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A. INTRODUCTION

The question of whether concentrated deposition of radiation dose in a limited volume is more or less damaging than diffuse delivery of the same quantity of energy has troubled health physicists for many years. It has recently assumed new prominence with the potential risk of exposure of large populations to PuO_2 aerosols from prospective nuclear power generation with breeder reactors. The problem is complex, and theoretical calculations based on microdosimetry and assumed single-cell response are of little help since this response is subject to all the factors of biological regulation, control, repair, and other cooperative reactions characteristic of tissue. The primary appeal must be to experimental data at this stage until the limiting mechanisms and interactions are identified. However, because of the peculiar requirements of health protection, specifically the application of the data to human exposures of long duration and the desire to limit the probability of damage to extremely low values, extrapolation of experimental results cannot be avoided. Extrapolation must be made from animal to man, from short to long times of exposure and induction, and from measurable to indetectable probabilities. Such extrapolations will be convincing in proportion to their basis on mechanistic detail. Therefore, it is important that experiments correspond as closely as possible to the actual situation to which they will be applied

and that at the same time enough independently controlled variables be available to test various hypotheses and to identify the controlling factors.

The hot particle studies in hamsters at the Los Alamos Scientific Laboratory (LASL) are simulation experiments to the extent that the target organ (the lung) and the radioactive sources replicate the exposure to inhalation of PuO_2 aerosols to some extent. However, to facilitate the analysis of the factors operating, certain unreal constraints have been introduced. A primary objective is determination of the minimal conditions of exposure leading to tumor induction, especially in terms of number and distribution of irradiation foci and of volume and distribution of tissue at risk. Thus, animals are exposed by jugular injection to a precise number of uniform microspheres which are retained quantitatively and permanently in the capillary bed of the lung. The exposure is thereby limited strictly to the lung itself, no other organ receiving a significant radiation dose, and the dosimetric parameters can be varied in a controlled manner. Because of the limited space available here, experimental methods will be presented only in outline. For details of procedures and numerical confirmations, the reader is referred to our annual reports (RICHMOND and VOELZ, 1972; RICHMOND and VOELZ, 1973; RICHMOND and SULLIVAN, 1974).

B. EXPERIMENTAL DESIGN

The experimental animal chosen was the Syrian (golden) hamster. The choice was primarily on the basis of the popularity of this animal in many types of cancer experiments, both chemical- and radiation-induced, which provide a large body of experimental data for comparison and interpretation of results as well as its freedom from primary lung disease. The route of exposure is unusual in that large (10-μm) microspheres are injected into the jugular

vein (HOLLAND et al., 1971) and are trapped in the capillary bed of the lung. Since the range of the alpha particle in the lung permits the traversal of several alveoli, the location of the source on the blood side of the membrane is not physically important. The immobility results in significant differences from inhaled aerosols; the local radiation fields are higher in intensity and more circumscribed in volume than for mobile particles of the same activity. However, by varying particle number and specific activity, the dose distribution can be manipulated to study the effects of this parameter.

The microspheres used are an inert, insoluble, high-fired ceramic of ZrO_2 to which PuO_2 has been added at concentrations chosen to simulate the radioactivity of respirable particles. They were prepared by generating (with a vibrating jet) uniform droplets of a ZrO_2/PuO_2 sol which where then gelled by dehydration and fired at 1000°C (FULWYLER, PERRINGS, and CRAM, 1973). Extensive studies were made of the physical properties of the spheres, including diameter, mass, density, and radioactivity. Their uniformity is indicated by the coefficients of variation within a given batch for volume (better than 4%) and for plutonium activity (about 2.6%). The emergent alpha spectra showed the plutonium to be somewhat depleted toward the center of the microspheres by 20-40% relative to the outer portions. Since the spheres are not large compared with the alpha range, energy degradation is not serious, the average energy loss being only about 1 MeV.

The range of plutonium activity covered in the microspheres is 0.01 to 59 pCi/sphere in 12 levels in an approximately geometric series. These activities correspond to pure PuO_2 particles in the diameter range of 0.06-0.9 μm for $^{238}PuO_2$ and 0.4-5.6 μm for $^{239}PuO_2$, thus spanning the range of respirable sizes. The actual chemical concentration of PuO_2 in ZrO_2 ranged from 0.04-1.1% by weight.

To facilitate measurement of the injected and retained dose, a low-level tag of ^{57}Co has been added to all batches of spheres. The only significant radiations from this nuclide are the gamma rays (122 and 136 keV). At a specific activity of 60 gammas/hr/sphere and a 3% absorption in the hamster, the calculated whole-body radiation dose is about 1.3 mR/yr or 1% of natural background, which is completely negligible in this experiment.

The first experiments were begun in early 1971 using 60 hamsters in each exposure group and 2000 spheres/animal at eight exposure levels. Microsphere activity ranged from 0.07 to 59 pCi and total lung burden from 0.14 to 119 nCi. About 1% of the total lung volume was within the radiation fields, and the fields were far enough apart that there was no overlap. The median alpha dose to the population of cells at risk was calculated to range from 0.8 to 650 k-rad/yr, while the "averaged dose" from the deposition of total energy in one gram of lung ranged from 13 to 12 000 rad/yr.

The possible tumor incidence from "hot particles" has been calculated by DEAN and LANGHAM (1969) and by GEESAMAN (1968) on the assumption that the rat skin tumor response curve observed by ALBERT, BURNS, and HEIMBACH (1967) could be applied to the individual cells of the lung. Such models, when used with the distribution of dose over the cell population at risk in this experiment, predict tumor incidence per group ranging from 2 at the lowest activity group to a maximum of 60 in the middle group and then declining to 0 for the highest. The total number of tumors predicted for the 480 hamsters is 162. As we shall show, this prediction is not confirmed by these experiments.

Additional experiments using larger numbers of microspheres have since been initiated. By the spring of 1974, a total of 1900 hamsters have been exposed to 160 000 000 microspheres in various combinations of sphere activity and number to produce lung burdens in the range of 0.1 to 1000 nCi, with

particular emphasis on the 10-100 nCi range. LITTLE, GROSSMAN, and O'TOOLE (1968, 1973) have shown a very high tumor incidence in hamsters whose lungs were instilled with ^{210}Po solutions in this range of activity. (We have recently begun experiments duplicating LITTLE's polonium studies with our hamsters, but no results are yet available.)

Other experiments are in progress using microspheres loaded with ^{147}Pm to provide exposures to the entire lung with low LET radiation from the 225-keV beta rays. In addition, 115 rats have been exposed by the intravenous injection of 6000 plutonium-loaded microspheres per animal (4 pCi/sphere) to give lung burdens of 25 nCi and to provide evidence from another species.

C. RESULTS

I. Distribution of Microspheres in the Lung

Measurements of distribution were made on hamsters which had received approximately 20 000 spheres of 4.3 pCi activity 4 weeks before sacrifice. Gamma counting of the specimens afforded a quick method of sphere counting using the ^{57}Co tag. The lungs were inflated with formalin and fixed for 24 hr before analysis. The distribution of spheres between the divisions of the lungs is summarized in Table 1. The variability is not unexpected in view of the differences in blood supply. The range of concentrations (through a factor of 2) should not affect the interpretation of results, since the actual sphere content of a given lobe can be determined by gamma counting. Table 1

Following the above experiment, the left lung was minced by successive subdivision in halves. All pieces were measured at each level of division; an average and a coefficient of variation (CV) were calculated, and the results are given in Table 2. The constancy of the average concentration indicates the reliability of the measurements, and the CV indicates the degree Table 2

of nonuniformity which increases with increasing subdivision but which appears to level out at about 30-40%.

To carry the study to the ultimate level, another lung was cut into 23-μm thick sections, which were scored visually for number of spheres. An examination of 16 sections showed 267 spheres. The CV among sections was 36%, of which 24% was expected from random statistics, leaving 26% for intrinsic variability. This is in good agreement with the larger dissection.

As a final test of the small-scale randomness of the distribution, the distances r between nearest-neighbor spheres in each section were measured with an optical micrometer. For a random distribution, the probability P(r) that the nearest-neighbor to a given sphere lies at a distance r in a section of thickness δ with bulk sphere concentration C is given as (UNDERWOOD, 1970):

$$P(r) = 2\pi\delta C r \exp(-\pi\delta C r^2) \qquad \text{(Eq. 1)}$$

From this equation we can calculate Δ_2, the mean value of r, to be

$$\Delta_2 = \Gamma(1.50)/\sqrt{\pi\delta C} = 1/2\sqrt{\delta C} \qquad \text{(Eq. 2)}$$

(where Γ signifies the gamma function), and the variance (mean square deviation) of r with respect to Δ_2 is:

$$\text{Var} = \frac{1 - \Gamma^2(1.5)}{\pi\delta C} = \frac{1 - \pi/4}{\pi\delta C} \qquad \text{(Eq. 3)}$$

The distances observed between nearest-neighbors in three dimensions are, of course, different from those in a section. The mean in three dimensions, Δ_3, is given by:

$$\Delta_3 = \Gamma(1.33)/\sqrt[3]{4/3\ \pi C} \qquad \text{(Eq. 4)}$$

The results of measurements of 114 nearest-neighbor distances in the 23-μm sections are shown in Fig. 1 as a histogram compared with the smooth curve given by Eq. 1. While there is a possible suggestion of structure, the general agreement is good. Statistically, the peak at 0-0.1 mm has an excess area above prediction of 2.5 times its standard deviation (SD), and the excess area between 1.4 and 1.8 mm is 2.2 times the SD. It is, of course, possible that geometric structure in the capillary bed could produce real effects of this sort. The variance of the data is 0.177 compared with 0.152 calculated from Eq. 3. It is concluded that at this level the distribution of spheres within the left lung is essentially random and that there is no large degree of clumping or association.

The measured Δ_2 was 768 μm in the sections. A contraction to 61% of original volume was measured for a similar left lung from fixation through paraffin embedding. The measured concentration of 11.6 spheres/mg in the fixed lung, therefore, corresponds to 19.2 spheres/mm^3 in the sections. From this a Δ_2 of 750 μm is calculated using Eq. 2 -- in excellent agreement with the 768 μm observed. The measured linear shrinkage from fresh lung to paraffin-embedded was to 0.72 of original dimensions; therefore, Δ_2 in fresh lung is 1067 μm. Using the ratio of Δ_3/Δ_2 given by Eq. 4, the mean three-dimensional nearest-neighbor distance in fresh lung is calculated to be 244 μm for 24 000 spheres and 559 μm for 2000 spheres.

II. Retention and Excretion

Several methods have been used to determine retention of the microspheres in the animals. The most sensitive for short time scales is the direct measurement of plutonium in the excreta. Results indicate an average rate of 0.032

± 0.006% per day for the first three days and 0.000 ± 0.005% per day during the remainder of the first week (see Table 3). These measurements were made with microspheres of Level 6, the highest specific activity. Total excretion over the first week measured 0.096%, corresponding to a half-time of 7000 days.

Table 3

A summary of whole-body retention measurements is given in Fig. 2 (all curves are based on in vivo measurement of the 120-keV gamma ray from a ^{57}Co tag of the microspheres). The upper curve is for a group of animals (initially eight) which received intravenous injection of 2000 microspheres of 60 pCi ^{238}Pu/sphere. Data extend to 500 days, at which time only three animals survive. The results give a biological half-time of the order of 7000 days, corresponding to an excretion rate of 0.01% per day after the initial drop of 5% (which may be due to leaching of ^{57}Co from the surface of the spheres, since direct measurement of plutonium in the excreta did not indicate so large an initial loss).

Fig. 2

The middle curve is a similar experiment in which six animals were injected with 300 000 spheres of 0.4 pCi ^{239}Pu/sphere. The slope corresponds to about 0.02% per day or a half-time of some 3500 days. The initial drop is not well documented, and there is a possibility of a calibration shift during the first month. It is also possible that, due to the much larger number of spheres injected, some 20% may really have escaped the lung. The constant excretion rates observed in these experiments indicate that the lungs are sustaining no damage which would cause increased loss of microspheres. The bottom curve is for intratracheal instillation of 500 000 spheres tagged with ^{57}Co but without any plutonium. Twenty-four animals were initially used; six remain (some were sacrificed). The half-time of the curve is 244 days, with no evidence of change with time.

Examination of lung sections shows that the intratracheal spheres, which were driven into the lung by pulsed saline-jet injection, are found in the alveolar spaces often in association with macrophages. Therefore, the observed clearance time is apparently that associated with the deep lung and is in agreement with the range of half-times reported for plutonium and uranium oxides in rats (135-289 days), as summarized by the TASK GROUP ON LUNG DYNAMICS (1966).

The data on retention of the intravenous spheres show that 90-95% of the initially retained dose is still in the body after almost 500 days, and measurements of body organs show no significant activity anywhere other than in the lung. Because of the measured rapid clearance from the alveoli, it would thus seem that the intravenous spheres must remain within the capillary bed of the lung. However, significant numbers appear in histological sections to be outside the capillary bed and associated with macrophages. The former criterion is not always rigorous because the extremely thin alveolar-capillary wall could be difficult to detect, but the latter suggests an alveolar location. If this is true, one must explain the failure to clear the lung as observed with the intratracheal spheres. Since the latter contained no plutonium, it may be that an alpha activity high enough to cause capillary wall breakage is also high enough to destroy macrophages attempting to transport spheres to the ciliary escalator. Movement of the spheres which have escaped the capillary bed could be limited to the dimensions of a small number of alveoli.

Another possibility of sphere movement which cannot be directly disproved is slow migration through the capillary bed. The retention data indicate that the spheres never escape into the post-capillary veinules; therefore, this movement would be limited by the diameter of the capillary network units, estimated by WEIBEL (1963) as 300-500 µm. A drift over distances of a few

undred microns at velocities of the order of 1 μm/day, therefore, is not inconsistent with the retention data. Since the mean range of an alpha particle in the lung of density 0.2 is 200 μm, the cumulation of dose to most of the cells at risk would be limited to a period of several months, and the number of such cells would be increased by a factor of several.

The principal effect of both motion within a few alveoli and movement through the capillary bed would be to eliminate the extremely high end of the cell dose distribution function, which is of little biological significance in that the comparatively few cells involved are certainly subjected to extreme overkill and sterilization. The majority of the cells at risk lie in the outer portions of the alpha range and would not be markedly affected by sphere migration of this sort.

III. Survival

The fraction of animals surviving as a function of time is useful as an indicator of the health of the population and as a nonspecific signal of possible radiation damage. The hamsters used in our experiments generally show mean survival time (MST) of about 700 days, indicating an unusual longevity. Typical curves for cumulative deaths as a function of time after injection (at age 100 days) are given in Fig. 3 for the original experimental groups receiving 000 spheres each with lung burdens of 0.1 to 120 nCi. The numbers at the beginning of each curve identify the plutonium level in the spheres. The line labeled "C" is for a control group receiving no spheres, and the line labeled 0" is for a group receiving nonradioactive spheres. Only the four extremes of the exposed groups are drawn for comparison. There seems to be no significant correlation of MST nor of pattern of deaths with the activity of the particles.

Fig. 3

The shortest survival time is shown by Level 5, while the highest dose level (curve 6) is indistinguishable from the controls. The longest survivals are shown by Levels 2 and 3. The remaining dose levels fall within the range of those plotted. The data suggest that MST values vary by some ± 100 days under the conditions of our experiments; this large span is due, in part, to the small group sizes (60 animals). In many cases, MST curves are obtained which appear to be bimodal with a high death rate at around 200 days which later declines. No specific pathology has been associated with these early deaths.

IV. Pathological Results

The response elicited by the presence of the microspheres in the lung and the relationship of that response to carcinogenesis are the end points of primary interest in this research. The most striking feature of the results so far is the unobtrusive nature and limited extent of the observed tissue reactions.

The negative results of the survival time studies were reported above. Blood studies, including white cell counts, absolute lymphocyte counts, serum protein, and serum alkaline phosphatase, have been equally negative. Many studies in which radioactive materials have been administered by inhalation have resulted in early and prolonged lymphopenia. In these cases, there has usually been an accumulation of radioactive material in the regional lymph nodes as well as in the lung proper. In our studies, no activity has been found outside the lung parenchyma, and the lymphopoietic organs have not been irradiated. Since 50% of the radiation energy is absorbed by the circulating blood, the dose rate to that tissue is estimated to range from 1 to 900 rad/yr in the 2000-sphere exposures. However, the hematopoietic system is not irradiated, and if any circulating blood elements are damaged, they appear to be adequately

replaced from the unaffected stem-cell populations.

Turning to the lung itself, at the histological level the microspheres are found trapped in the interalveolar septa in both peripheral and central locations as well as in the other portions of the capillary bed. Because of the extreme thinness of the alveolar-capillary tissue layer, it is not always possible to demonstrate the continuity of the enclosure of the microsphere, but this can usually be inferred from the local morphology. Spheres have also been observed near respiratory bronchioles so that some portion of the bronchiolar epithelium is well within range of the alpha particles.

The microspheres themselves are chemically inert and do not appear to evoke any foreign body reactions as long as they remain within the capillaries. When microspheres of any radioactivity level are found (as they occasionally are) extruded into an alveolar space, there is an associated mild foreign body response with hemosidrin-bearing macrophage accumulation and occasional granuloma formation. The higher activity microspheres seem to be associated with macrophages containing more hemosidrin pigment. In the early experiments, macrophage accumulations were seen after about 30 days of exposure to Level 6 microspheres (59 pCi/sphere). There seemed to be a progression of response with time, and by four months post-injection, occasional micro-granulomas were seen usually clearly associated with a microsphere. In Level 5 spheres (13 pCi/sphere), a similar response was observed at a later time.

Near the end of the normal life span (15-20 months post-exposure), additional histological changes have been observed in some animals exposed at the three highest levels to relatively small numbers of spheres (2000-6000). An extension of bronchiolar epithelium into alveolar ducts has occurred, and alveoli become lined with cuboidal or columnar epithelial cells. A similar phenomenon has been noted with animals exposed to 60 000 spheres of 0.9 pCi

per sphere for only 6 months. These changes could be considered as precursors of peripheral adenomas.

In the experiments with comparatively small numbers of spheres (a few percent of the lung irradiated) of lower specific activity, no gross involvement of the lung results, but close inspection does reveal evidence of dead and dying cells in the midst of seemingly undamaged parenchyma which retains its delicate architecture. Even here one can note that a superficially normal alveolar wall near a sphere, on closer examination, may prove to be ischemic and acellular.

With the highest numbers of spheres (100 000-1 000 000), preliminary observations do show more extensive damage similar to a radiation pneumonitis. Sphere deposition is often nonuniform, and some regions of the lung show a thousand or more spheres in a low power field of a 6-μm tissue section, while other similar areas contain only 10 spheres/field. Those areas with large numbers of spheres reveal epithelization of alveoli, greatly thickened alveolar walls, and incipient fibrosis. The capillaries are devoid of red cells and are often surrounded by edematous connective tissue. While the specific activity of the spheres involved is low (0.02-0.07 pCi), the large number and tendency to cluster cause moderately high local radiation doses (tens of krad/yr) to extend over comparatively large volumes of tissue. Mechanical impairment of the blood supply to these areas by the large numbers of occluding spheres cannot be overlooked as a contributing factor to the fibrotic reaction.

Thus far, only three animals (out of some 1900 total exposed) have died of neoplastic disease originating in the lung. Two of these were from the original experimental group (and from the same dose level of 0.4 pCi/sphere, 2000 spheres/animal). The other lung tumor was from a later group (59 pCi

per sphere, 6000 spheres/animal). Of the two pulmonary tumors in the original group, one was a hemangiosarcoma found 9.5 months after injection. This tumor replaced almost entirely the left lung and severely compressed the adjacent normal lung tissue. There was no evidence of metastases to the rest of the lung or to any other organ. The other tumor from this group was an undifferentiated sarcoma found after one year exposure. In this case, there were multiple nodules in both lungs. No microspheres were found within the tumor tissue in either case, but they were observed in the adjacent normal lung. A mucinous adenocarcinoma of the lung was found in a hamster after two years of exposure to 6000 microspheres of the highest specific activity level. This tumor involved one lobe of the right lung and was locally invasive. Microspheres were observed in adjacent normal lung, showing little if any biological response. Several adrenal carcinomas have been seen during the course of the experiments. This is not an unusual tumor in the hamster and does not appear to be associated with the microsphere exposures.

. CONCLUSIONS

Our results confirm the observations of LITTLE, GROSSMAN, and O'TOOLE 1970, 1973) that locally concentrated alpha irradiation is less damaging in he hamster lung than the same amount of energy delivered over larger volumes. n their work, ^{210}Po was adsorbed onto hematite particles to produce localization. Probably 10^8-10^9 particles were involved for 3 mg hematite compared ith the 10^3-10^6 spheres used in the present experiments. Thus, our exposures re several orders of magnitude more extreme in terms of both limited number nd high specific activity of the foci.

A number of other significant differences exist between the two experiments, ncluding polonium vs plutonium, mobile vs fixed particles, and exposure of

other organs by the polonium, but it seems probable that the degree of localization is the principal variable. The inefficiency resulting from localization is already evident in the polonium results and becomes extremely marked with the microspheres. Several factors no doubt contribute to the inefficiency of "hot particle" irradiations, including overkill in the extremely high fields close to the spheres, the ability of the tissue to control and repair such localized damage, the lack of synergistic involvement of other organs and other insults, and the probable importance of cooperative multi-cell interactions (which could result in a strong nonlinearity of response with respect to number of cells at risk).

Our results are in definite contradiction to all simplistic models (GEESAMAN, 1968; DEAN and LANGHAM, 1969) which assume that tumor induction can be calculated solely on the basis of cellular radiation exposure. The indication is that much more complicated mechanisms are involved and that the volume of tissue irradiated is an important factor. Of the experimental exposures, only the earliest ones have been completed in the sense that the animals have lived out their normal life spans. These involved comparatively small numbers of spheres irradiating only a few percent of the total lung mass. However, 1142 hamsters were exposed to a total of some 5 700 000 spheres in these experiments, and only two lung tumors were observed, which already sets a very low limit on the probability of tumor induction per particle. The additional experiments begun through 1973 will raise the totals to 1900 animals and 160 000 000 spheres and will greatly increase the fraction of lung irradiated.

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TABLE 1

Distribution of Microspheres in Hamster Lung

Entity	Wet Weight (mg)	Spheres (number)	Concentration (spheres/mg)
Both lungs	2844	23 600	8.3
Left lung	975	11 200	11.6
Right lung: diaphragmatic lobe	790	5 200	6.6
Cardiac lobe	408	2 300	5.6
Intermediate lobe	366	1 800	4.8
Right apical lobe	305	3 000	9.7

TABLE 2

Distribution of Spheres within the Left Lung

Number of Pieces	Average Concentration (spheres/mg)	Coefficient of Variation (%)
1	11.6	-
2	11.4	4
4	11.4	11
8	11.8	15
16	11.6	18
32	13.1	31
64	11.8	39

TABLE 3

Excretion of Plutonium-238 (% of Injected Dose/Day ± S. E.[a])

Day	Urine	Feces	Total
1	0.055 ± 0.013	0.003 ± 0.001	0.058 ± 0.013
2	0.011 ± 0.008	0.011 ± 0.006	0.022 ± 0.010
3	0.003 ± 0.004	0.013 ± 0.003	0.016 ± 0.005
4	-0.001 ± 0.001	-0.004 ± 0.004	-0.005 ± 0.004
5-7	+0.000 ± 0.002	+0.002 ± 0.002	+0.002 ± 0.003

[a]Average for eight animals with 10 000 spheres each. S. E. = standard error of the mean calculated from the scatter of three determinations about their own mean.

FIG. 1. Observed (histogram) and expected (smooth curve) frequency distribution of nearest-neighbor distances in lung section.

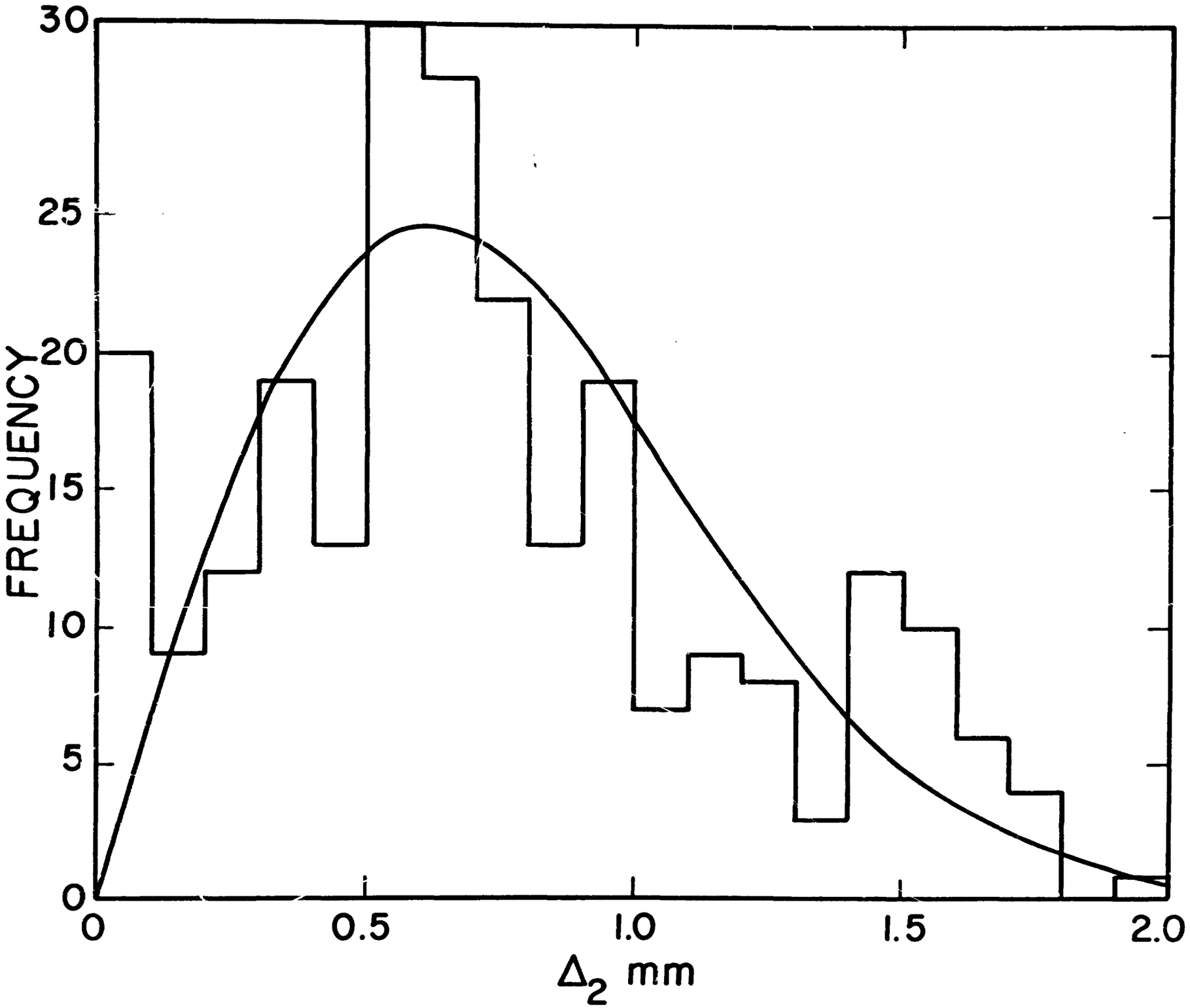

30
25
20
15
10
5
0
FREQUENCY
0
0.5
1.0
1.5
2.0
Δ_2 mm

FIG. 2. The retention of mi:rospheres as a function of time: (-■-) ntravenous, 2000 microspheres; (-▲-) intravenous, 300 000 microspheres; nd (-●-) intratracheal, 500 000 microspheres.

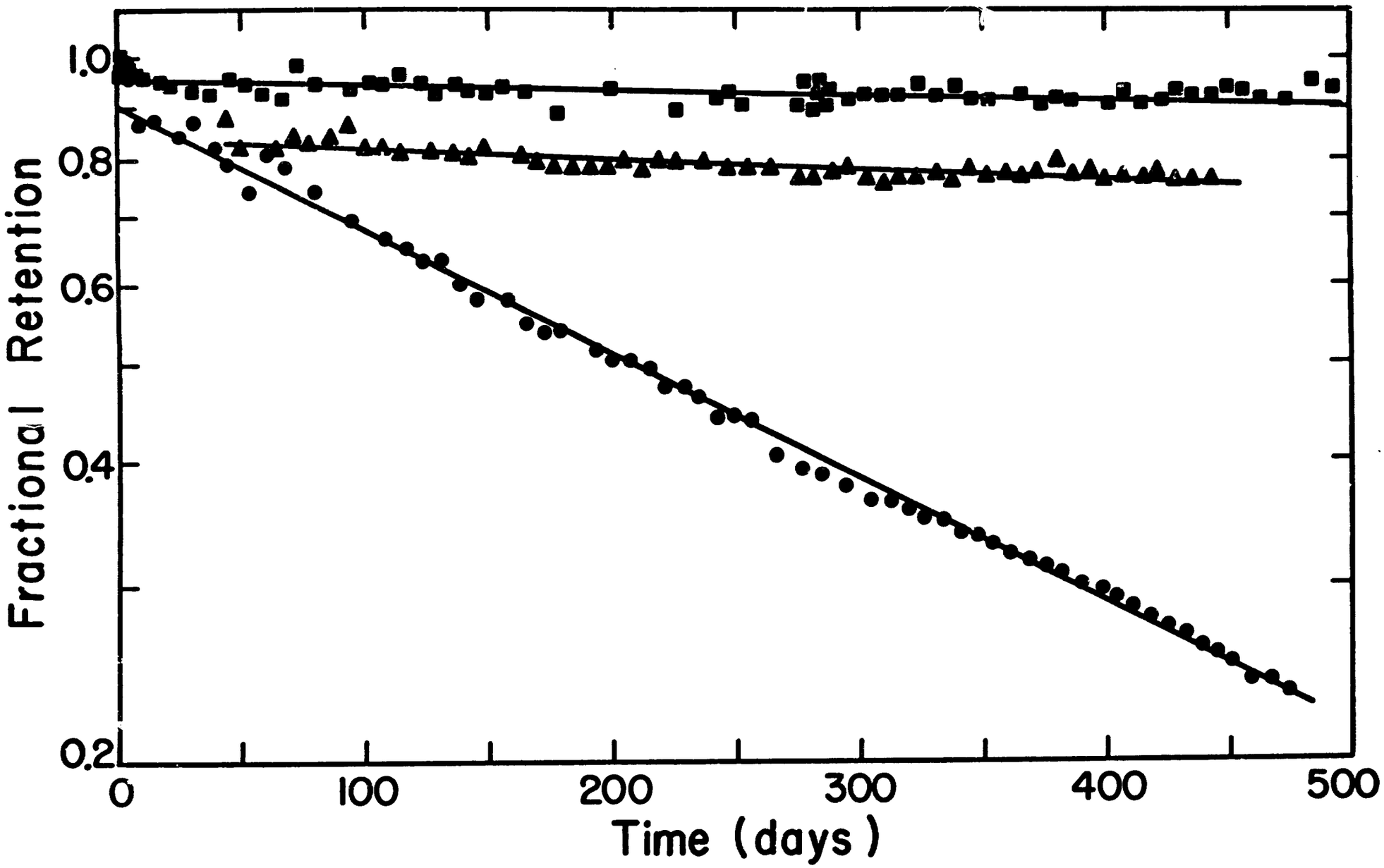
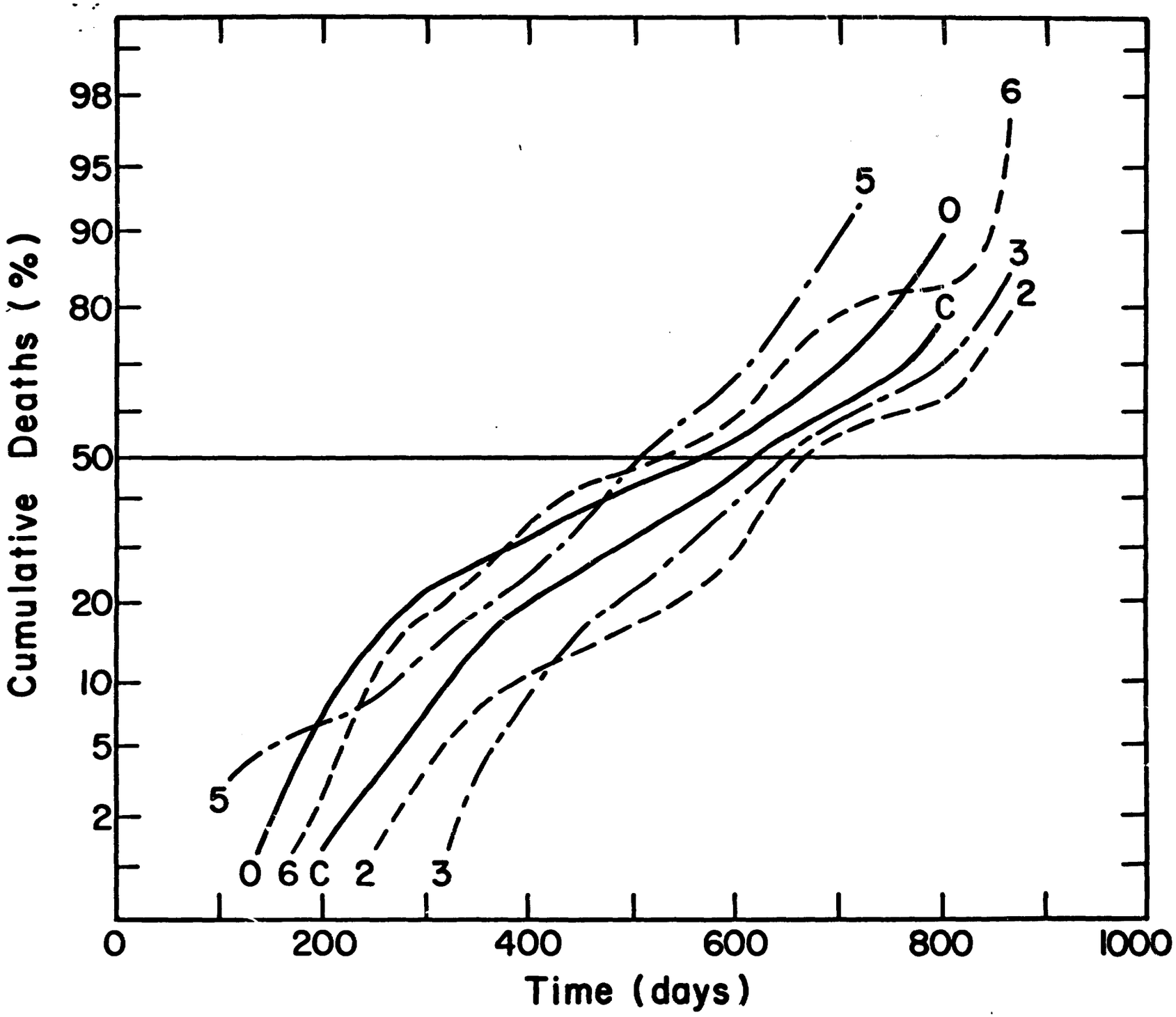

1.0
0.8
0.6
0.4
0.2
Fractional Retention
0
100
200
300
400
500
Time (days)

FIG. 3. Survival curves for hamsters receiving 2000 microspheres intravenously. Time is in days post-injection (age = 100 days at injection). The number of each curve identifies specific activity level: (0) nonradioactive spheres and (C) control group, no spheres.


Cumulative Deaths (%)
98
95
90
80
50
20
10
5
2
0
200
400
600
800
1000
Time (days)
6
5
0
C
3
2
5
0 6 C 2 3