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BIOLOGICAL EFFECTS OF NEGATIVE PIONS[†]

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ABSTRACT

Most pion radiobiological work in the past was done at low dose rates using biological systems sensitive to small doses. Biological effects at the beam entrance were found to be nearly the same as conventional radiations, although some reports have indicated a higher RBE. LET distribution at the peak of a nearly monoenergetic pion beam is not much different from fast neutrons; therefore, one would expect similar biological responses, and the results are consistent with this hypothesis. The RBE at the peak for a nearly monoenergetic pion beams is significantly higher than at the entrance. The RBE peak/RBE plateau ratio is decreased with increasing width of the peak. The OER (~1.6) at the peak for a nearly monoenergetic pion beam is also similar to fast neutrons and is expected to increase with increasing width of the peak. No OER data for broad peaks relevant to therapy are available. Preliminary measurements on radiosensitivity variation as a function of cell cycle indicate that there is a slight reduction in variation at the plateau, compared to X-rays, and a significant reduction at the narrow peak. With the availability of increasing intensity of pion beams, more radiobiological work relevant to radiotherapy is in progress at Los Alamos, Vancouver, and Zurich.

Pion radiotherapy, RBE, OER

INTRODUCTION

A brief review of the biological effects of negative pions and some recent results obtained at Los Alamos are presented in this report. Biophysical studies of negative pions with reference to their use in radiotherapy were started at Berkeley, California, and at CERN, Switzerland, soon after Fowler and Perkins[10] published their calculations proposing the use of negative pions in radiotherapy. Thereafter, studies were also started in Great Britain using the high-energy physics facility (NIMROD) at Harwell. The radiobiology work performed at Berkeley, CERN, and NIMROD has been reviewed.[24,26,27] Pion physics facilities with intensities suitable for radiotherapy applications have been constructed recently in Los Alamos, Vancouver, and Zurich. A pion collecting device with a large solid-angle collector that permits the use of less intense pion facilities and multiport irradiation was built at Stanford, a similar device is also under construction in Zurich, and radiobiology work is now in progress at all of the above facilities. The dose rates at which biological experiments were done at these facilities are shown in Table 1. Higher intensities are expected at Los Alamos, Vancouver, and Zurich in the near future.

The biological effects of negative pions in the pion stopping region depend upon pion energy distribution. Figure 1A shows depth-dose distributions of a nearly monoenergetic pion beam. Figures 1B and 1C show depth-dose distributions in which two beams with 5- and 10-cm peak widths were produced by using a dynamic range shifter.[1] It can be seen that the peak-to-entrance ratio decreases with increasing width of the peak. The fraction of dose deposited by star events decreases with increasing peak width, with a concomitant

reduction of LET. However, with increasing peak width (or stopping volume), the dose fraction resulting from neutrons produced by stars increases, compensating somewhat for the decrease in LET. Schillachi and Roeder[31] calculated that the per cent dose deposited by neutrons from stars in the pion stopping volumes of 0.01, 0.1, and 1 liter were 2, 10, and 20%, respectively. The physical aspects of pions must be taken into consideration in comparing the biological effects of pions. The LET distribution of nearly monoenergetic pions at the peak position is similar to that of fast neutrons currently used in therapy with one major exception: in the case of pions, the LET distribution extends to much lower values than for neutrons.[27]

The energy spread in pion beams used at Berkeley, CERN, and Zurich is quite similar to curve A in Fig. 1. The beam used at NIMROD has a wider spread and is more closely related to curve B, although the dose in the peak region follows a more nearly Gaussian distribution than the flat distribution shown in Fig. 1B.

PLATEAU RADIOBIOLOGY

The biological effects on different biological systems measured at the point of beam entrance at various centers are shown in Table 2. The relative biological effectiveness (RBE) at the beam entrance is nearly 1.0, although some results indicate that it may be as high as 1.5 to 1.8. Further work is needed at higher pion dose rates to clarify the differences, if any, between conventional radiations and pions at the beam entrance.

OXYGEN ENHANCEMENT RATIO

Raju *et al.*[22,25] reported an oxygen enhancement ratio (OER) of about 1.5 at

the peak, and they also found[28] that the OER at the beam entrance was approximately 1.4 times larger than at the peak using mammalian cells in culture. Winston *et al.*[34] measured OER using a bean root system and reported values of 2.0 at the plateau and 1.7 to 1.8 at the peak, compared to 3.0 for ^{60}Co gamma rays. These results are not totally inconsistent because the energy spread of the beam used by Winston *et al.*[34] was much larger than that used by Raju *et al.*[22,25]

PEAK RADIOBIOLOGY

Results of the biological effects at the peak position are shown in Table 3. RBE values ranging from 1.4 to 5.4 were reported by the Berkeley and CERN groups. The highest RBE value obtained at Berkeley was in ascites tumor cells. This system is highly dose-rate-dependent, and 5- to 7-day-old ascites tumor cells are known to be hypoxic. Hence, this RBE value applies to hypoxic cell populations. The high RBE of 5.2 reported by the CERN group is just beyond the peak where the dose fraction due to stars is higher than at the peak. The system also utilized bean roots which are known to give higher RBE values compared to mammalian systems. Mill *et al.*[19] presented evidence for recovery when HeLa cells were exposed at the plateau and peak but no evidence of recovery at the post-peak position. Todd *et al.*[33] also reported recovery at the peak.

Purrott[21] reported measurements for fractionated doses of pions on chromosome aberrations in human lymphocytes. He concluded that no significant enhancement at the peak is expected, compared to the plateau, for fractionated doses at dose levels commonly used in radiotherapy.

Coggle *et al.*[6] from Great Britain reported no significant difference in biological effects (normal tissues *in vivo*) between the plateau and peak and also provided evidence that the biological effects of pions are not significantly more effective than conventional radiations. The end points used were

thymic weight loss, oocyte and bone marrow cell survival, and induction of macroscopic lens opacities. These sensitive end points are probably single-event phenomena and, hence, may be insensitive to changes in LET. More radiobiology work using pions at higher dose rates must be carried out utilizing mammalian systems such as the skin and gut.

The RBE of peak pions measured in Zurich ranged from 1.5 to 2.1 in mammalian systems. Recent data obtained by Professor Fritz-Niggli and her associates (private communication) at a dose rate of 3 to 5 rads/min confirmed the data shown in Table 2. RBE values obtained at Los Alamos are also in the same range.

Considering the uncertainties in radiation dosimetry, radiation quality, and different radiobiological end points used at various centers, the results are fairly consistent. In summary, the biological effects at the plateau are nearly the same as for conventional radiations, and the RBE (~ 2) at the peak for nearly monoenergetic pions is significantly higher than at the plateau. Additional studies involving pions should be carried out at higher dose rates utilizing different peak widths and various mammalian systems relevant to radiotherapy.

The radiobiology studies at Berkeley, CERN, and NIMROD have provided an important contribution in making the expectations of potential pion application more realistic. The work at Berkeley and CERN has been discontinued, although work is still under way at NIMROD. Extensive radiobiological data are expected from Los Alamos, Vancouver, and Zurich in the near future.

RECENT DATA FROM LOS ALAMOS

Most of the work in the past was done using pion beams that produced narrow peaks and at dose rates of less than 5 rads/min. We have recently conducted

experiments using pion beams at dose rates of 10 to 20 rads/min with cells in culture. A brief review of our recent results follows.

Since the radiation quality of conventional radiations and fast neutrons does not change significantly with depth of penetration, cell-survival curves as a function of dose are commonly measured. However, the radiation quality for pions changes with energy spread in the beam and also with depth of beam penetration. Measurement of cell survival as a function of depth for a range of incident doses is very appropriate in such situations. Palcic and Skarsgard[32] proposed the use of gel to suspend cells for such measurements. Cell-survival measurements as a function of depth using human kidney cells (T_1) were made for a series of incident pion doses at the unmodulated peak and at the 5- and 10-cm modulated peaks. The depth-dose distribution of these beams is shown in Fig. 1. The procedure suggested by Palcic and Skarsgard was employed to prepare the gelatin, and the method utilized to expose cells suspended in gelatin and to plate cells was described previously by Raju *et al.*[28] Figures 2, 3, and 4 show cell-survival data as a function of depth for three pion beams of different energy spread.

Enhanced cell killing at the peak is clearly depicted for the narrow peak and even for the 5-cm wide peak. However, cell killing at the entrance and at the 10-cm wide peak tends to be nearly the same. Within the peak region for 5- and 10-cm wide peaks, cell killing is slightly enhanced with depth due to the increasing dose fractions from high LET with depth in the peak region. It is necessary, therefore, to compensate for the difference by modifying the depth-dose distribution. Such measurements are very valuable in shaping the depth-dose distributions to obtain uniform killing in the region of interest. Cell-survival curves at any depth for any one of these beams can be obtained

from these data. Figure 5 shows cell-survival curves derived from the data shown in Figs. 2 and 4 for a pion beam with narrow peak and for a pion beam at the 10-cm peak. Data for 250 kVp X-rays are also shown for comparison. The RBE values calculated at the 10% survival level at the plateau and peak for the narrow beam were approximately 1.0 and 1.9, respectively. The RBE values for the 10-cm wide peak beam at the beam entrance, peak center, and distal peak were 1.1, 1.2, and 1.4, respectively. Thus, the biological effects at the peak, compared to the entrance, are reduced with increasing width of the peak.

In another experiment, recovery of V79 cells between two fractionated exposures separated by 2 hr was measured using a narrow peak pion beam and X-rays. Exponentially growing cells plated in a Falcon flask (25 cm^2) were exposed to pions and X-rays. Cells in the central 2-cm region in the flask where the dose was nearly uniform were trypsinized and plated for colony formation, and the results are shown in Fig. 6. The RBE calculated at 10% cell survival for single doses was only about 1.4, which is much less than the value obtained in gel experiments using T_1 cells. In the gel experiments, cells were in a 0.75-cm diameter tube and were exposed, therefore, well within the 90% dose contour. In the V79 cell experiment, cells were in a 2-cm diameter tube and were exposed, therefore, to within the 90 to 70% dose contour. This discrepancy points out clearly the problems in dosimetry where the target area is relatively large and where the highest dose rate possible is obtained by focusing the beam. These results indicate a significant recovery for pion exposures at the peak and is not unexpected, since nearly 70% of the peak dose is at low LET.

No experimental data have been available in the past regarding variation in radiation sensitivity as a function of cell cycle. Preliminary results

obtained recently at Los Alamos using CHO cells for peak and plateau pions (for the narrow peak) and for X-rays are shown in Fig. 7.

CHO cells synchronized at the G_1/S boundary were obtained by using mitotic selection and hydroxyurea techniques described previously.[29] Falcon flasks containing the cells were exposed to a fixed dose at different times after release from hydroxyurea. Cells in the central portion of the flask (2-cm diameter) were trypsinized after exposure and plated for colony formation. The magnitude of variation for X-rays was smaller than previously obtained. Cell progression on that particular day of the experiment was slower than usual; therefore, cell synchrony was probably not as good as before. However, variations in radiosensitivity for X-rays as a function of cell cycle were consistent with those reported in the literature. No differences in the position of the radioresistant peaks were observed compared to X-rays, and variation was slightly less at the plateau compared to X-rays and was further reduced at the peak.

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Table 1. Pion radiobiology

Location of Facility	Dose rate (rads/min)
Berkeley, California	~1
CERN, Switzerland	~0.05
England	~0.5 - 2.5
Zurich, Switzerland	~1 - 4
Vancouver, British Columbia	~2
Los Alamos, New Mexico	~5 - 20
Stanford, California	~0.5 - 1.5

Table 2. Negative pion plateau radiobiology

Biological system	Reference radiation and dose rate	π^- Dose rate	RBE	OER	Reference
Berkeley					
Polyploidy induction in ascites tumor cells (5 to 7 days old)	^{60}Co; 5, 12.5, 20 r/hr	5 r/hr	1	-	16
England					
Vicia faba 10 days growth (3.5°)	radium gamma rays; 32 r/hr	~15 r/hr	1.3	2	34
Frozen HeLa cells	300 kVp X-rays; 100 r/day, 100 r/min	10-65 r/hr	1	-	20
HeLa cells	^{60}Co gamma rays; 55, 195 r/hr	100-150 r/hr	1.5	-	18
Chromosome aberrations in human lymphocytes	^{60}Co; 18 r/hr 50 r/min	18-70 r/hr	1.5 1.2-1.3	-	15
Thymic weight loss, oocyte survival, bone marrow survival, lens opacities	^{60}Co, 220 kVp X-rays, 14 MeV X rays, 14 MeV electrons; various dose rates: 12.5 r/hr to 400 r/sec	100 r/hr	~1	-	6
Zurich					
Chinese hamster cells (V79)	^{60}Co, 360 rads/min	2.5 rads/min	1.1	-	7
Los Alamos					
Immunocompetent spleen cells	^{60}Co, 5 rads/min	~2 rads/min	1.8	-	5

Table 3. Negative pion peak radiobiology results

Biological system	Reference radiation and dose rate	π^- Dose rate	RBE	OER	Reference
Berkeley					
Abnormal anaphases in *Vicia faba* root meristems	plateau π^-	5 r/hr	2.2-2.6	-	30
Chromatid aberrations in *Vicia faba*	plateau π^-	30 r/hr	3.8	1.8	12
Vicia faba 10-day growth at room temperature and 4°C	^{60}Co, 90 r/hr	30 r/hr	~3	1.35-1.5	22
Arginine reversions in yeast	^{60}Co, 40 r/hr, 40 r/min	30-60 r/hr	1.4	1.9	23
Proliferative capacity of ascites tumor cells (5 to 7 days old)	^{60}Co, 5, 12.5 r/hr	5 r/hr	5.4±1.8	-	8
Polyploidy induction in ascites tumor cells (5 to 7 days)	^{60}Co, 5, 12.5, 20 r/hr	5 r/hr	2.5	-	16
Proliferative capacity of ascites tumor cells (2 days old)	^{60}Co, 150 r/hr 45 r/min	30 r/hr	5.4±0.6 2.9±0.5	-	9
Human kidney cells (frozen)	^{60}Co, 1-40 r/min	30 r/hr	1.6	-	4
Human kidney cells (room temperature)	^{60}Co, 240 r/hr	~30 r/hr	2.2-2.4	1.5	25
Human lymphocytes	^{60}Co, 65 r/hr, 60 r/min	~60 r/hr	2.0	-	17

Table 3 (continued)

Biological system	Reference radiation and dose rate	π^- Dose rate	RBE	OER	Reference
CERN					
Spermatogonia	gamma rays, X-rays	4 r/hr	3.7	-	2
Vicia faba 10-day growth (4°C)	^{60}Co, 15 r/hr	3 r/hr	2.5-5.2	-	3
England					
Vicia faba 10-day growth	Radium gamma, 32 r/hr	20-25 r/hr	2.5	1.7-1.8	34
Frozen HeLa cells	300 kVp X-rays; 100 r/day, 100 r/min	10-65 r/hr	1.86	-	20
Chromosome aberrations in human lymphocytes	^{60}Co, 184 r/hr 50 r/min	18-70 r/hr	2.1-2.3 1.4-1.5	-	15
HeLa cells	^{60}Co, 55, 195 r/hr plateau	40-150 r/hr	2.1 1.4	-	18
Thymic weight loss, oocyte survival, bone marrow survival, lens opacities	^{60}Co, 220 kVp X-rays, 14 MeV X-rays, 14 MeV electrons Various dose rates: 12.5 r/hr-400 r/sec	150 r/hr	~1.0	-	6
Los Alamos					
Human kidney cells	250 kVp X-rays, 200 r/min	5 r/min	2.6 (compared with plateau)	1.5	28
Human kidney cells	250 kVp X-rays, 23, 200 r/min	5 r/min	1.4-1.5	-	33
C_3H mouse mammary tumor	250 kVp X-rays, 300 r/min	5 r/min	1.7±0.2	-	13
Human skin reaction	140 kVp X-rays, 500 r/min	5 r/min	1.5	-	14
Immunocompetent spleen cells	^{60}Co, 5 rads/min	5 r/min	2.2	-	5

Table 3 (continued)

Biological system	Reference radiation and dose rate	π^- Dose rate	RBE	OER	Reference
Zurich					
Mouse embryos	200 kVp X-rays, 1-2 rads/min	1-2 rads/min	2.1	-	11
Chromatid aberrations	200 kVp X-rays, 1-2 rads/min plateau, ~0.75 rad/min	1-2 rads/min	~1.0 1.7	-	11
Inhibition of mitotic activity in mouse small intestine	plateau, ~0.75 rad/min	1-2 rads/min	1.5	-	11
Mutation induction in male germ cells (Drosophila)	200 kVp X-rays, 1-2 rads/min	1-2 rads/min	0.4-1.8	-	11
V79 monolayers	^{60}Co, 360 rads/min	4 rads/min	1.8	-	7
V79 spheroids	^{60}Co, 360 rads/min	4 rads/min	1.5	-	7

Fig. 1. Depth-dose distribution of negative pions. The 5- and 10-cm wide peaks were obtained by using a dynamic range shifter.

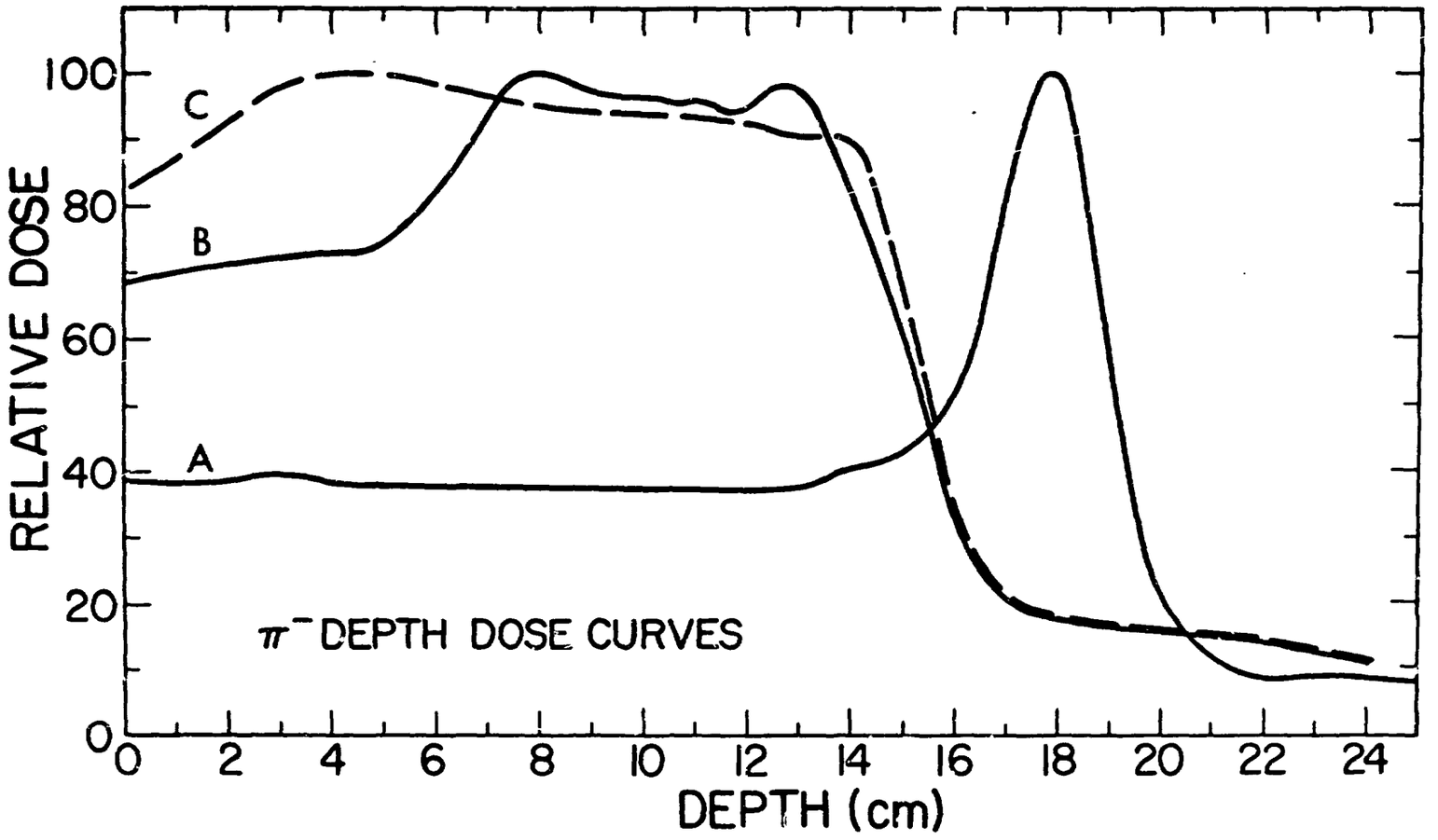

RELATIVE DOSE
100
80
60
40
20
0
C
B
A
π^- DEPTH DOSE CURVES
0
2
4
6
8
10
12
14
16
18
20
22
24
DEPTH (cm)

Fig. 2. Per cent cell survival (human kidney) vs depth to various negative pion doses at the peak position for a pion beam (narrow peak).

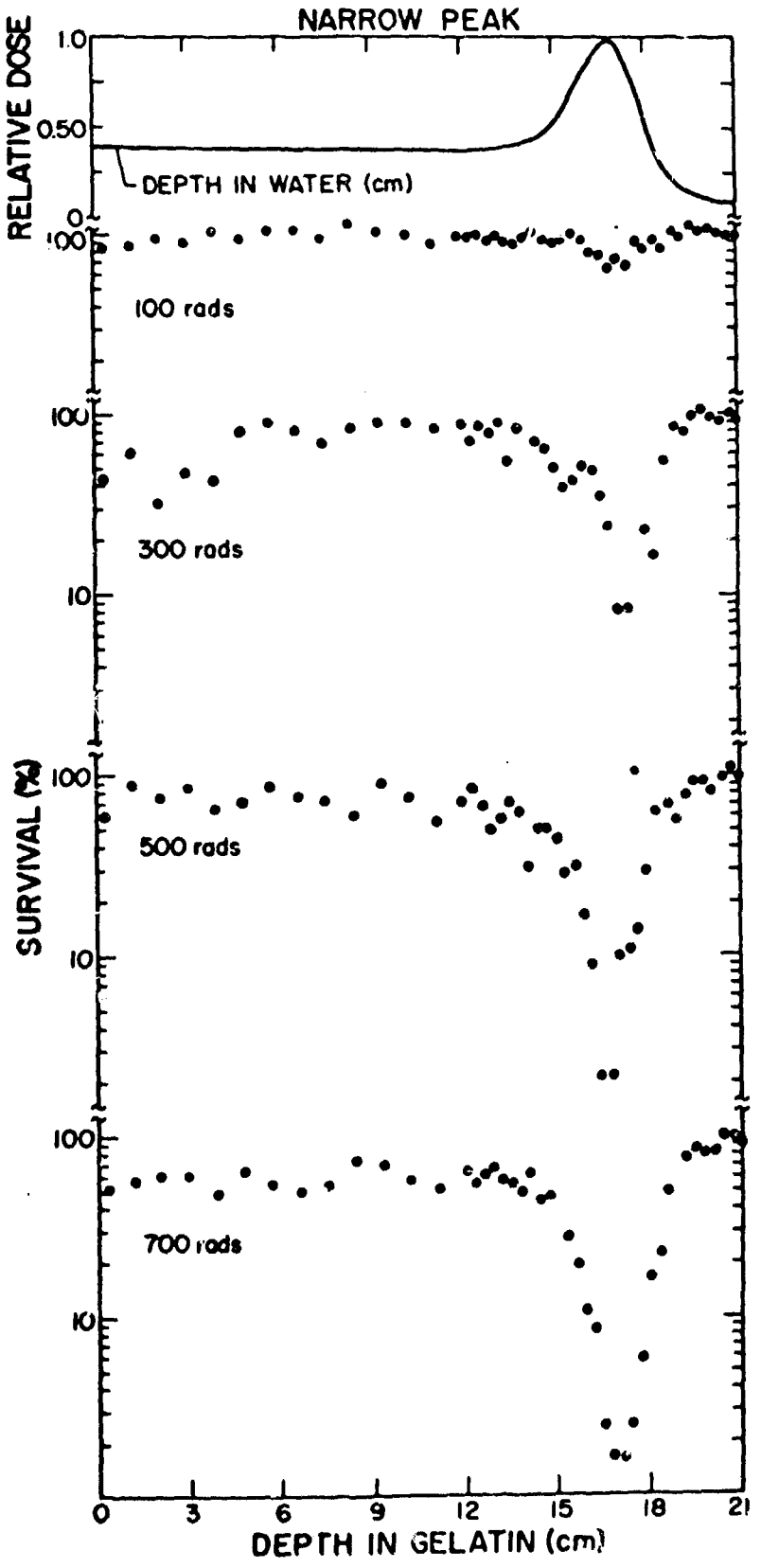

NARROW PEAK
RELATIVE DOSE
1.0
0.50
0
DEPTH IN WATER (cm)
100 rads
300 rads
500 rads
700 rads
SURVIVAL (%)
100
10
100
10
0
3
6
9
12
15
18
21
DEPTH IN GELATIN (cm)

Fig. 3. Per cent cell survival (human kidney) vs depth to various negative pion doses at the peak position for a 5-cm wide peak.

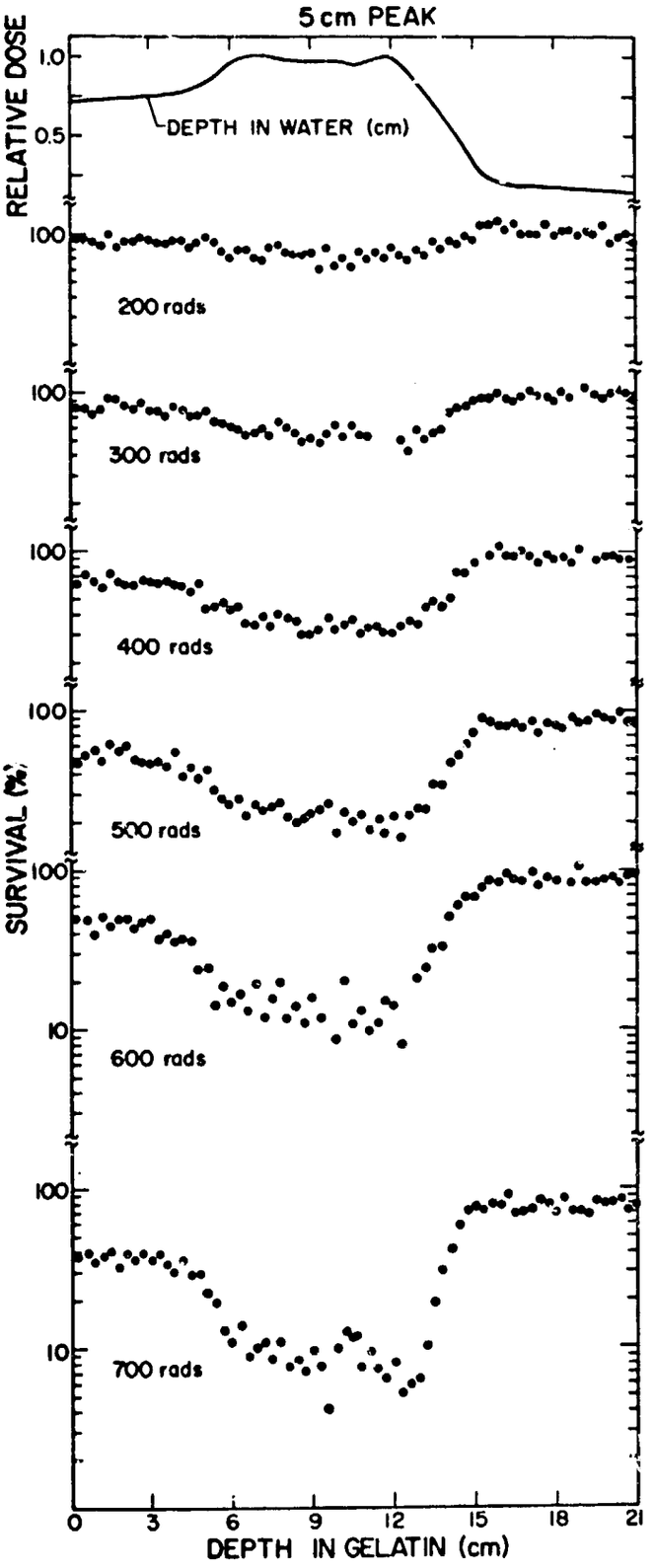

5 cm PEAK
RELATIVE DOSE
1.0
0.5
DEPTH IN WATER (cm)
100
200 rads
100
300 rads
100
400 rads
100
500 rads
100
10
600 rads
100
10
700 rads
SURVIVAL (%)
0
3
6
9
12
15
18
21
DEPTH IN GELATIN (cm)

Fig. 4. Per cent cell survival (human kidney) vs depth to various negative pion doses at the peak position for a 10-cm wide peak.

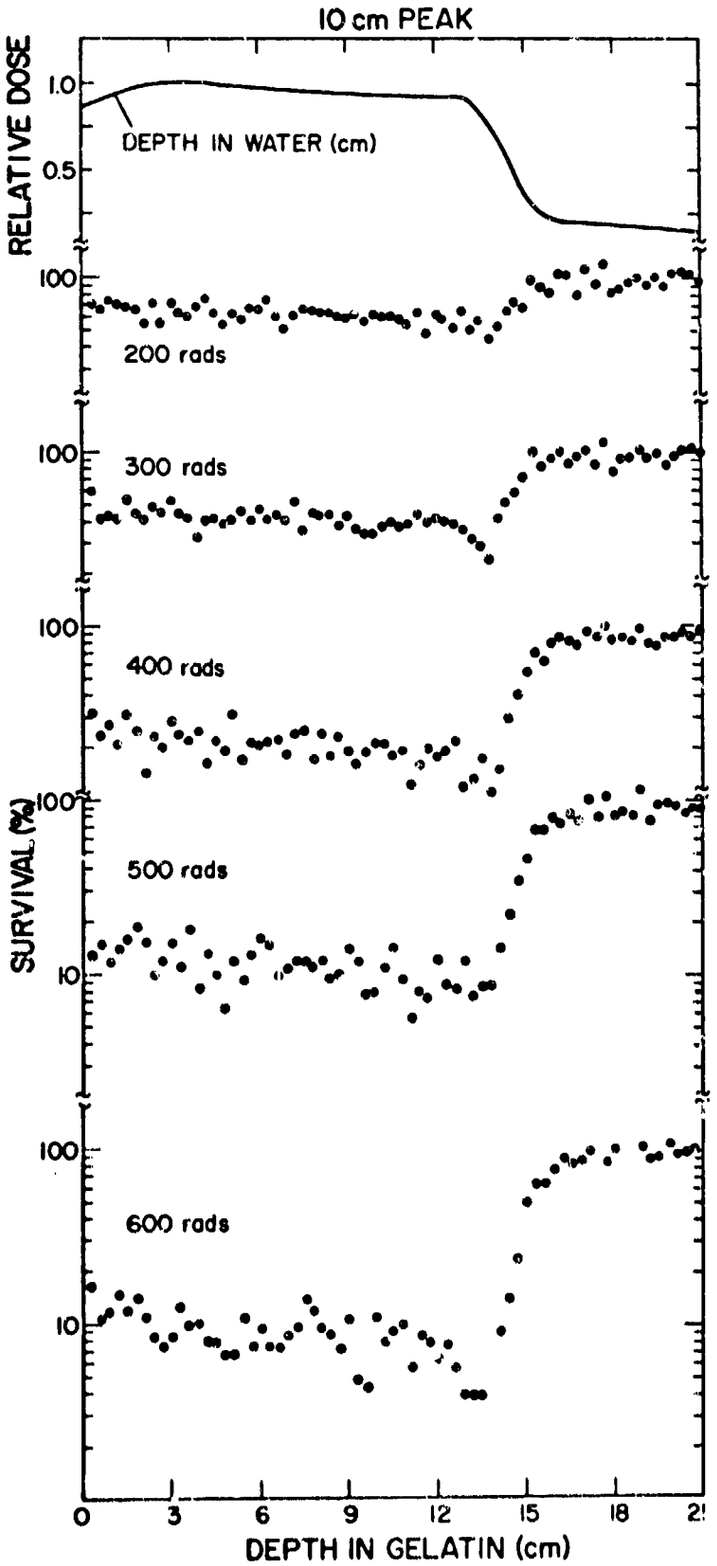

10 cm PEAK
RELATIVE DOSE
1.0
0.5
DEPTH IN WATER (cm)
100
200 rads
100
300 rads
100
400 rads
100
500 rads
10
100
600 rads
10
SURVIVAL (%)
0
3
6
9
12
15
18
21
DEPTH IN GELATIN (cm)

Fig. 5. Per cent cell survival vs dose at the plateau and peak for a narrow peak beam, at the plateau and at the peak center, and peak distal for a 10-cm wide peak. These data were obtained from the data shown in Figs. 2 and 4.

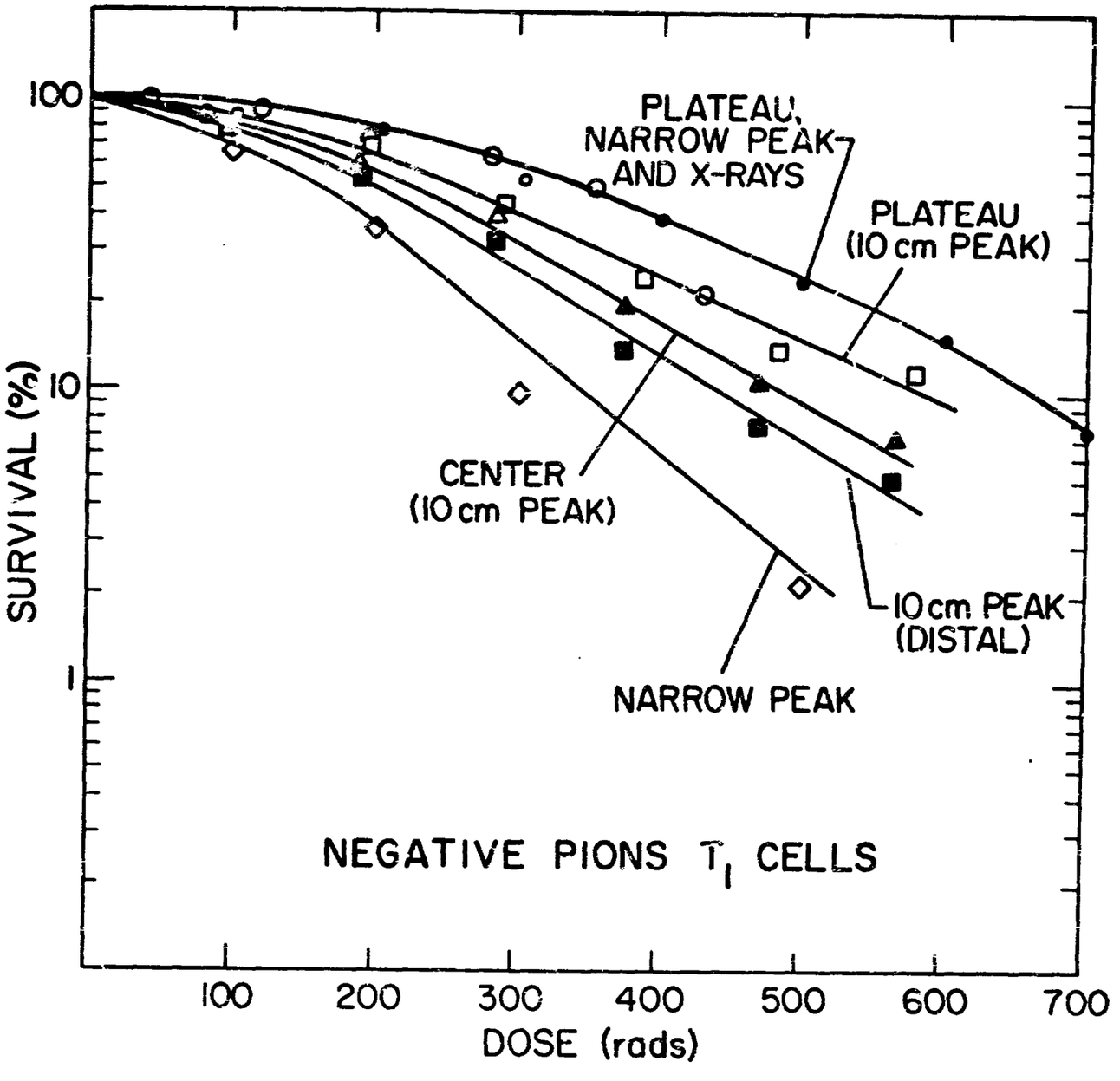

100
10
1
SURVIVAL (%)
PLATEAU, NARROW PEAK AND X-RAYS
PLATEAU (10 cm PEAK)
CENTER (10 cm PEAK)
10 cm PEAK (DISTAL)
NARROW PEAK
NEGATIVE PIONS T1 CELLS
100
200
300
400
500
600
700
DOSE (rads)

Fig. 6. Per cent cell survival (V79) vs dose for single and two fractionated exposures at the pion peak (narrow) and for X-rays.

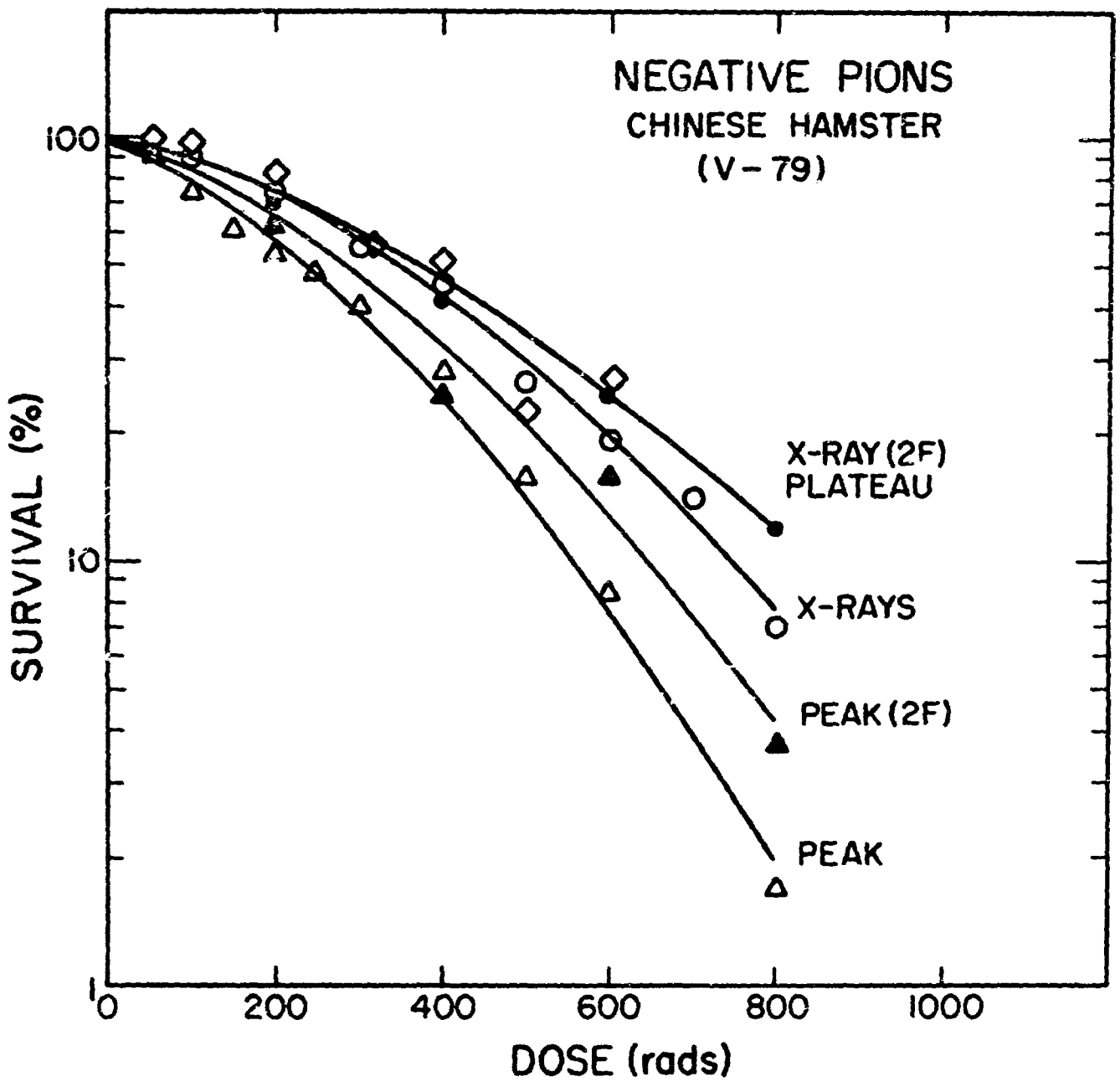
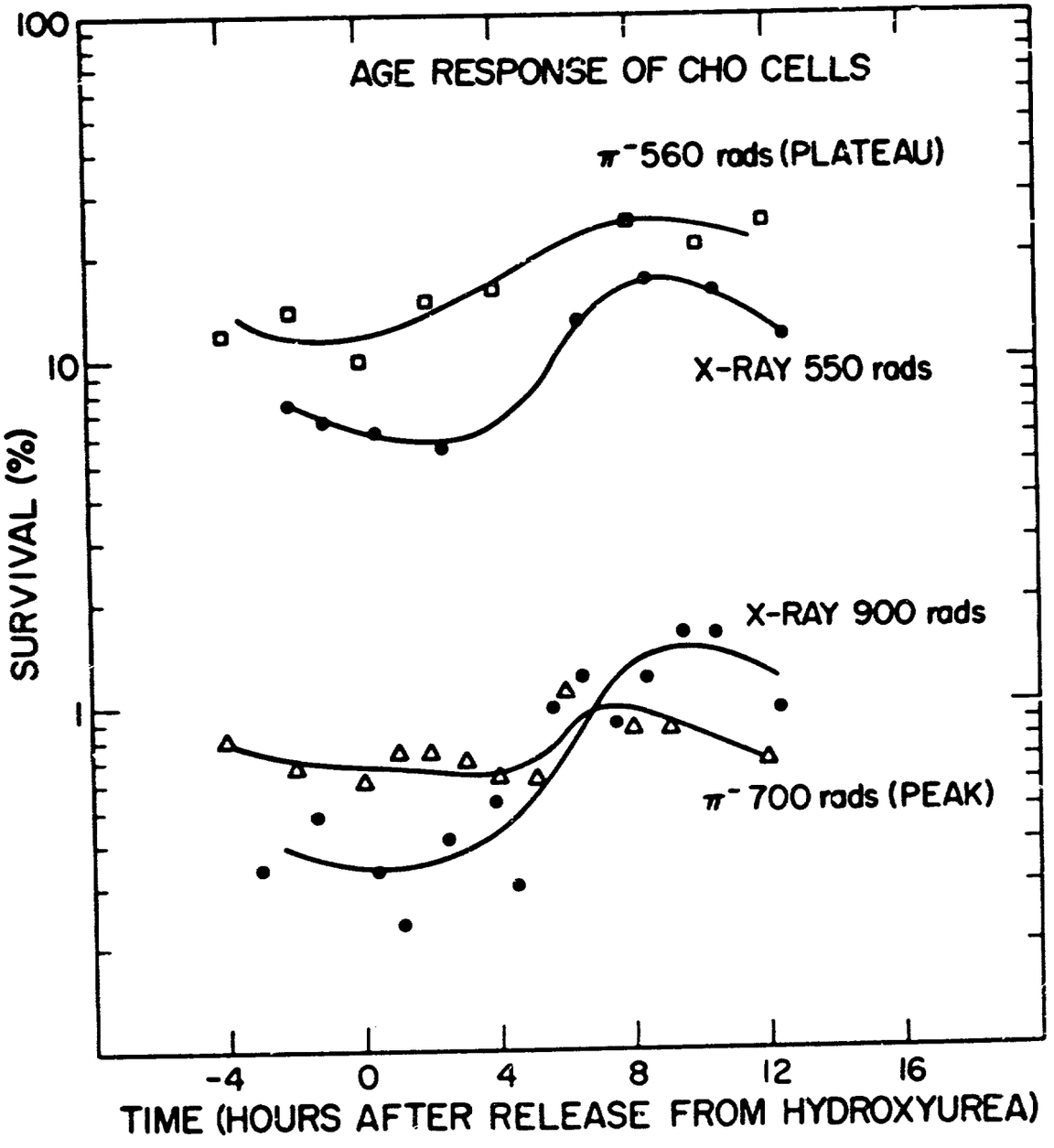

NEGATIVE PIONS
CHINESE HAMSTER
(V-79)
100
10
1
SURVIVAL (%)
X-RAY (2F)
PLATEAU
X-RAYS
PEAK (2F)
PEAK
0
200
400
600
800
1000
DOSE (rads)

Fig. 7. Per cent cell survival vs time after release from hydroxyurea for peak pions (narrow peak) at 700 rads, plateau, plateau pions at 560 rads, and for X-rays at 550 and 900 rads.


AGE RESPONSE OF CHO CELLS
π⁻560 rads (PLATEAU)
X-RAY 550 rads
X-RAY 900 rads
π⁻ 700 rads (PEAK)
100
10
1
SURVIVAL (%)
-4
0
4
8
12
16
TIME (HOURS AFTER RELEASE FROM HYDROXYUREA)