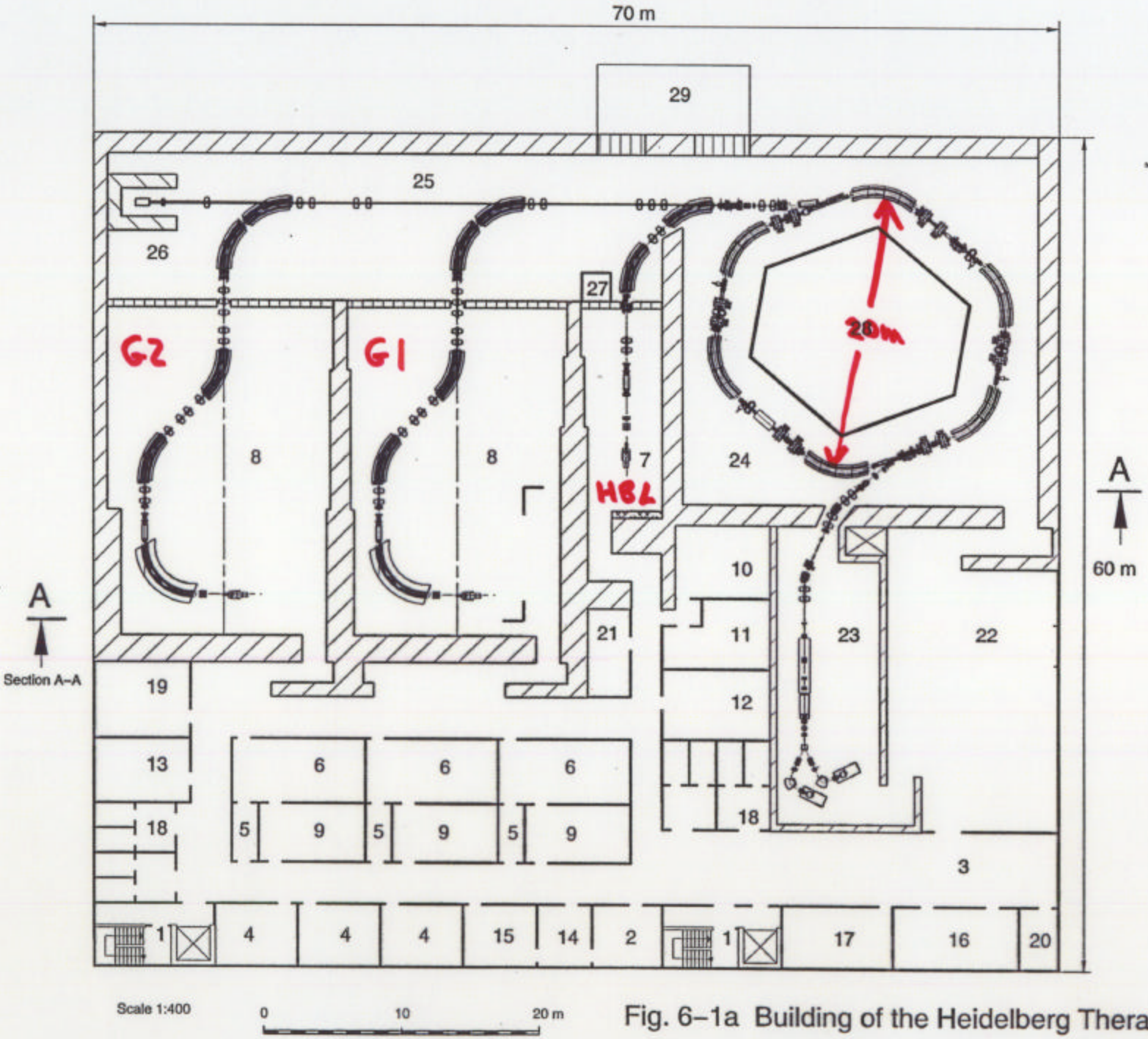
Respiration-Gated Irradiation Based on Variable Operating Period and Flat Top Length





Layout of the ACS Proton Synchrotron (Mitsubishi Electric Corporation)

New GSI Light Ion Facility (proposed)



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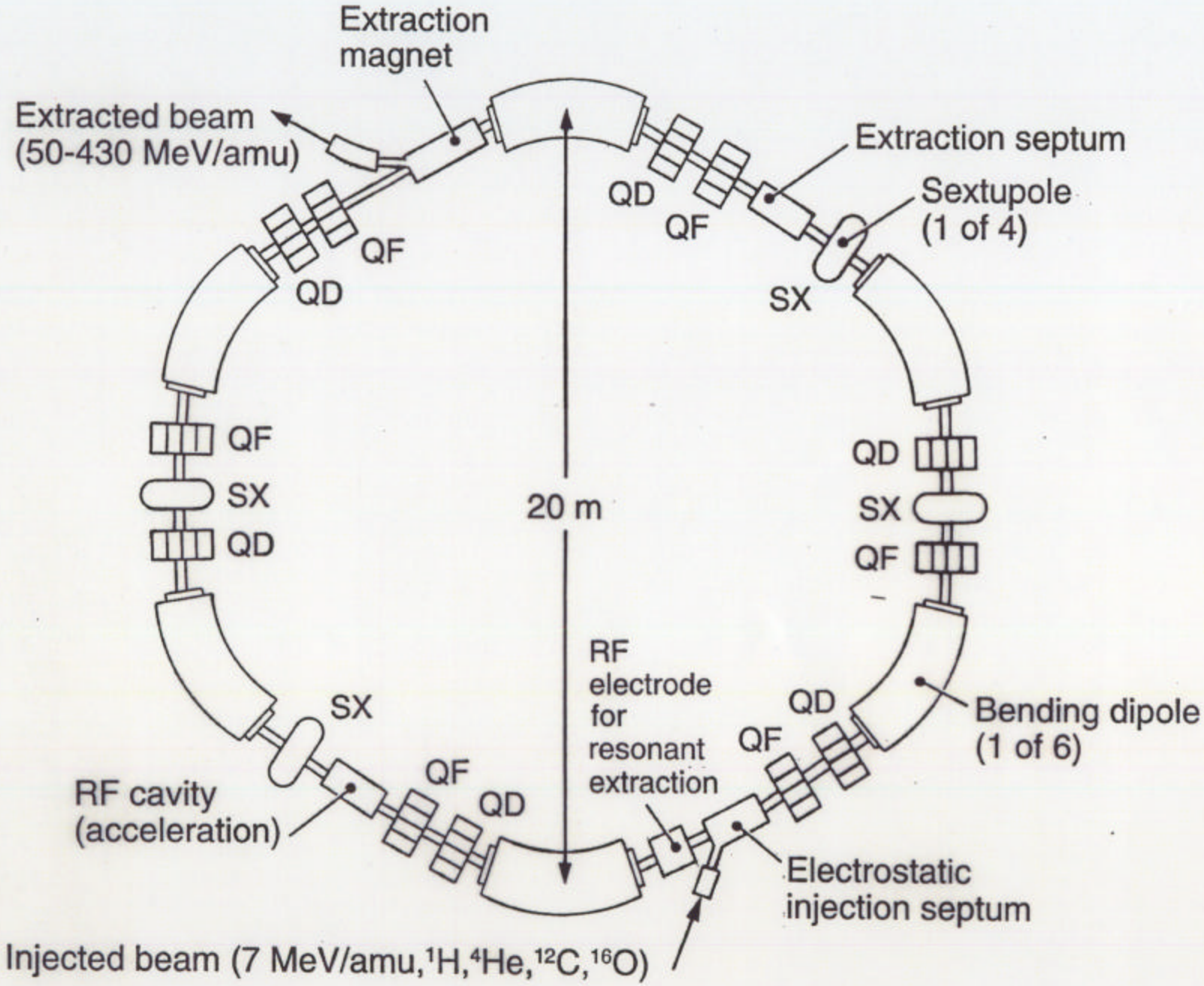
11 Dosime
12 Rasters
13 Health
14 Patient
15 Secreta
16 Meeting
17 Person
18 WC
19 Store
20 Housek
21 Electric
22 Acceler
23 Linac
24 Synchro
25 HE Bea
26 Machin
27 Access
28 Cooling
29 Pit for

Fig. 6–1a Building of the Heidelberg Therapy Facility


Extraction magnet
Extracted beam (50-430 MeV/amu)
Extraction septum
Sextupole (1 of 4)
QD
QF
SX
QF
QD
QF
SX
QD
20 m
QD
SX
QF
RF electrode for resonant extraction
Bending dipole (1 of 6)
QD
QF
SX
QF
QD
RF cavity (acceleration)
Electrostatic injection septum
Injected beam (7 MeV/amu, ^{1}H, ^{4}He, ^{12}C, ^{16}O)