Future Prospects in Medical Applications: Advanced Nuclear Techniques in Funtional Imaging, Pharmacology and Oncology

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Outline of the talk

- **Historical background**
- **Particle Physics and Medical Physics**
- **Vertex detector and tracking - Diagnostic Radiology - Morphological Studies**
  Analog vs Digital
  Digital Detectors (Gas Chamber, Solid State)
- **Calorimetry - Nuclear Medicine - Functional Studies**
  Anger Camera and coincidence technique (SPECT and PET)
  Dedicated machines:
  (intraoperatory probes, scintimammography,drug development)
- **Accelerators – Radiotherapy – Treatment**
  Radioisotope production and treatment
  Particle treatment (x-rays, electrons, protons, neutrons, heavy ions)

IX International Conference on Calorimetry in Particle Physics
CALOR2000- Annecy, France – 8-14 October 2000

"Autoradiography"

Henri Becquerel 1896 discovery of radioacti

(Uranium salt + photographic plate)

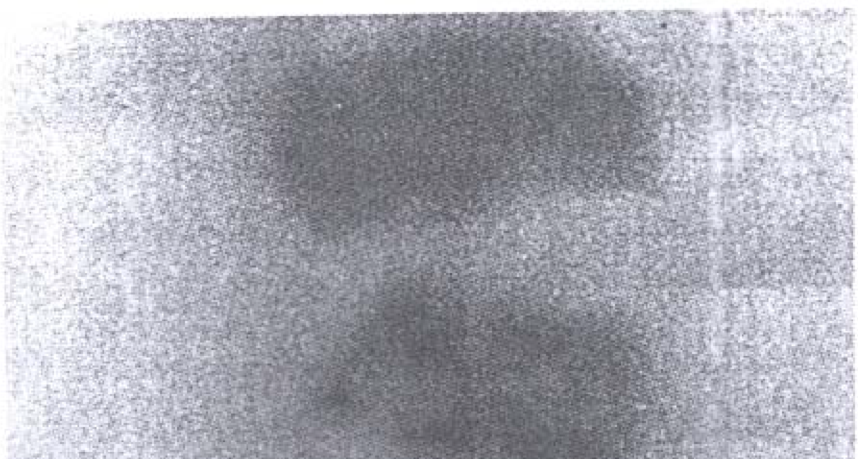

Figure 1
First autoradiograph constituting the discovery of radioactivity in Paris on Sunday, 1 March 1896. (from *Nobel Lectures: Physics 1901–1921*. Amsterdam: Elsevier Publishing Company, 1967; 47–73).

from: Radiographics, 1989, 9(6), 1189

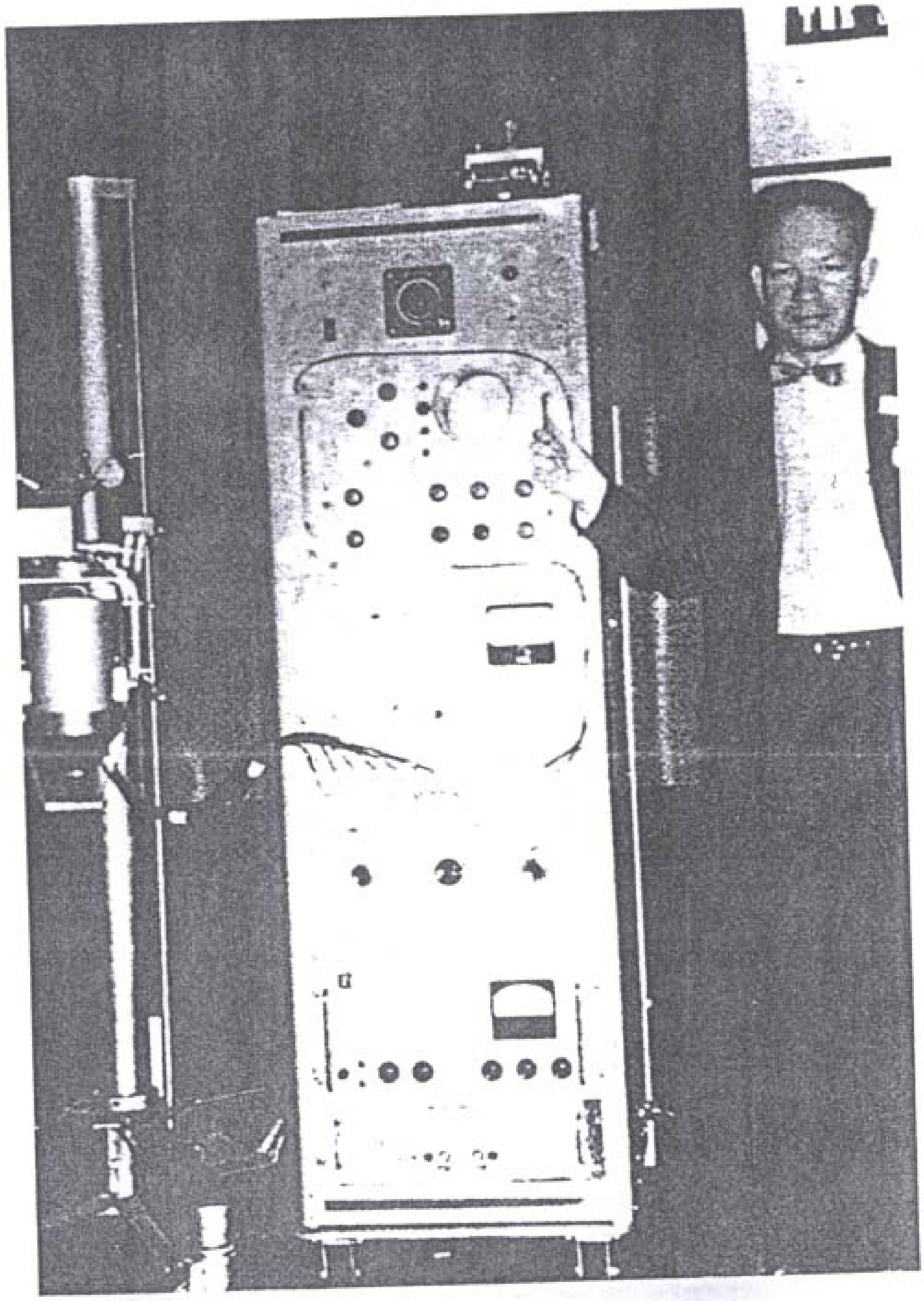

Figure 9
This is the prototype scintillation camera built by Hal Anger at Donner Laboratory of the Lawrence Berkeley Laboratory (from Myers WG. The Anger scintillation camera becomes of age. *J Nucl Med* 1979; 20:565–567).

- 1957 $^{99}Mo \rightarrow {}^{99}Tc^m$ (Richards)
- 1958 Anger Camera (Hal Anger)

Radiographics, 1989, 9(6), 1196

	Experiment in HEP	Exp in Medical Phys
Group size:	10^2 - 10^3 people	1 or 2
Preparation:	5 - 10 years	5' - 10'
Data collection:	1 - 5 years	1' - 5'
Data analysis:	1 - 5 years	1' - 5'
Run by:	physicists	technician
Analyzed by:	physicists w/ hardware & software	physician "mostly by experi

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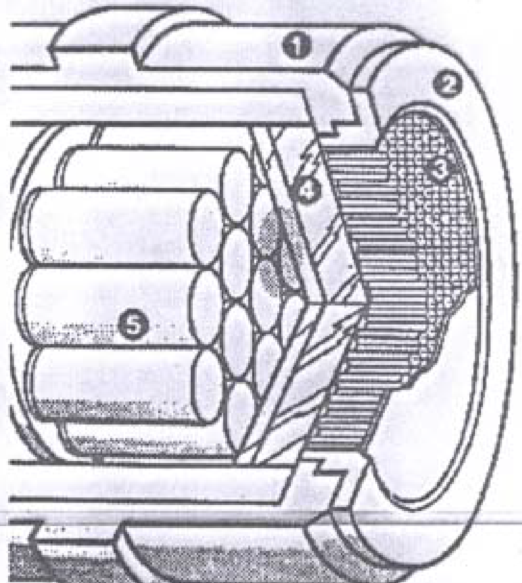
However in both cases the right approach is the same:

- *I have the best detector for .. what??*
- *I have this experiment to do w/ these requirements. Which is the best detector?*

ANGER CAMERA

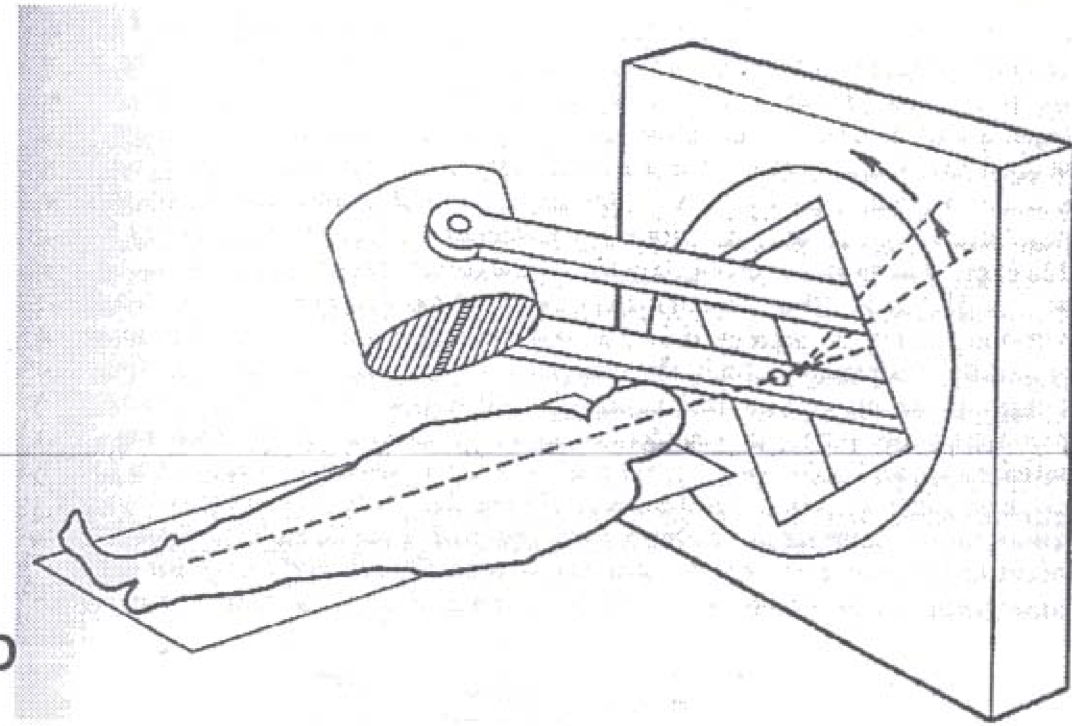


CROSS SECTION OF
COMMON DETECTOR HEAD

1 Shielding around head
2 Mounting ring
3 Collimator core
4 Sodium Iodine crystal
5 Photomultiplier cells or tubes

SPECT

(Single Photon Emission Computed Tomography)



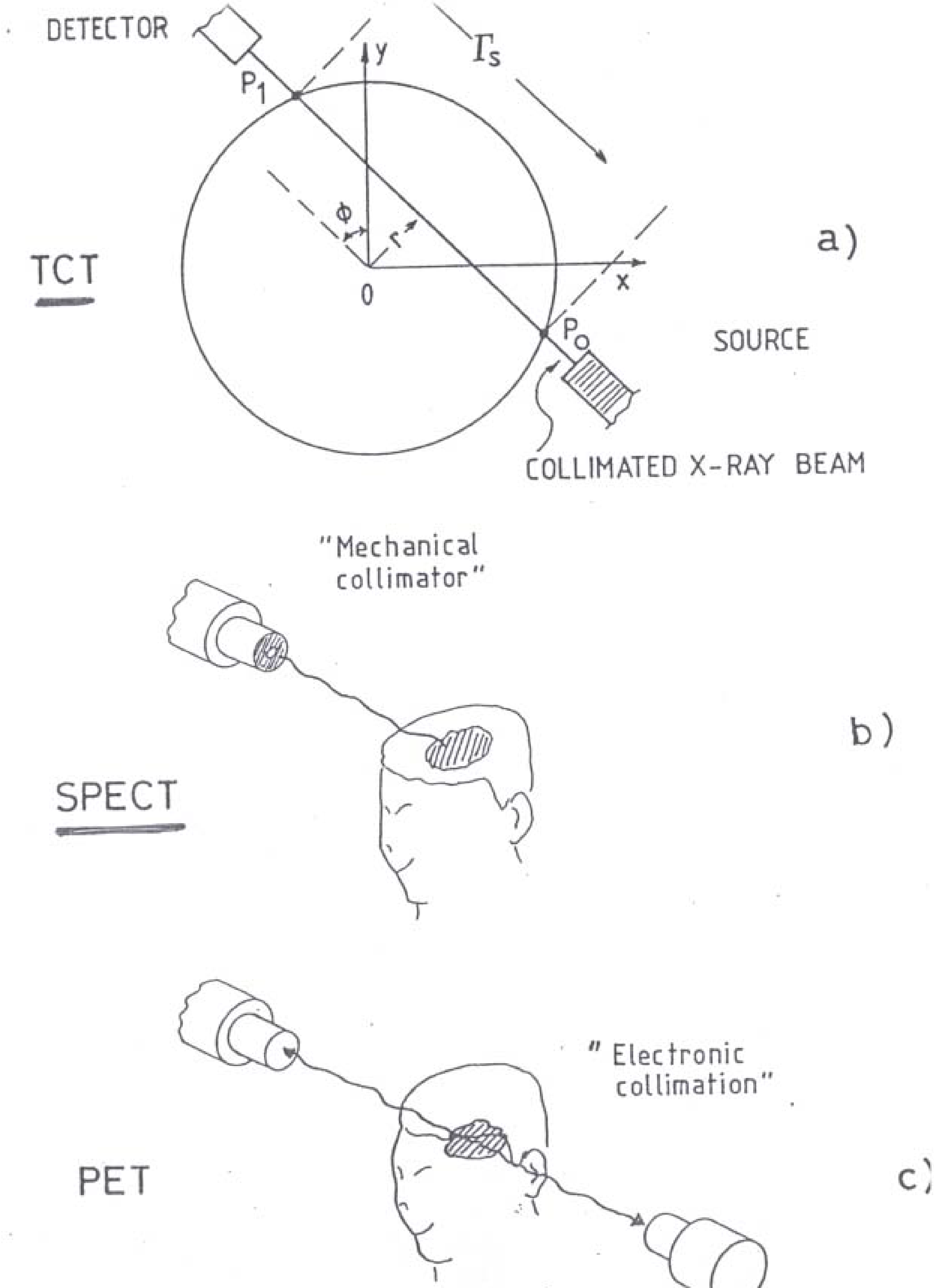


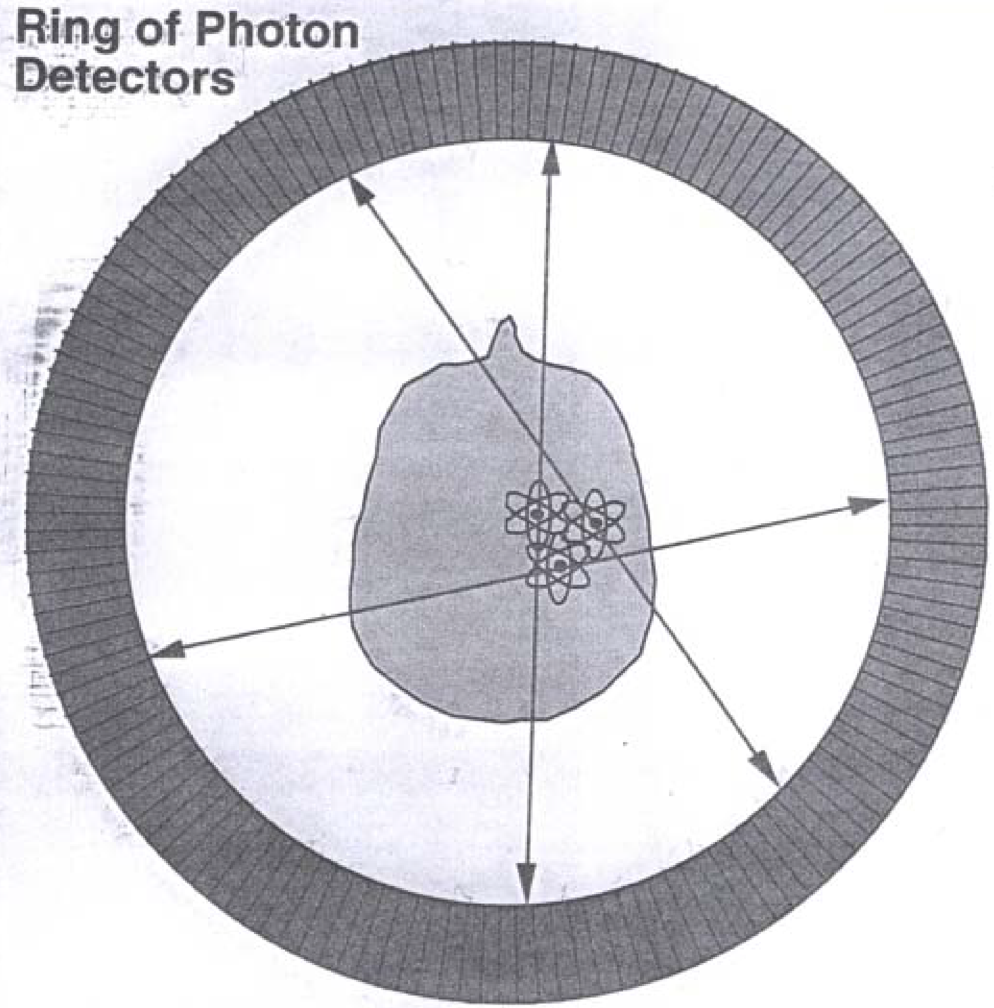
Fig. 1 - Principle of image reconstruction in TCT, SPECT and PET.

Ideal Tracer Isotope

- **Interesting Chemistry**
  Easily incorporated into biologically active drugs.
- **1 Hour Half-Life**
  Maximum study duration is 2 hours.
  Gives enough time to do the chemistry.
- **Easily produced**
  Short half life ⇒ local production.

^{18}F	2 hour half-life
^{15}O, ^{11}C, ^{13}N	2–20 minute half-life

Step 2: Detect Radioactive Decays

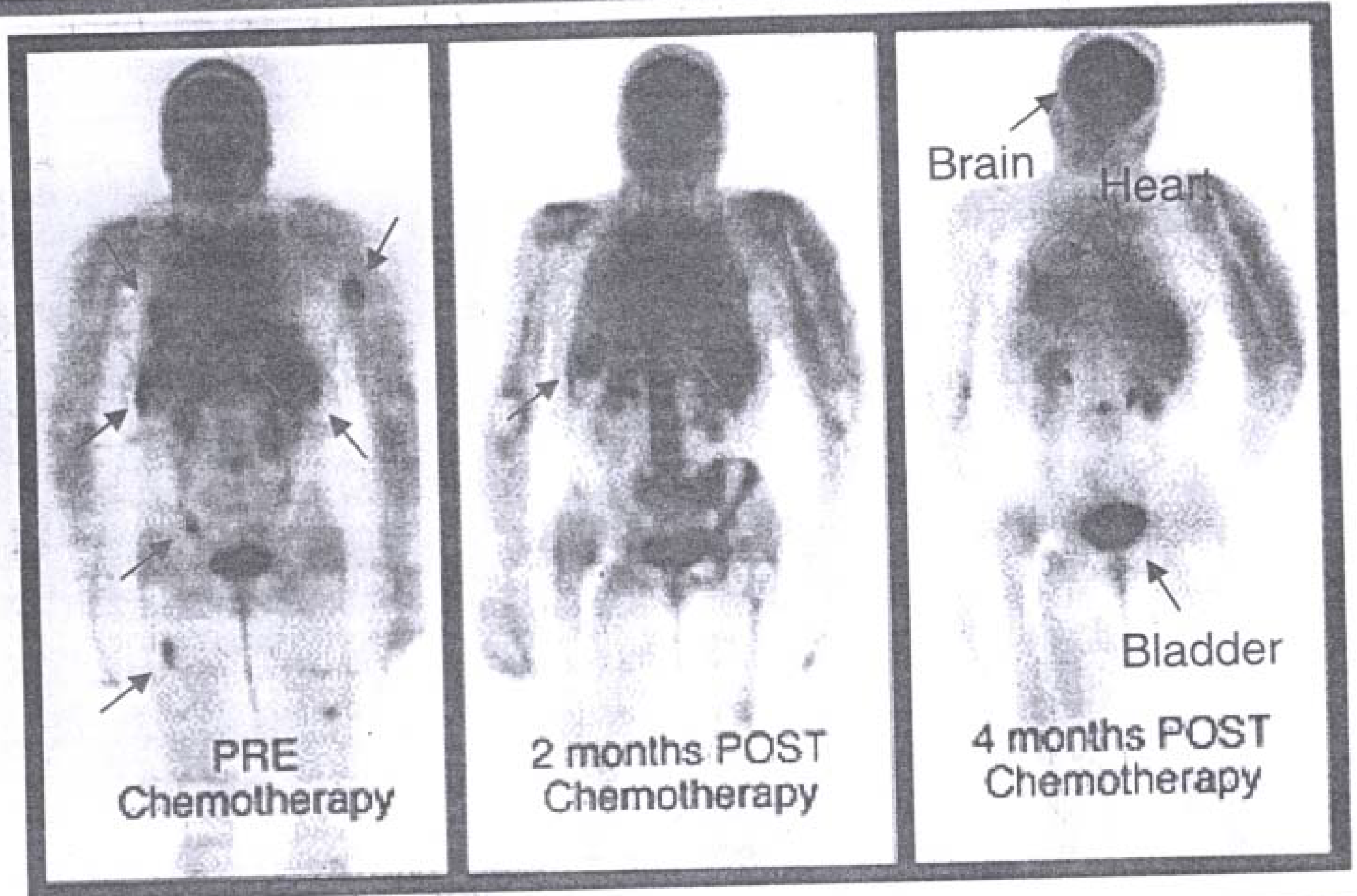


- Isotope decays, emitting β^+.
- β^+ annihilates with e^- from tissue, forming back-to-back 511 keV photon pair.
- 511 keV photon pairs detected via time coincidence.
- Positron lies on line defined by detector pair (a *chord*).

Detect Pairs of Back-to-Back 511 keV Photons

PET Images of Breast Cancer Patient

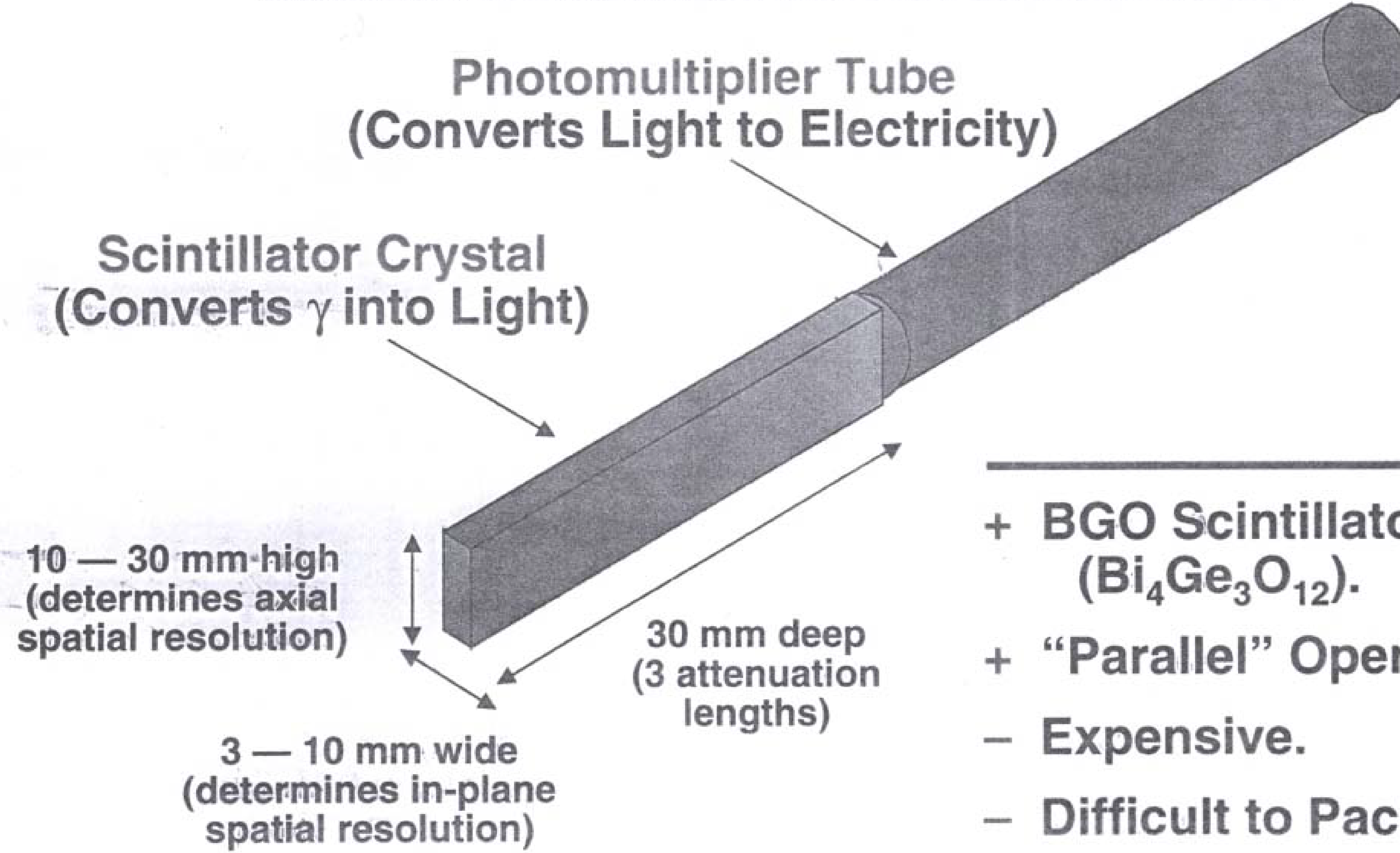
Metastases Shown with Red Arrows



Normal Uptake in Other Organs Shown in Blue

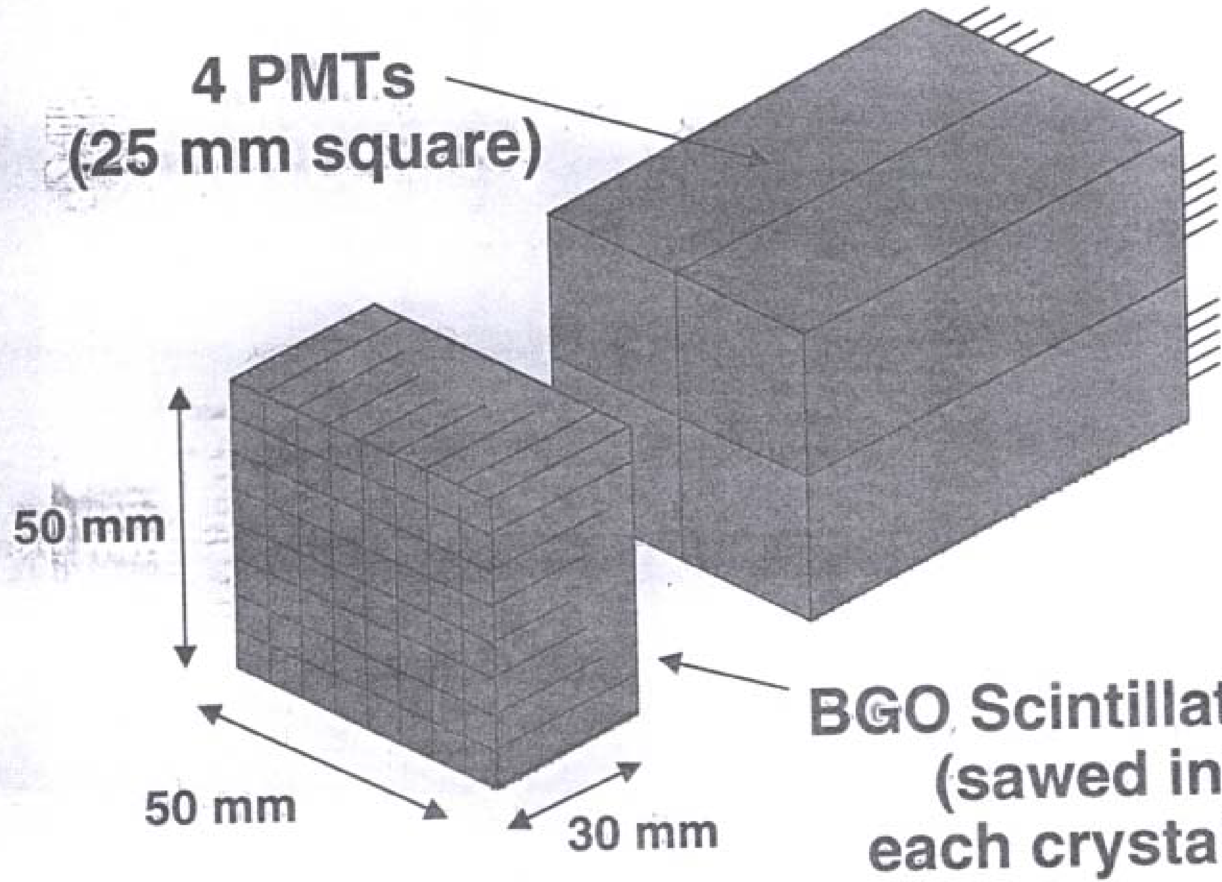
- Tumors Easily Seen (~5 mm spatial resolution)
- Typical Contrast ~400%

Early PET Detector Element



+ BGO Scintillator ($Bi_4Ge_3O_{12}$).
+ "Parallel" Operation.
– Expensive.
– Difficult to Pack.

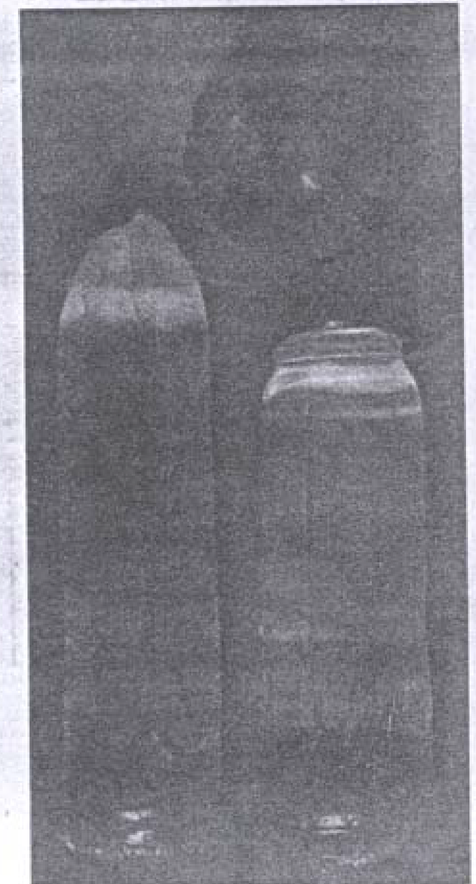
Modern PET Detector Module



- Saw cuts direct light toward PMTs.
- Depth of cut determines light spread at PMTs.
- Crystal of interaction found with Anger logic (*i.e.* PMT light ratio).

Good Performance, Less Expensive, Easy to Pack

Lutetium Orthosilicate (LSO) Scintillator



Compared to BGO, LSO has:

Same Attenuation Length:

⇒ Good Spatial Resolution

Higher Light Output:

⇒ Decode More Crystals per Block

⇒ Better SNR for "Enhanced" Readout (*e.g.* Depth of Interaction)

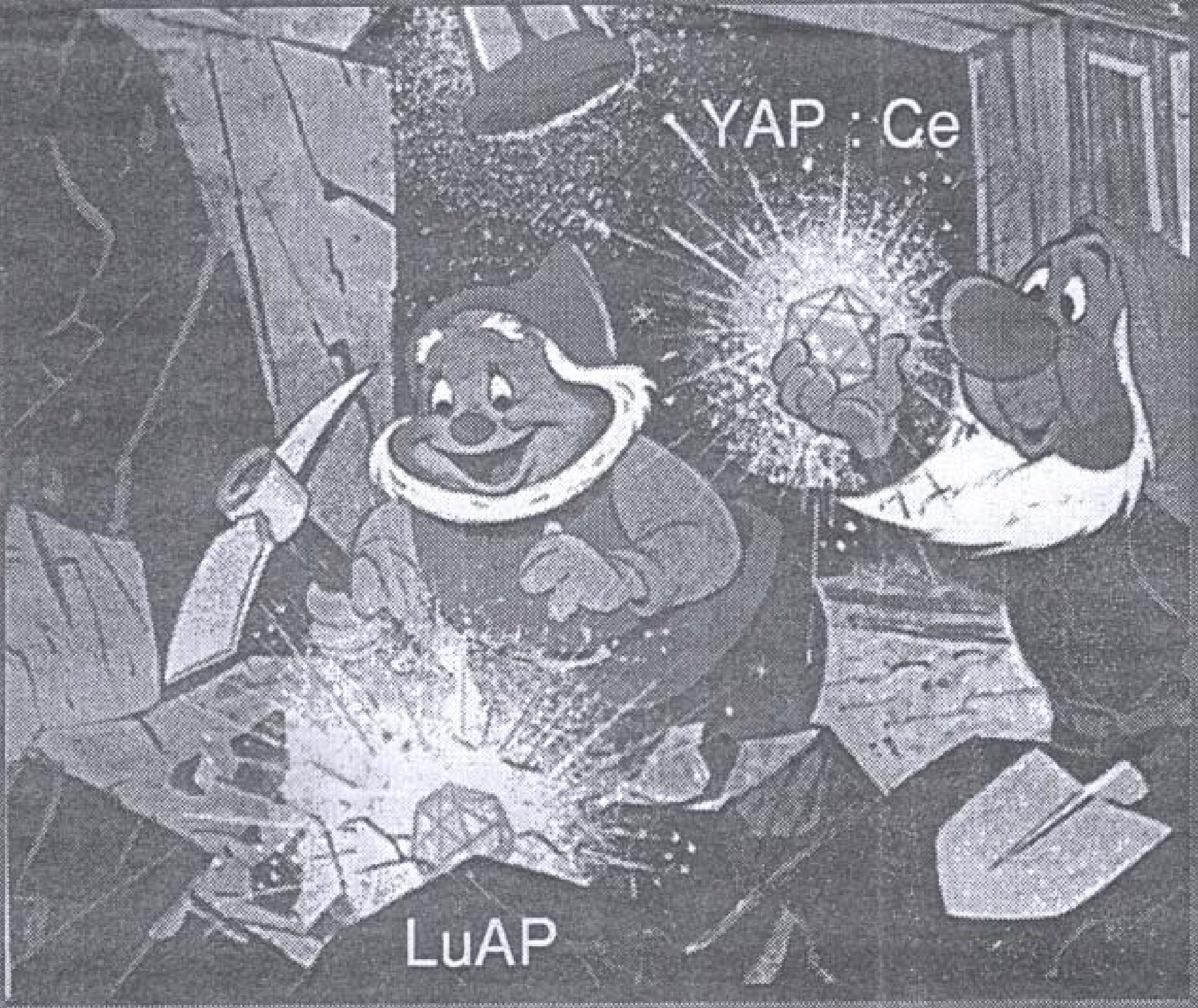
Shorter Decay Time:

⇒ Less Dead Time (Allows Larger Block Areas)

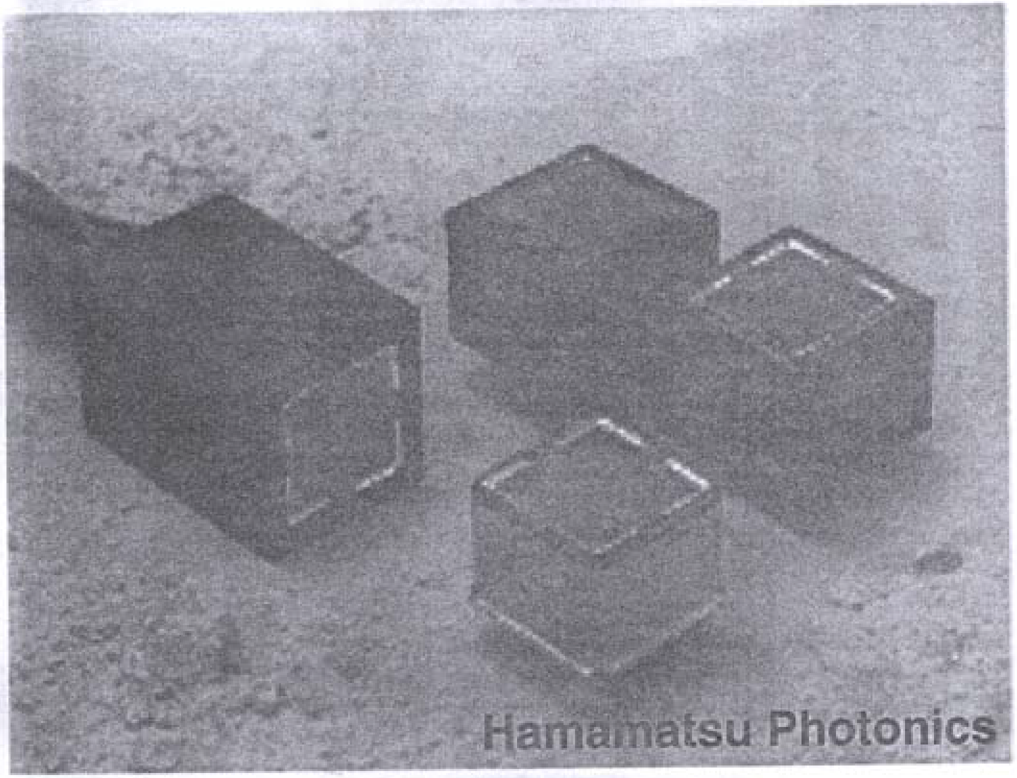
⇒ Better Timing Resolution

Reduce Cost OR Increase Performance

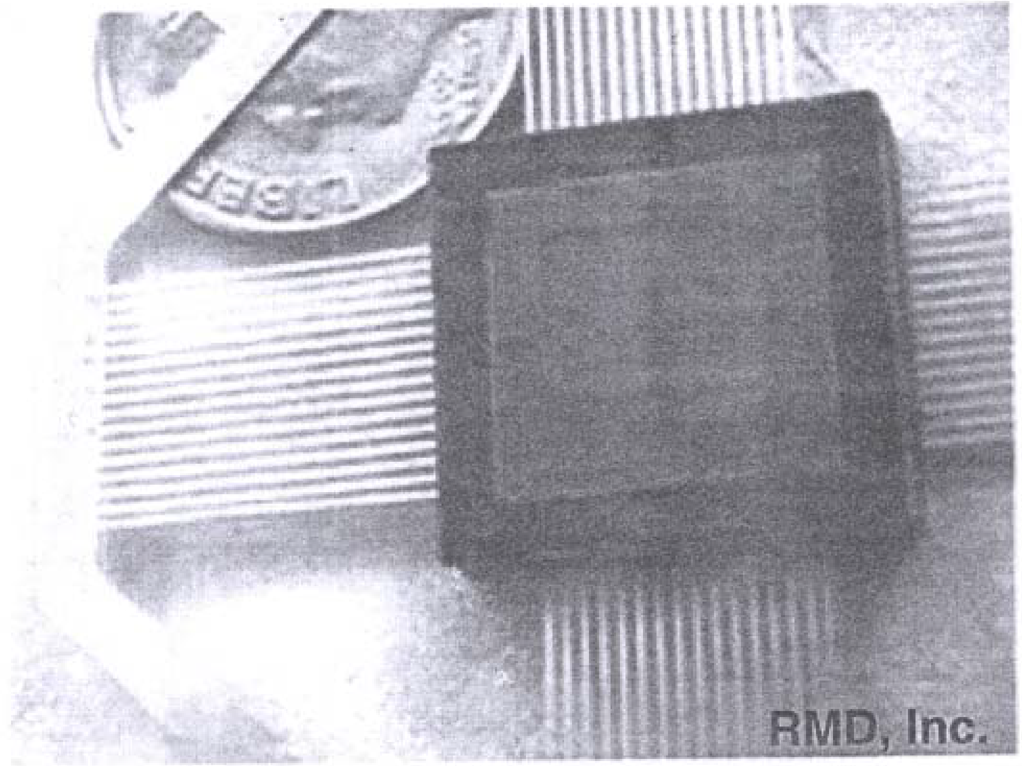
NEW TRENDS IN CRYSTAL GROWING



Pixellated Photodetectors



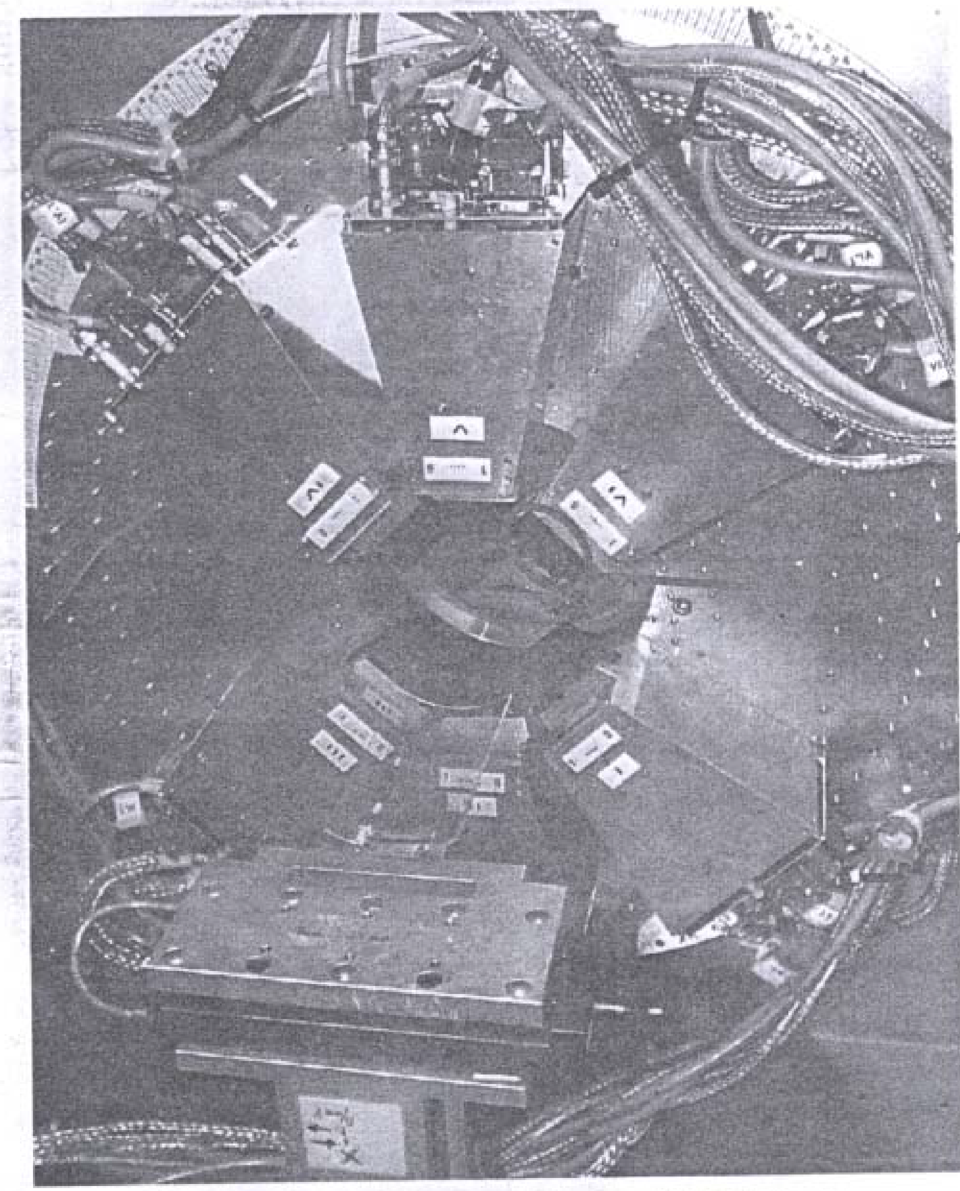
Multi-Anode Photomultiplier Tube



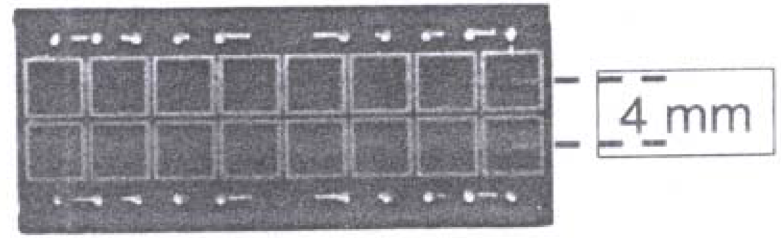
Avalanche Photodiode Array

- Advantages: Smaller Pixels ⇒ Higher Resolution
- Challenges: Dead Area Around Perimeter, Reliability (for APDs), High Cost

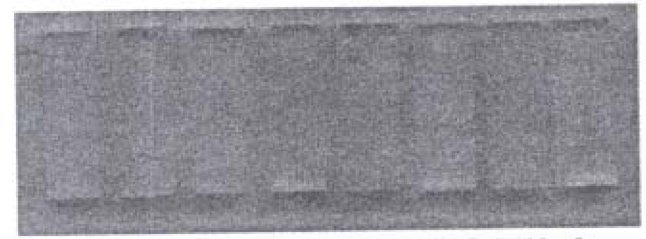
PET with Avalanche Photodiodes



*Images courtesy of Sibylle Ziegler, T.U. München



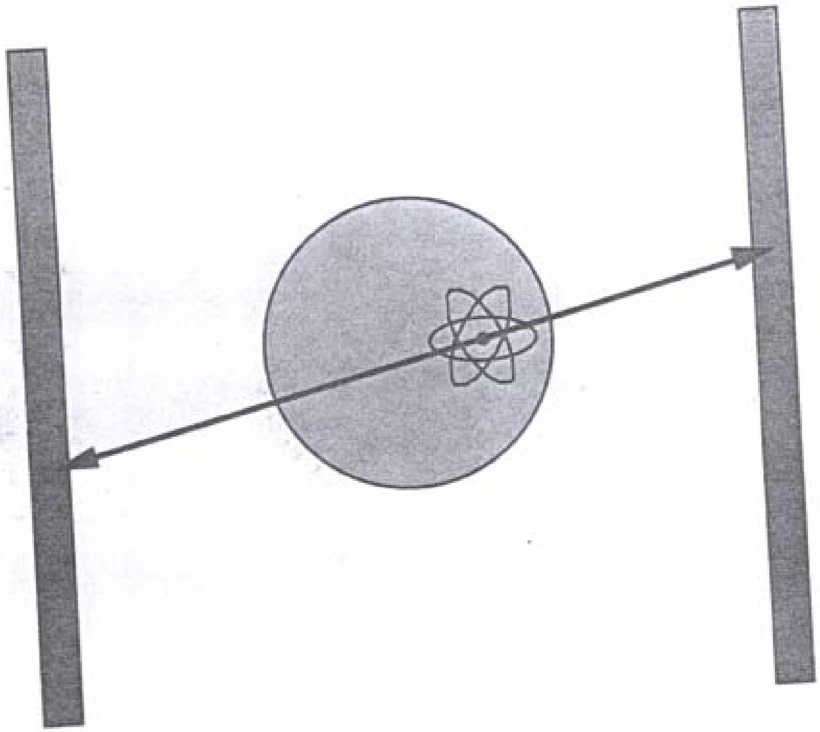
Avalanche Photodiode Array
(Hamamatsu Photonics)



LSO Crystals *(CTI Inc.)*
(3.7 x 3.7 x 12 mm^3)

APD Technology is Steadily Advancing...

Dual Modality: PET / SPECT
(Use SPECT Camera for PET)

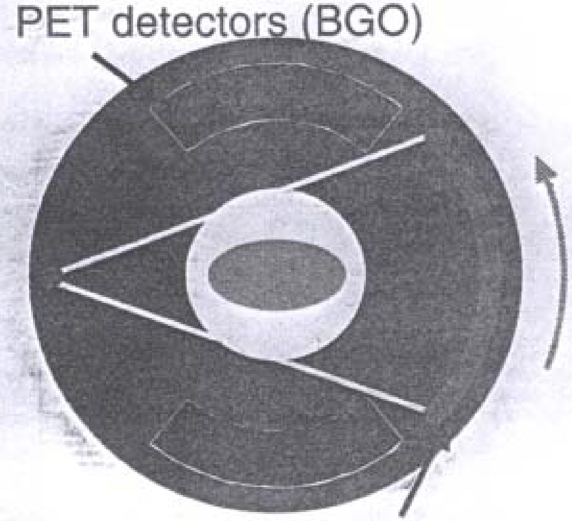


- SPECT optimized to image 140 keV (not 511 keV) photons.
- Detectors are "thin" (only 0.8 attenuation lengths thick) NaI:Tl.
- Large gaps in angular coverage
  $\Rightarrow$ rotate detectors for complete sampling.

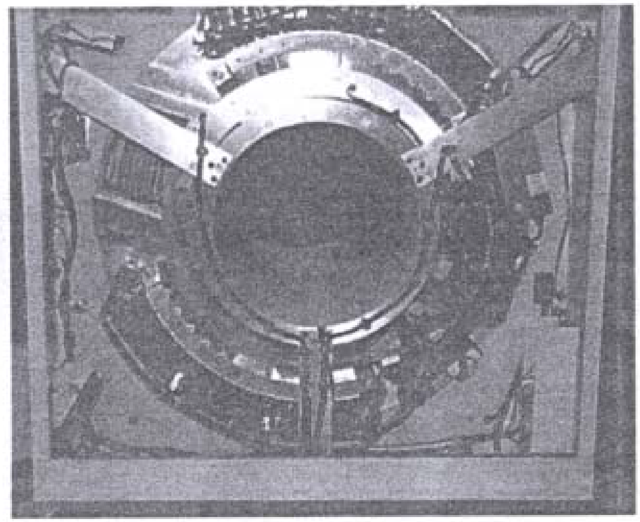
Less Expensive, But Not Optimized for PET

Dual Modality: PET / X-Ray CT

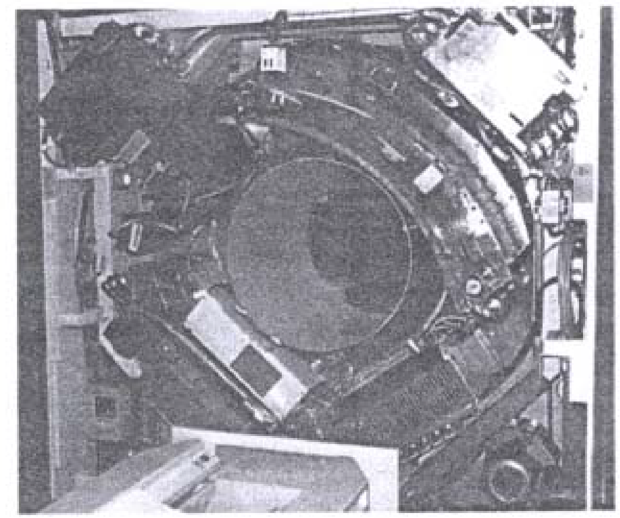
Artist's Conception



Reality



ECAT ART

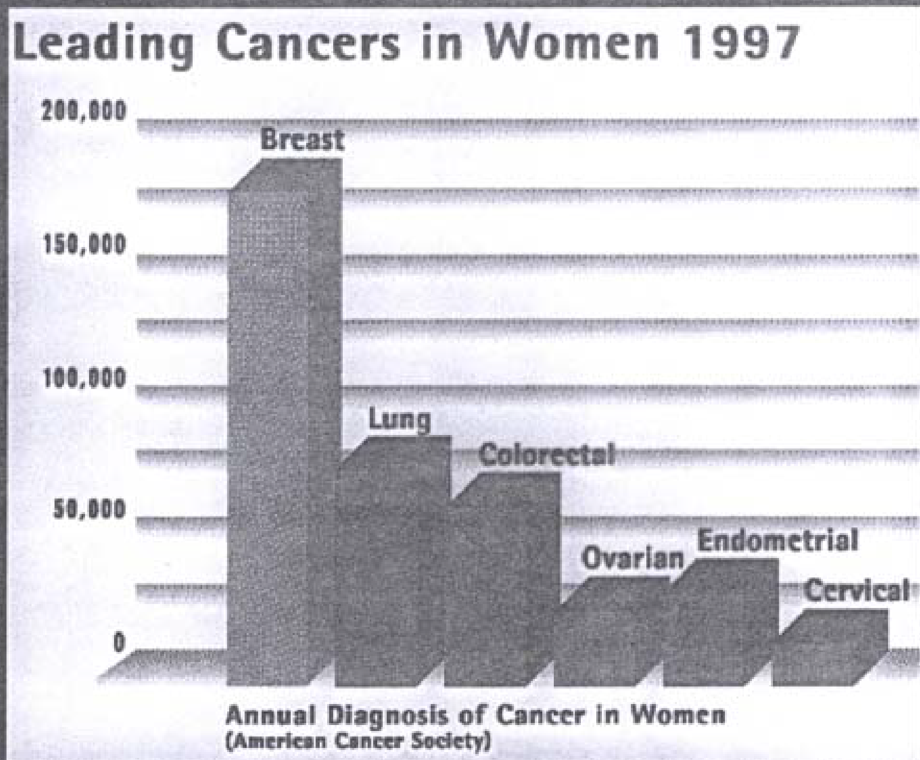


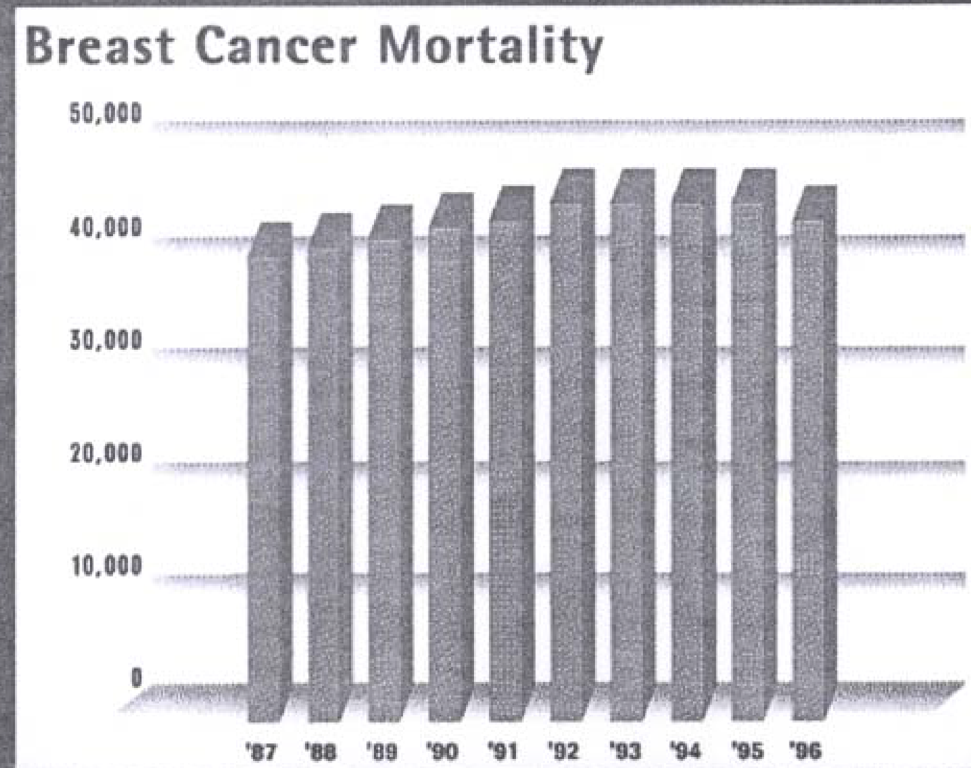
Somatom AR.SP

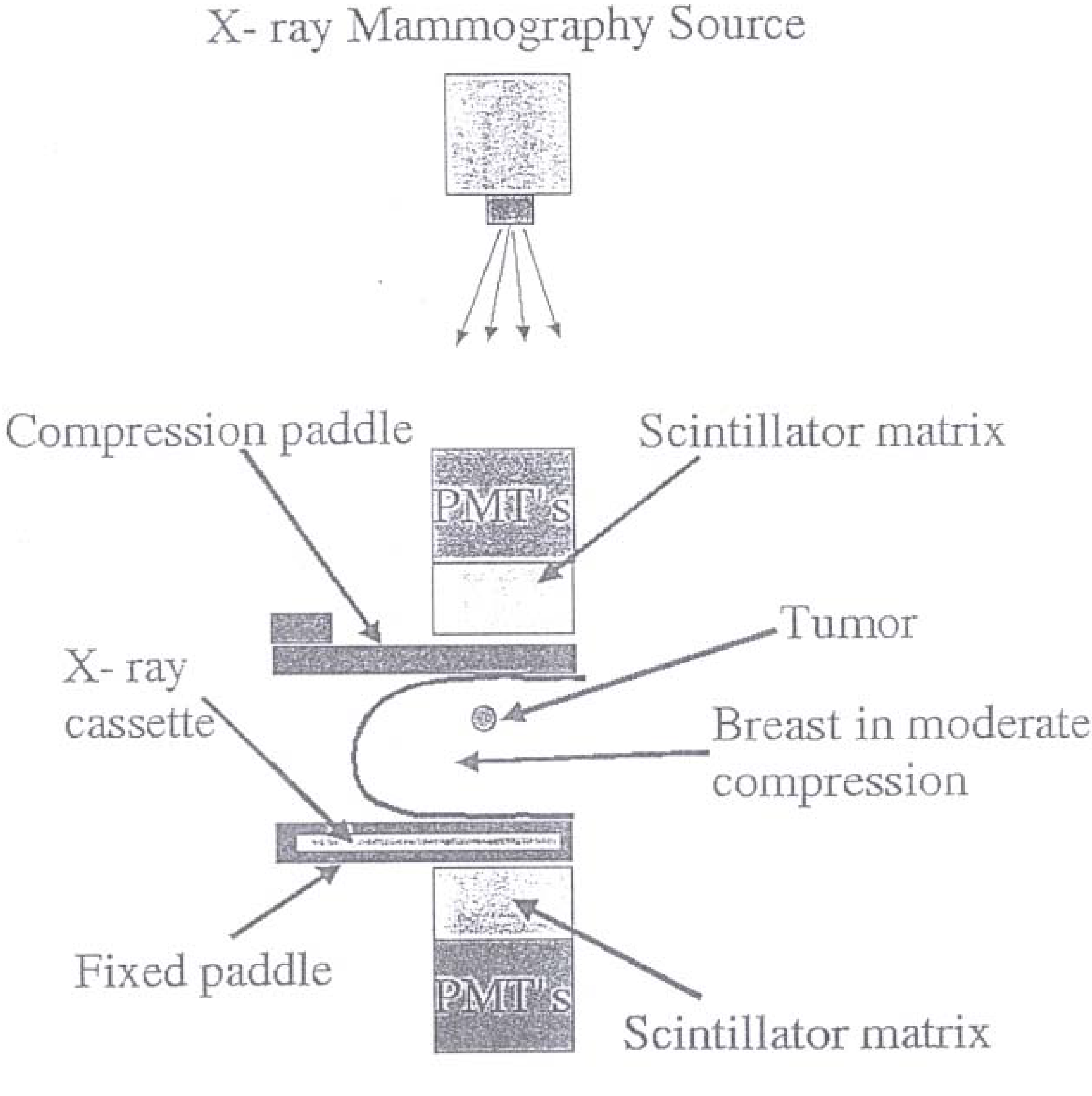
*Data courtesy of David Townsend, U. Pittsburgh

PET & CT Scanners Must Be Separated Axially
⇒ Cannot Image Same Slice Simultaneously!

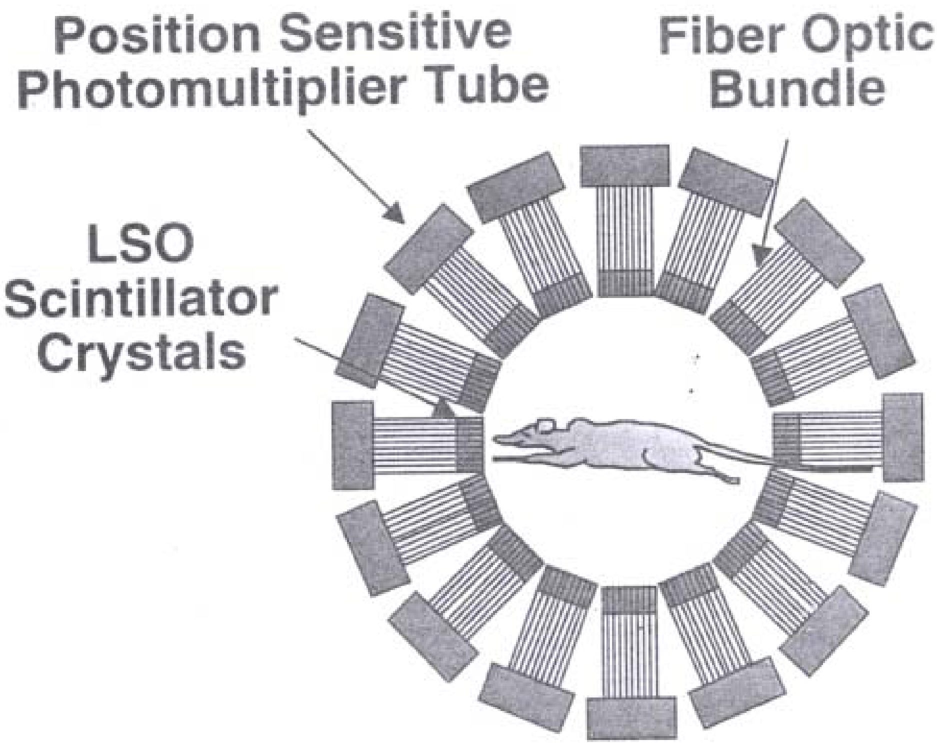
Breast cancer incidence






X- ray Mammography Source
Compression paddle
Scintillator matrix
PMT's
Tumor
X- ray
cassette
Breast in moderate
compression
Fixed paddle
PMT's
Scintillator matrix

Small Animal PET Camera



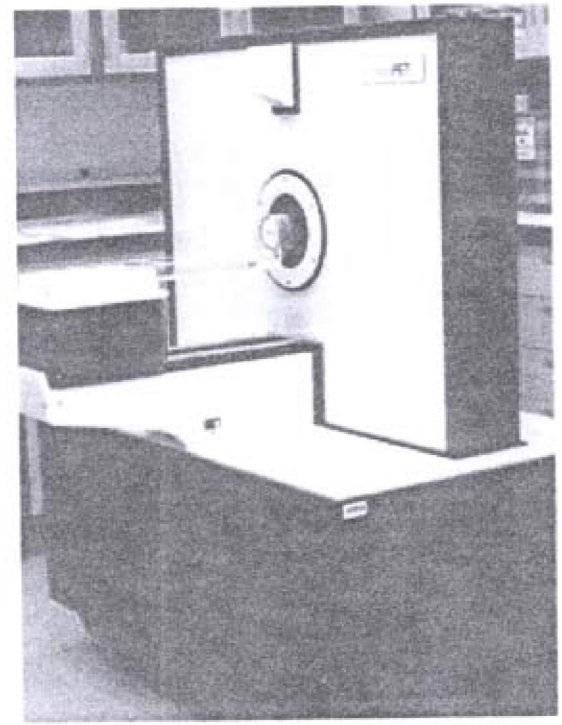
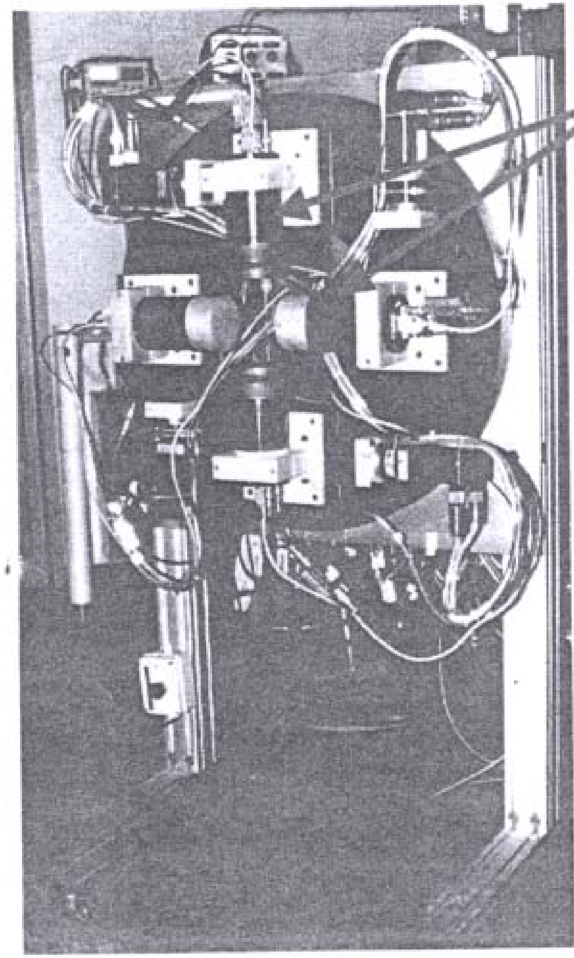
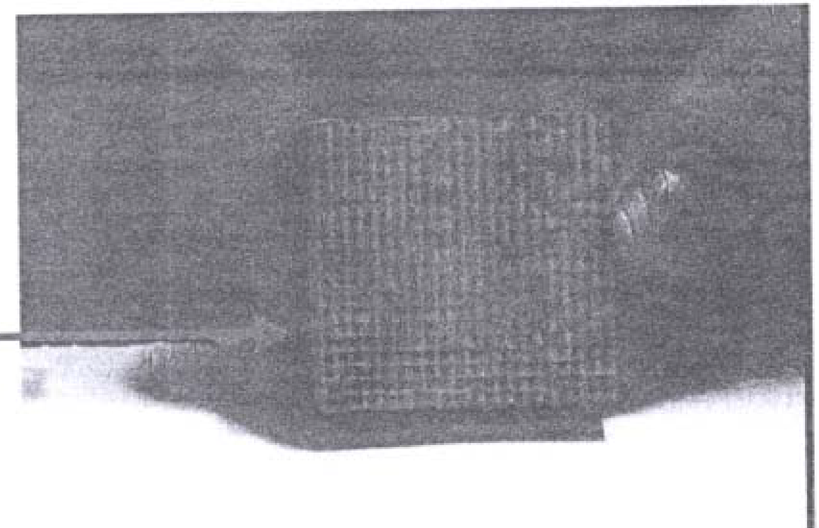


*Image courtesy of Simon Cherry, UCLA

- Miniature Version of "Standard" PET Camera
- Significant Interest by Drug Developers

Animal PET / SPECT



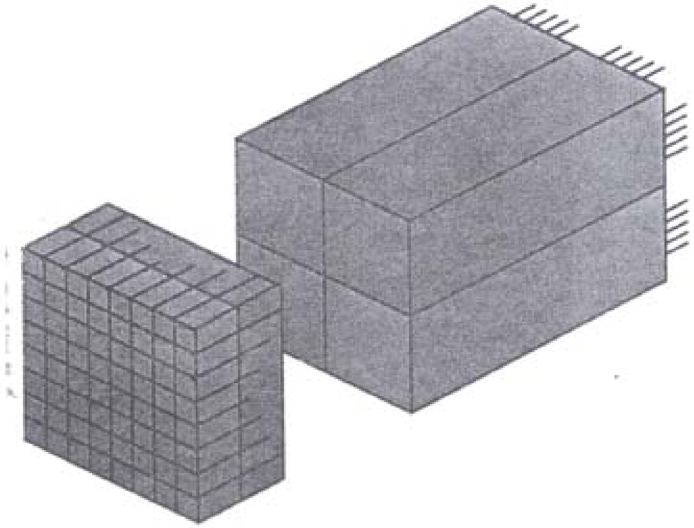


- Dual Modality (PET/SPECT)
- New Scintillator (YAP:Ce)
- Position Sensitive PMT
- Small Animal Imaging

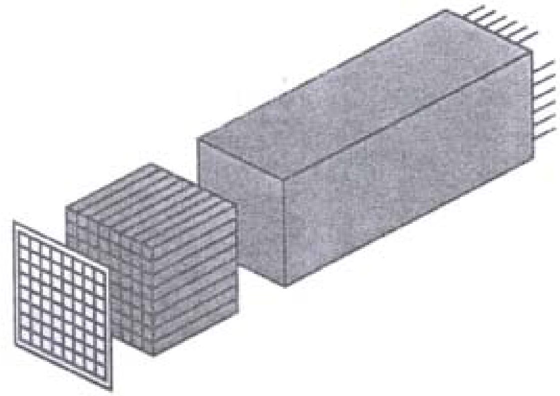
*Images courtesy of Alberto DelGuerra, INFN Pisa

Measuring Interaction Depth

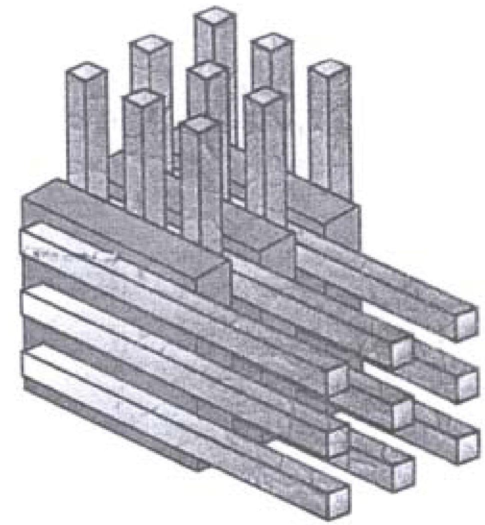
Phoswich



Light Sharing

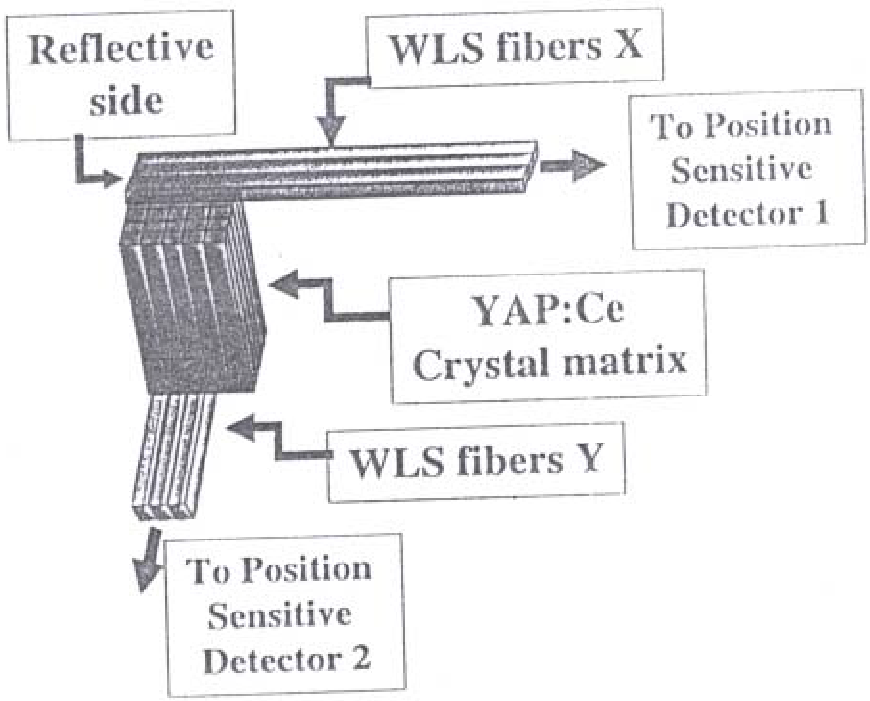


Optical Fibers



Need 5–10 mm Depth Measurement Accuracy

Scintillator- Fibers Montage



YAP :Ce Matrix

900 crystals 2x2x30 mm^3 each

↓

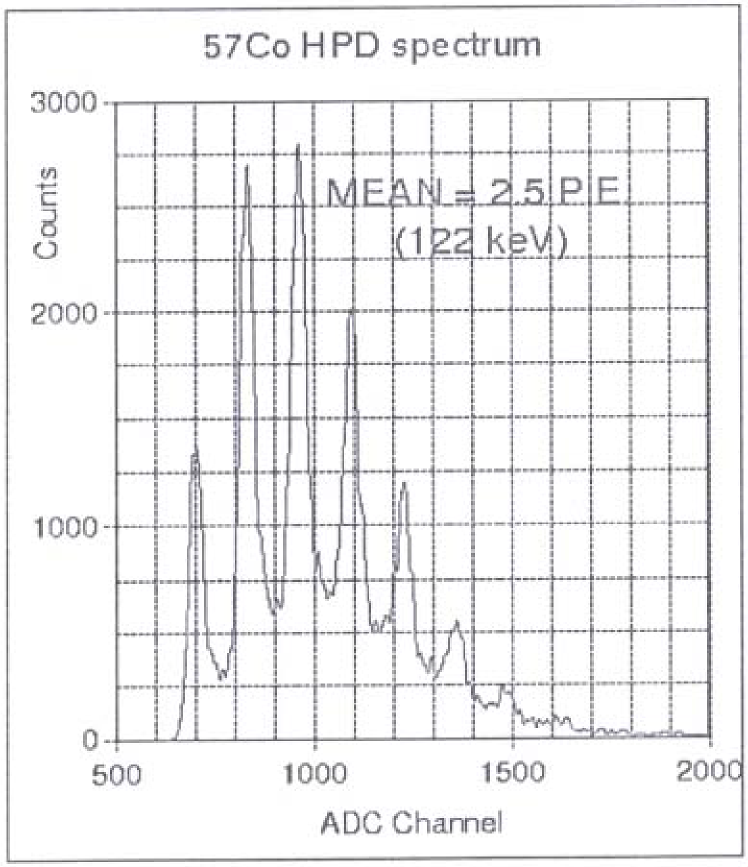
900 channels to be read directly or indirectly

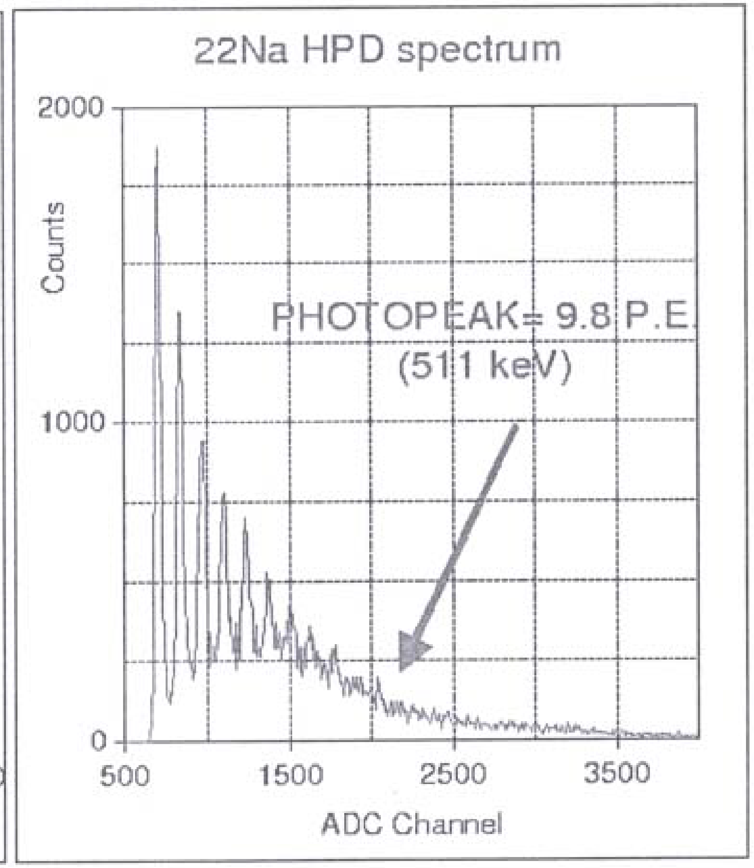
Fibers read-out

↓

30+30 channels to be read

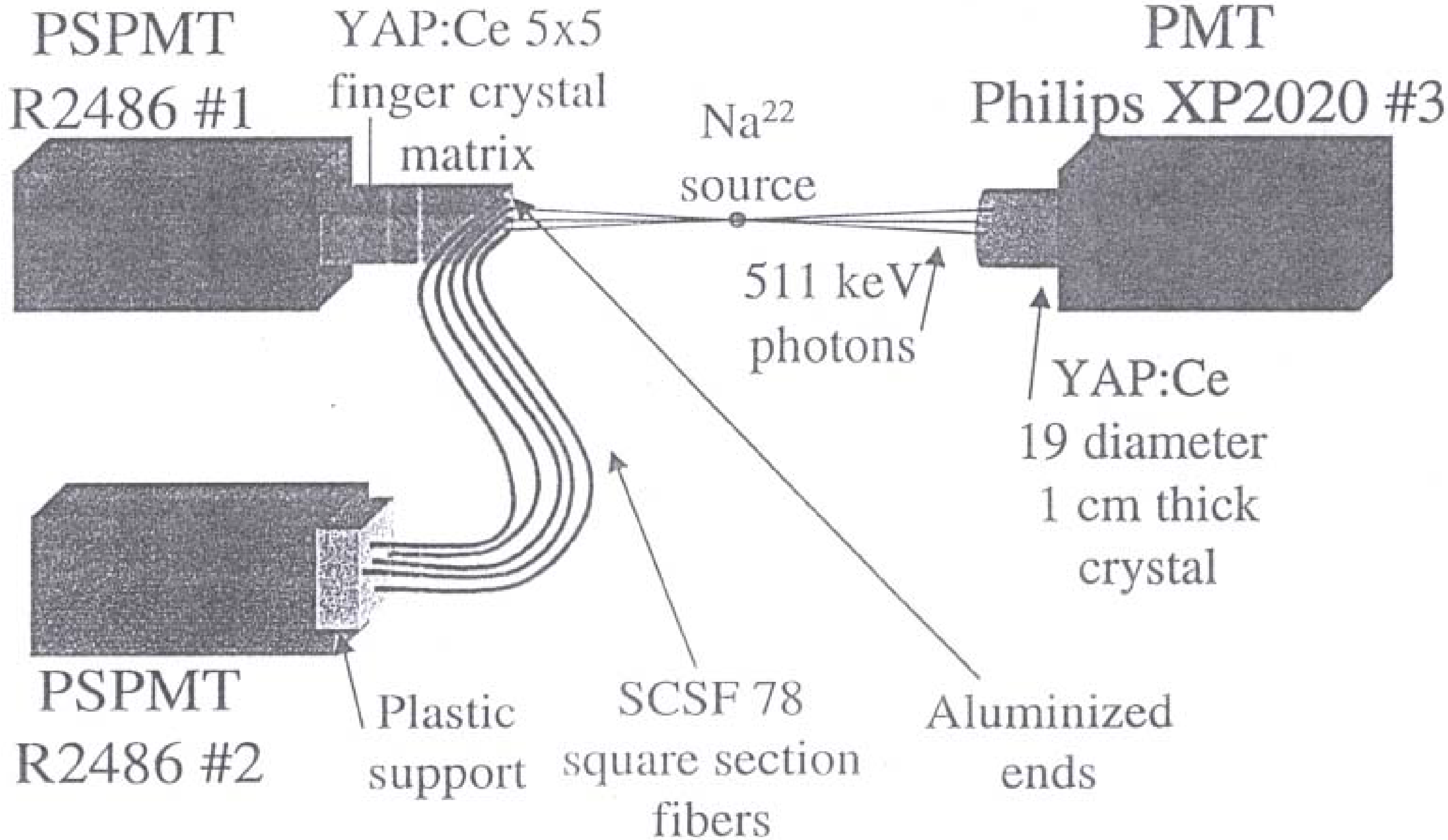
Experimental light yield measurement: HPD side



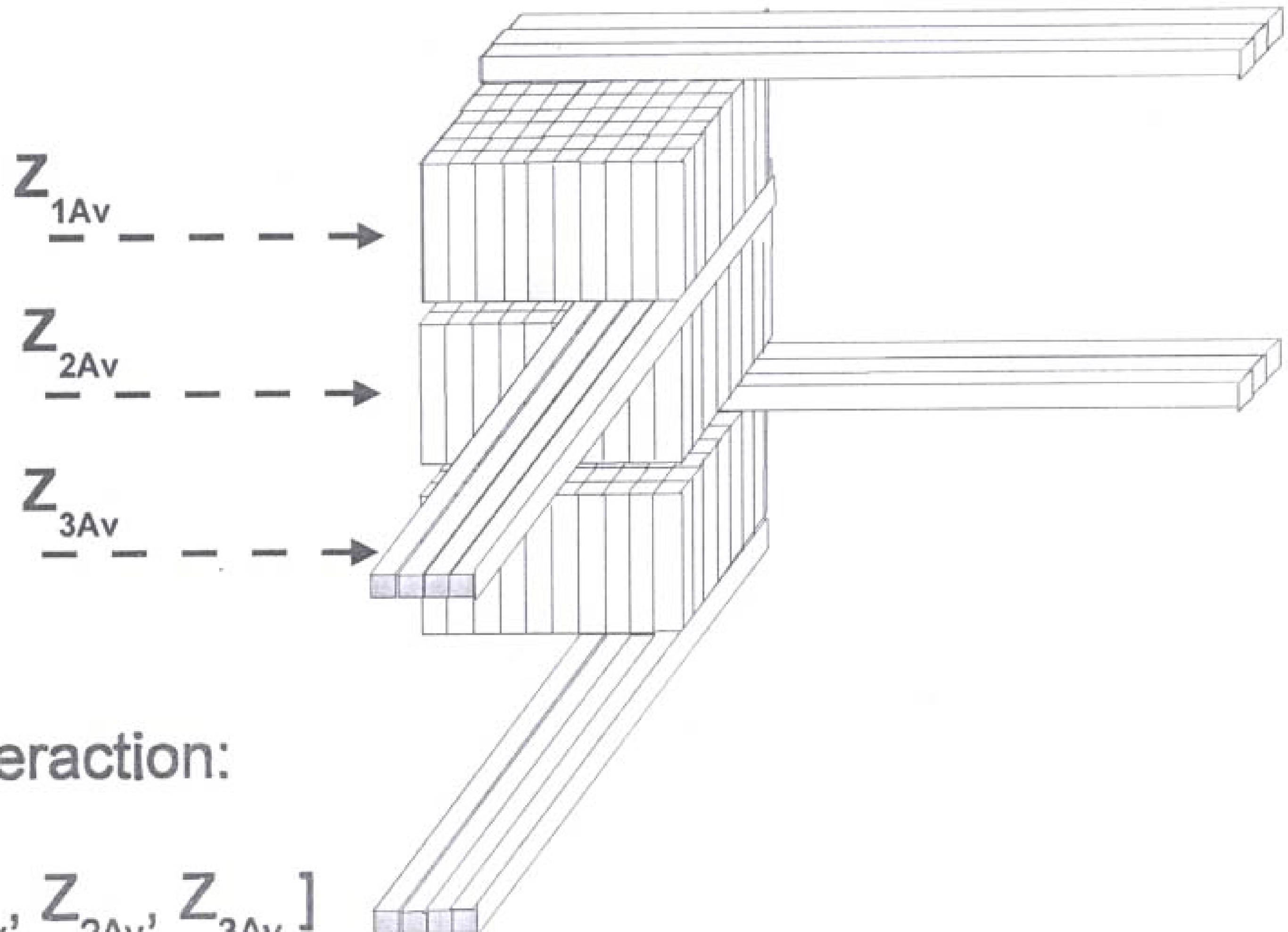


Experimental Position measurement 1

Experimental set-up



Sandwich Read-Out method



Depth of interaction:

$$Zint \in [Z_{1Av}, Z_{2Av}, Z_{3Av}]$$

OUTLINE OF THE PROGRESS OF RADIOTHERAPY

50 % of cancer patients are treated by radiotherapy
18 % of cancer patients are cured by radiotherapy either alone (12%) or in combination (6%)

DATE	PROCESS	ENERGY IN MeV	COMMENT
	X-RAY THERAPY		
1905	X-ray tube	0.05 - 0.2	Superseded
1947	Van de Graaff	3	Superseded
1948	Betatron	20	Superseded
→ 1953	Linac	6 - 30	More effective for deep tumours
	GAMMA-RAY THERAPY		
1910	Radium needles	1 - 3	Superseded
1951	Cobalt "bomb"	2	Still used
	ELECTRON THERAPY		Useful for superficial cancers
1947	Van de Graaff	3	
1948	Betatron	20	
→ 1963	Linac	6 - 30	Still used
	NEUTRON THERAPY		Treatment of tumours insensitive to gamma therapy thanks to a better *biological effect* (for instance prostate, head and neck cancers)
1969	Cyclotron	30	
1975	Deuterium-tritium accelerator	14	
1968	Californium-252		
	PROTON THERAPY		Treatment of tumours with *very high accuracy*, required when the tumour is close to a vital structure (spinal cord, brain, etc.); 11 machines in operation (1 in EEC) and 9 under construction (3 in EEC).
→ 1955	Cyclotron [and synchrotron]	60 - 250	

NEW THERAPIES UNDER DEVELOPMENT:

BORON NEUTRON CAPTURE THERAPY		*High accuracy* treatment of tumours which take up boron, for instance gliomas. Pilot studies underway in Japan, treatment facility under construction in Petten (NL)
LIGHT ION THERAPY	5'000 to 10'000 MeV	Combines the advantages of neutron and proton therapies, i.e. treatment of tumours insensitive to γ therapy thanks to greater biological effect plus high accuracy to spare healthy tissues. Pilot studies in the USA and full-scale facility being built in Japan.

Fig. 1.2 Annex C of the report "Towards Co-ordination of Cancer Research in Europe" describes the progres of radiotherapy in about hundred years.

Category	Approximate number
"High Energy" research accelerators	110
Accelerators in industry	1'500
Ion implanters	6'000
Surface modification	
Synchrotron radiation sources	60
Radiotherapy	
– with X-rays	4'500
- with hadron beams	30
BiomedicalResearch	1'000
Medical Radioisotope Production	200
Total in 1998	**13'400**

1. W.H. Scharf and W. Wiesczycka, private comunication.
2. W.H. Scharf and O.A.Chomicky, Phys. Medica, 12 (1996) p.199.

Table 3
The three European strategies described in Ref. [3]

Problem		Remedy	
I	Late diagnosis	Screening	
II	a) Poor treatment	Quality control	
	b) Tumours with difficult localisation	– conformal treatment – protons – light ions – BNCT	improved local treatment
	c) Tumours currently radio resistant	Light ions and BNCT	
III	Conventional treatments not effective	Improved local treatments combined with improved systemic treatments	

Table 3 explains the three Strategic Approaches indicated by the *Cancer Research Working Party*:

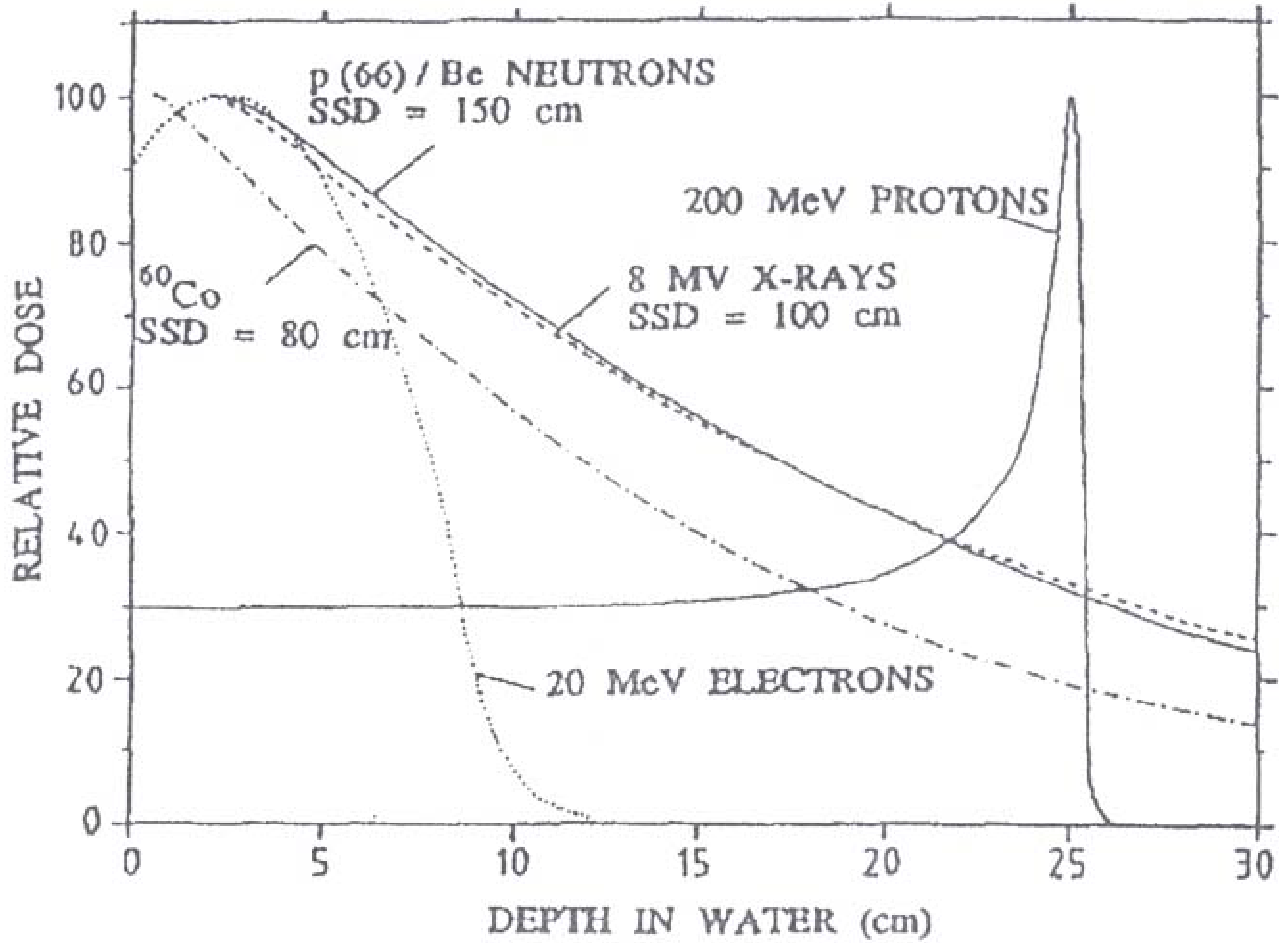


Figure 2. Depth-dose curves in water for electrons (20 MeV), photons (from a Cobalt source and an 8 MV linear accelerator), neutrons and 200 MeV protons. The proton peak is high and narrow because the protons are monoenergetic (SSD means 'Source-Skin Distance).

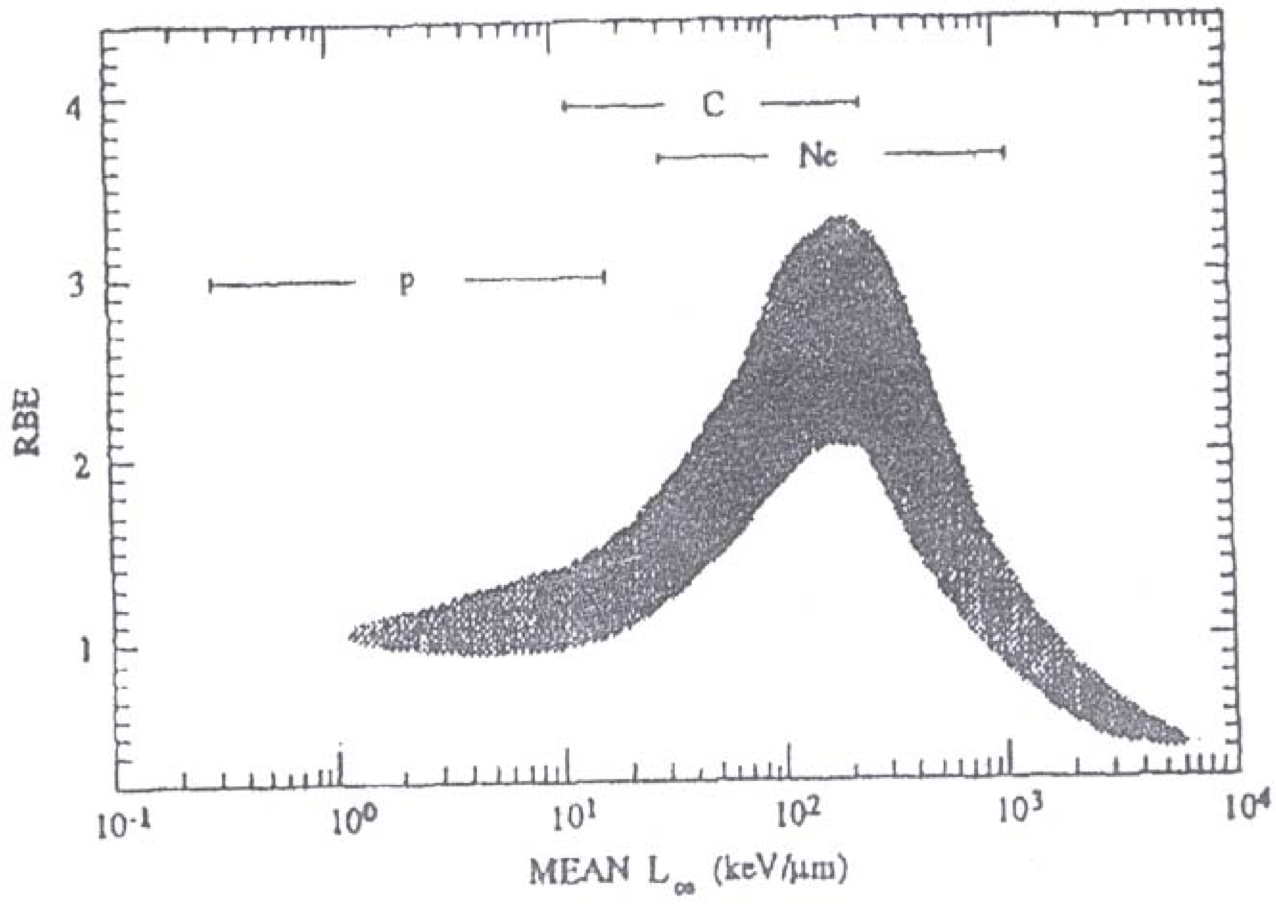


Figure 9. Variation of the RBE as a function of LET for many cell lines. The general trend is that RBE is maximal for LET around 100 KeV/μm (10 MeV/cm), and decreases again for very large local energy depositions [Belli et., Chapter 3 of Ref 19].

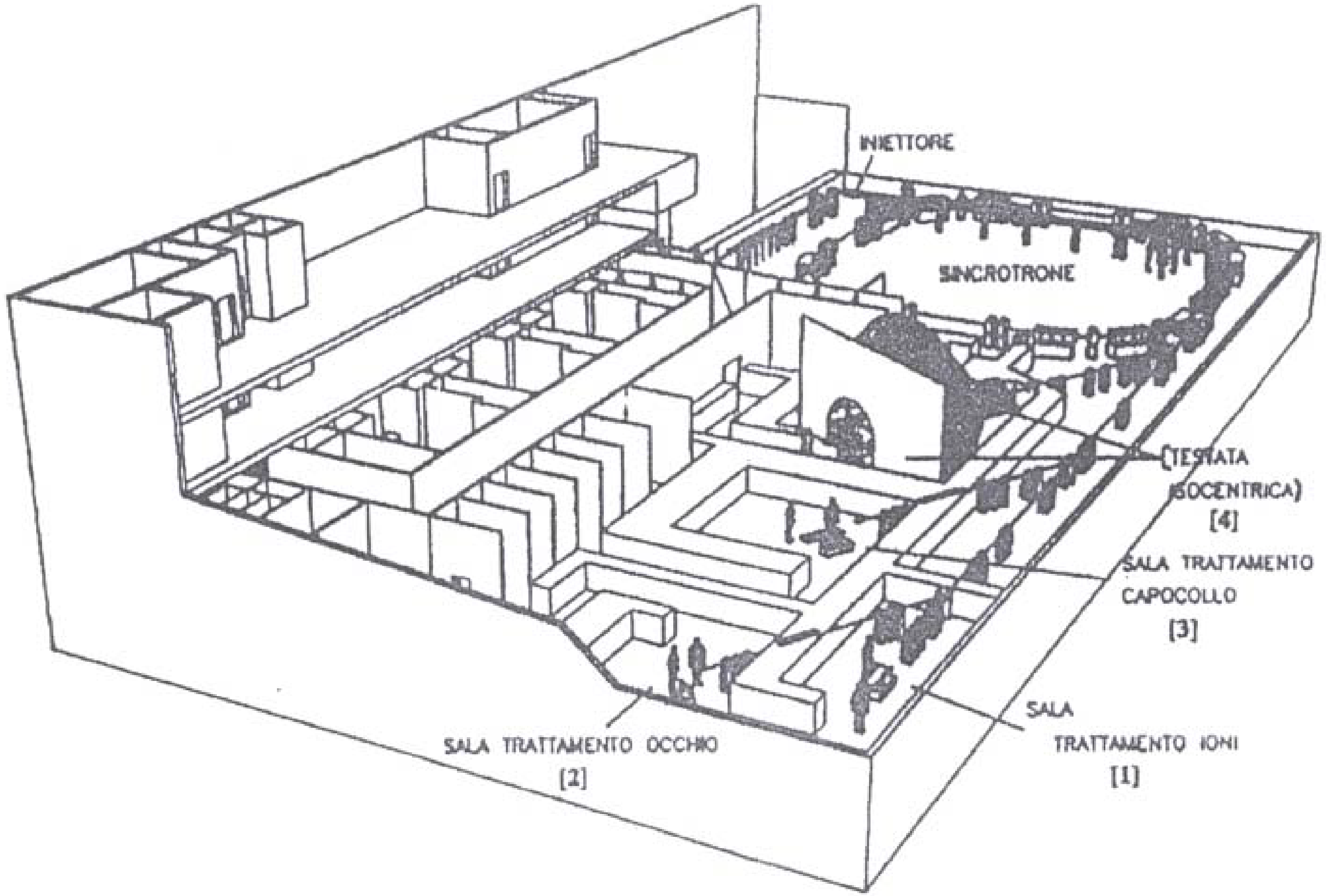


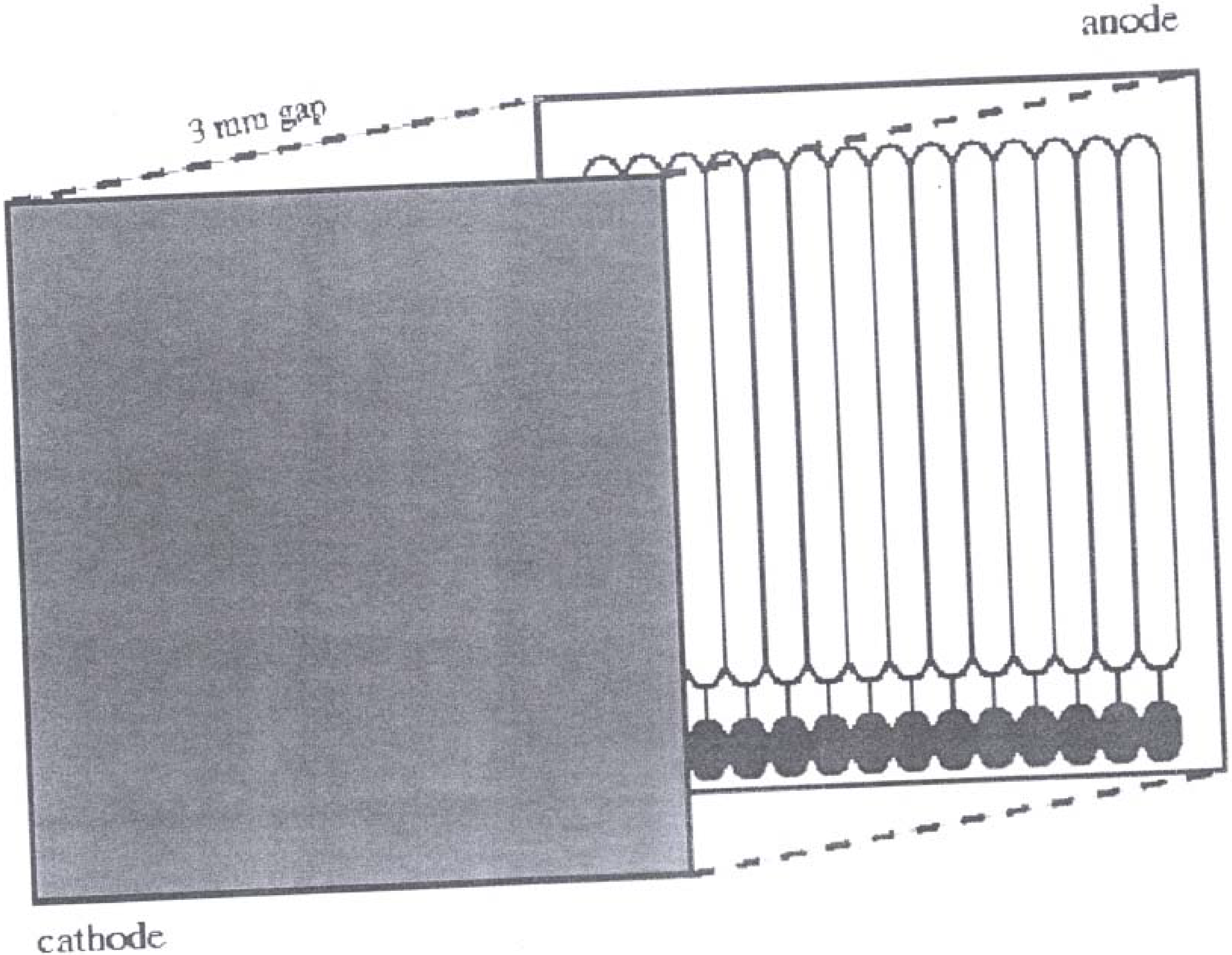
Figure 14. The TERA project described in the "Red Book" [29]. According to the decision taken by the Italian radiotherapists, initially only a horizontal carbon ion beam will be available (room 1). In a second stage ion gantries will be installed in a prolongation of the building.

The Magic Cube: principle

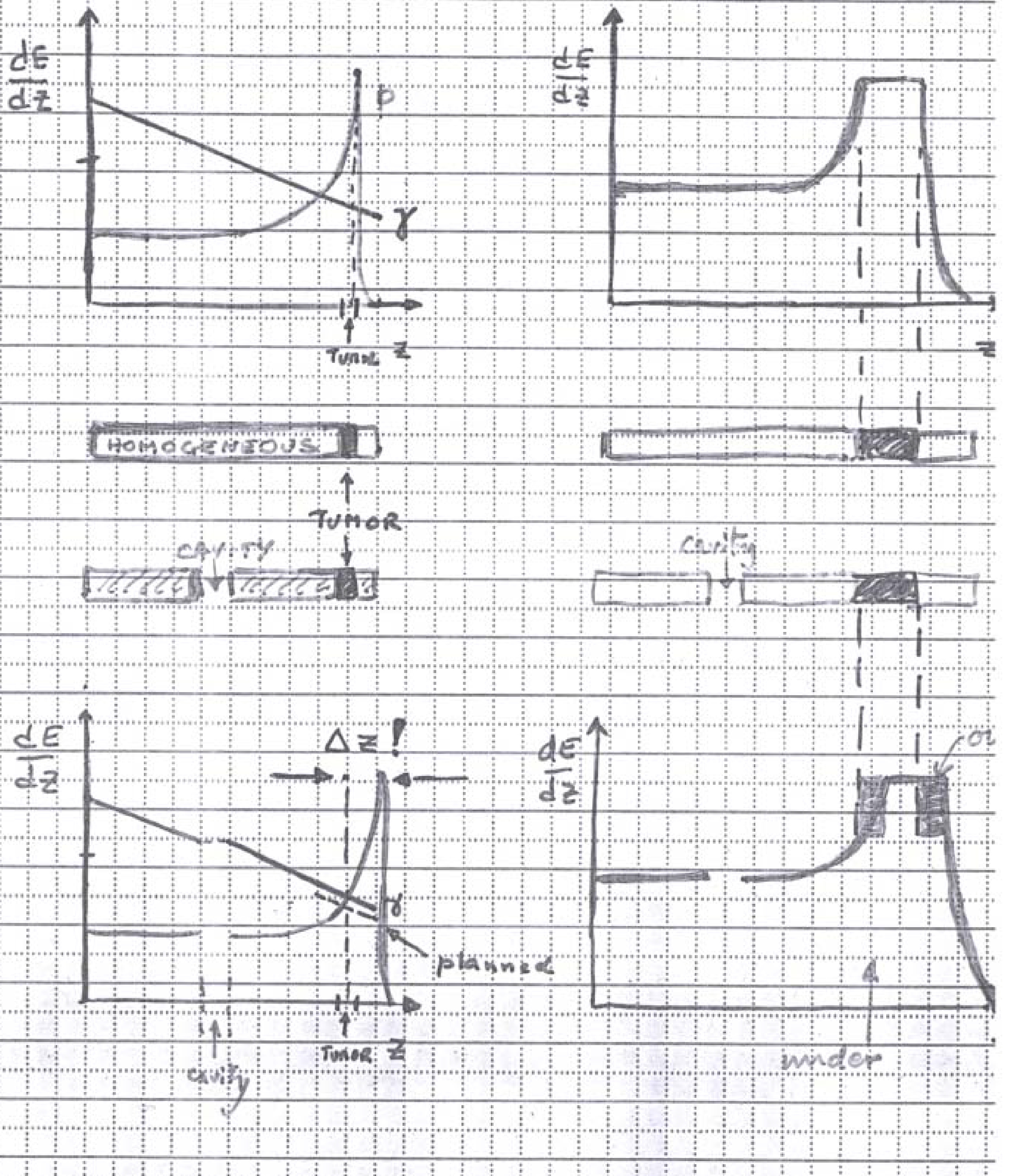
- Goal: measure the 3D dose distribution with:
  - good spatial resolution
  - short acquisition time ('online')
- Architecture: sampling calorimeter:
  - 12 (strip segmented) ionization chambers
  - water equivalent slabs in between
- Designed and built at INFN Torino

The Magic Cube:architecture

- Each ionization chamber:
  - 64 strips, 25cm long, 4mm wide
  - 3mm gas gap (either air or N_2)
  - 25*25cm^2 fiducial area
- Frontend electronics:
  - 12 custom VLSI chips
  - each one has 64 independent channels, recycling integrator with 16-bit counter, 100fC minimum charge quantum, 100pA-3μA dynamic range for input current
- Data acquisition:
  - PC based with LabView


anode
3 mm gap
cathode

"Rationale" for "in vivo" dosimetry for hadron radiotherapy



Quality assurance of Heavy Ion Therapy by Means of Positron Emission Tomography

W. Enghardt[a], J. Debus[b], Th. Haberer[c], B.G. Hasch[a], R. Hinz[a], O. Jäkel[d], K. Lauckner[a], J. Pawelke[a]

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[c]Gesellschaft für Schwerionenforschung, Planckstr. 1, D-64220 Darmstadt, Germany

[d]Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-69120 Heidelberg, Germany

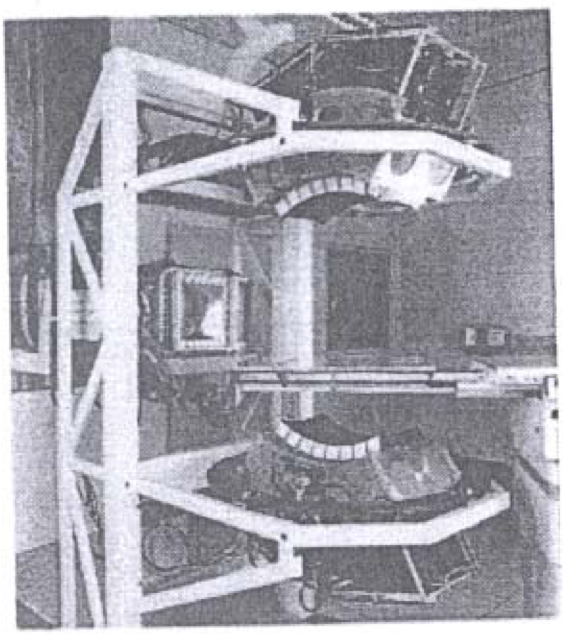


Fig. 1 The heavy ion tumor treatment site at GSI Darmstadt with the positron camera. The horizontal therapy beam comes from the left. The detector heads are mounted above and below the patient couch.

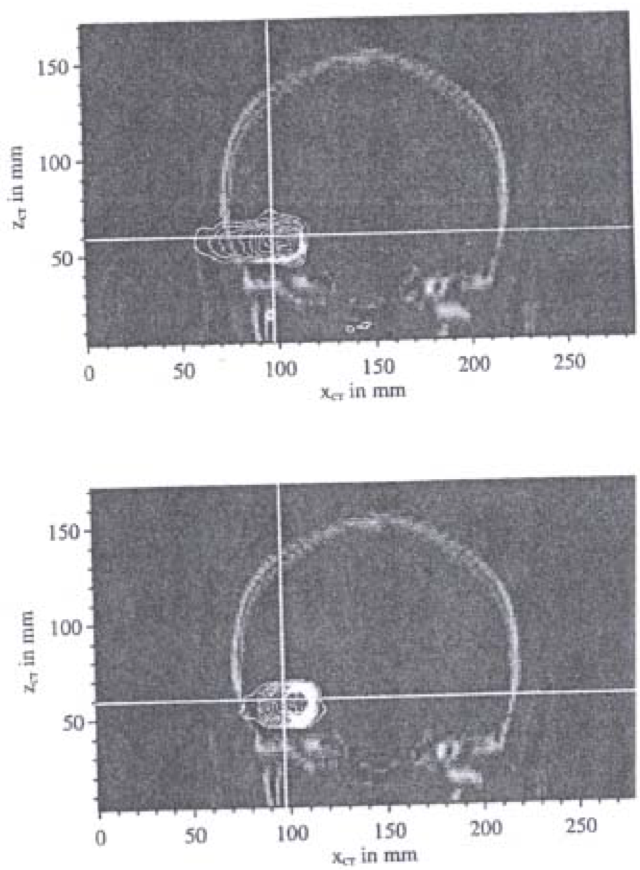
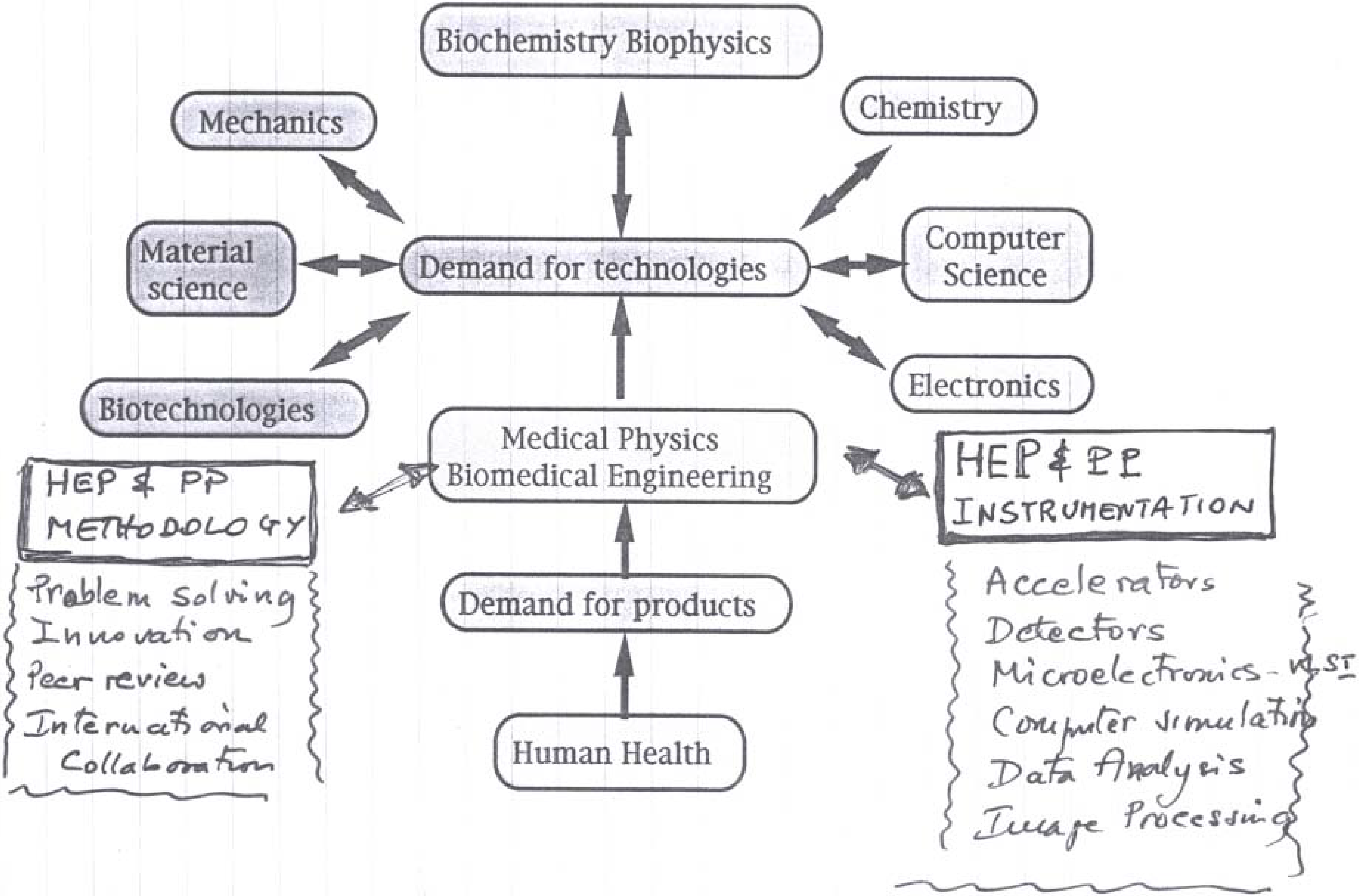
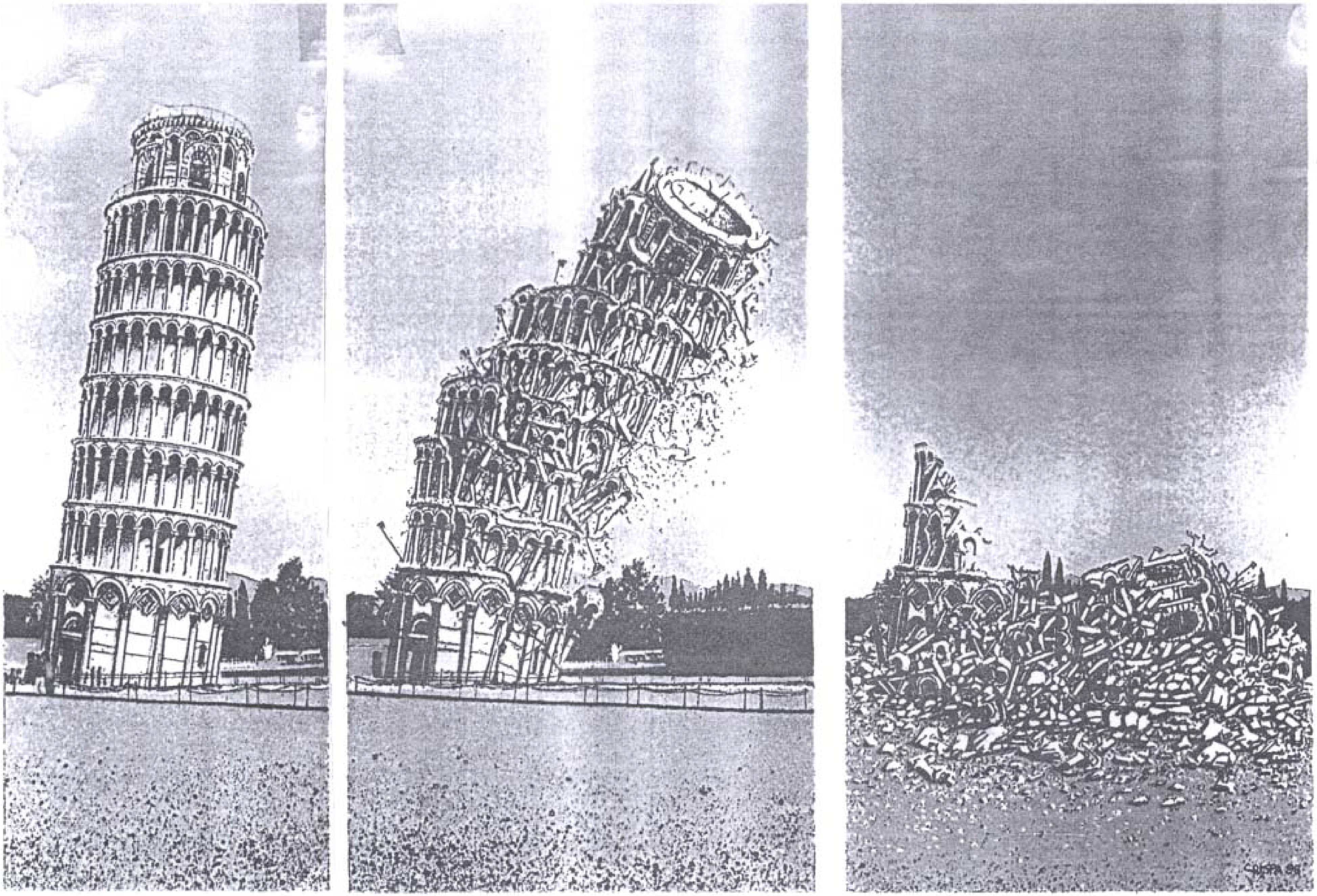


Fig. 3 Frontal X-ray computed tomograms through an ALD head phantom (grey scale) superimposed by β^+-activity distrib (contour plot) from measured (upper) and simulated (lower) data. The experiment simulated the irradiation of the brain fr right with a dose of 2 Gy in a spread out BRAGG peak of 14 22 mm³. The isocentre of the treatment facility being identic the centre of the FOV of the positron camera is indicated crosshair.

FOR HUMAN HEALTH





Pisa