BNL 7343
SM-44/23

CONF-205-9

THE EFFECTS OF 2.0 BeV PROTONS IN MICE

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Available from the
Office of Technical Services
Department of Commerce
Washington 25, D. C.

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Research supported by the United States Atomic Energy Commission.

The Brookhaven proton synchrotron (Cosmotron) is capable of accelerating protons to energies as high as 3.0 BeV. The biologic effects of particle bombardment at these energies have not been investigated but are of considerable radiobiologic interest. In addition, particle beams have long been discussed with regard to their potential usefulness in medical therapy, and actual clinical applications have been made, although at lower particle energies.[1,2,3,4,5] Recent rapid advances in space technology have raised serious questions regarding the dosimetry of cosmic and solar radiations, the spectra of which contain energies in excess of those which have been investigated experimentally. For all of these reasons, we have recently begun a study of the effects of protons at 2.0 - 2.2 BeV, using the external beam of the Cosmotron.

All experiments were performed in a portion of the proton beam which was as nearly parallel as possible. Calibration of beam intensity was performed by activation of polyethylene foils through the reaction,

$$C^{12}\ (p,\ pn)C^{11},$$

and counting of the 0.511 MeV annihilation gammas in a well scintillation counter. Proton distribution within the beam was determined by counting individual small circles of foil within the area of interest (Fig. 1).

Lethality Studies

Having no precedent upon which to base an estimation of the whole body lethal dose of protons at 2.2 BeV, an $LD_{50/30}$ study was for the purpose of establishing this value in mice. A total of 335 male Swiss mice, 8 weeks of age were exposed in tandem groups of 5 as shown in Figure 2. Doses ranging from 1.20×10^{10} to 9.69×10^{11} protons were used, at eleven approximately equal dose intervals (Fig. 3). The death rate for each group is also shown, and it is seen that most of the deaths occurred in the first five days, suggesting a relatively high linear energy transfer. The calculated $LD_{50/30}$ from these observations was 4.94×10^{10} protons.

It was recognized that the proton beam is not of uniform intensity in cross-section, and that the concentration of particles toward the central axis of the beam could modify the response of the mice in that the exposure might not be truly uniform over the whole body. One solution to this defect is to rotate the target animal in the beam. Figure 4 shows a device built for this purpose. The axis of the target-holding Lucite cylinder is oriented parallel to the axis of a somewhat de-focused beam, and rotated at any of several rates from 4 to 24 rpm. To determine the effectiveness of this method, polyethylene dosimeters were constructed as shown in Figure 5. Each of the 21-inch holes contains a disc of plastic 10 mil. in thickness; the dosimeters are oriented normal to the proton beam and rotated at a constant rate during exposure (12 rpm). Each disc is then punched out into a separate specimen tube and C^{11} activity estimated in an automatic well-type scintillation counter. Each disc is weighed and specific activities calculated. Plots of typical specific activities in two axes across the dosimeter are shown in Figure 6. The total variation in activity (variance from "flatness") is about 20 percent.

The $LD_{50/30}$ experiment will be repeated using the rotation technique, and from the approximation gained from the earlier experiment, it is hoped to determine LD_{50} with considerable accuracy.

Tissue Activation

Light element activation through p, pn reactions are well known, and it is of interest that their occurrence can be assessed quantitatively in bombarded mice.[5] After whole-body exposures at several dose levels, mice were immediately positioned in a known, standard geometry before a 2" NaI crystal connected to a gamma spectrometer (Fig. 7) and the induced activity recorded. Figure 8 shows the results of such an observation. The composite (observed) curve can be reduced to three exponential decays, consistent respectively with the presence of O^{15} ($T_{1/2}$ = 2.8 min.), N^{13}($T_{1/2}$ = 11 min.) and C^{11}($T_{1/2}$ = 20.4 min.). The observed C^{11} activity in counts per minute at T_o when divided by the weight of the mouse in grams can be related to the proton flux as follows:

$$\frac{A_{T_o}}{(1 - e^{-\lambda t})} = k\phi$$

where A_{T_o} = observed activity at end of exposure

λ = decay constant of C^{11} = 5.66×10^{-4} sec.$^{-1}$

t = duration of exposure in seconds

ϕ = flux = protons/sec./in.^{2}

The value of k as calculated from a number of observations is 4.09 ($\pm$0.4) x 10^{-5}.

Although the half-lives of the nuclides produced are short, the implications of such a method of dosimetry are intriguing. The method may be useful in studying a number of physiologic processes, such as respiratory function and transport mechanisms.

Future Studies

Detailed information concerning LET will be needed before the exact biological effectiveness of protons at these energies can be assessed. By inference from mouse death rates, the LET is apparently high. It is intended also to study sublethally and lethally bombarded animals with respect to changes in levels of circulating leukocytes, body weight and intestinal epithelial changes. Our long-range program will also include histologic examinations of the responses of the central nervous system, including the eye.

Summary

The high-energy beam of the Brookhaven proton synchrotron (Cosmotron) is under study with regard to fundamental tissue and whole-body responses of mammals to this form of energy transfer. Lethality and *in vivo* activation of certain light elements have been partially characterized. Physical studies of particle distribution and depth dosimetry are continuing, and are critical to complete interpretation of the biologic data.

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Figure Legends

Figure 1 To determine distribution of protons in the Cosmotron beam, a sheet of 10-mil polyethylene foil is exposed normal to and centered in the external beam. After exposure, the foil is cut into 1 cm. portions, and the C^{11} activity (relative numbers in squares) estimated. The central 2.5 cm. circular area was separately calibrated for measurement of total dose to mice.

Figure 2 After beam calibration, mice are arrayed for exposure in the calibrated 2.5 cm. "core" of the beam.

Figure 3 The total (whole-body) proton doses used and total 30-day deaths in mice.

Figure 4 The rotational device used to provide uniform whole-body exposures of mice. The animals placed individually in light plastic centrifuge tubes, and placed in the long Lucite tube in groups of four or five. Rotation rate can vary from 6 to 24 rpm. The same device is used to rotate plastic dosimeters.

Figure 5 Solid (left) and multiple-foil dosimeters (right) are used to calibrate proton beam intensity and to determine distribution. Each of the 21 holes of the distribution dosimeter holds a wedged polyethylene foil of approximately 1 mm. thickness which is punched out and counted (C^{11}) after exposure.

Figure 6 Transverse proton distribution as measured by the 21-hole dosimeter. The solid and broken lines represent results from dosimeters at each end of the 18" Lucite rotator tube.

Figure 7 The gamma spectrometry apparatus used to estimate and analyze induced activity in mice. The animal is placed before a 2" NaI (Th) crystal in known geometry, and total positron emission (0.511 gamma of annihilation) recorded.

Figure 8 Induced tissue activity (X-X) can be resolved into decays consistent with C^{11}, N^{13} and O^{15}.

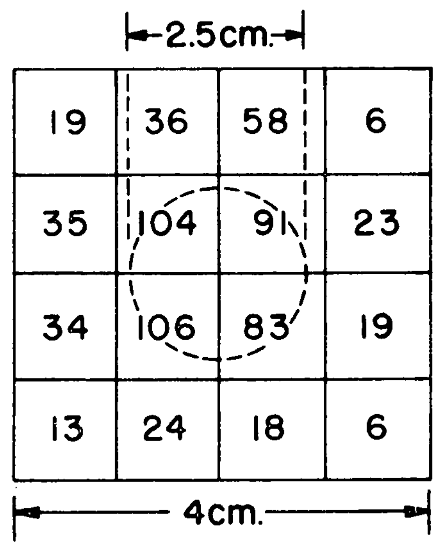

FIGURE 1

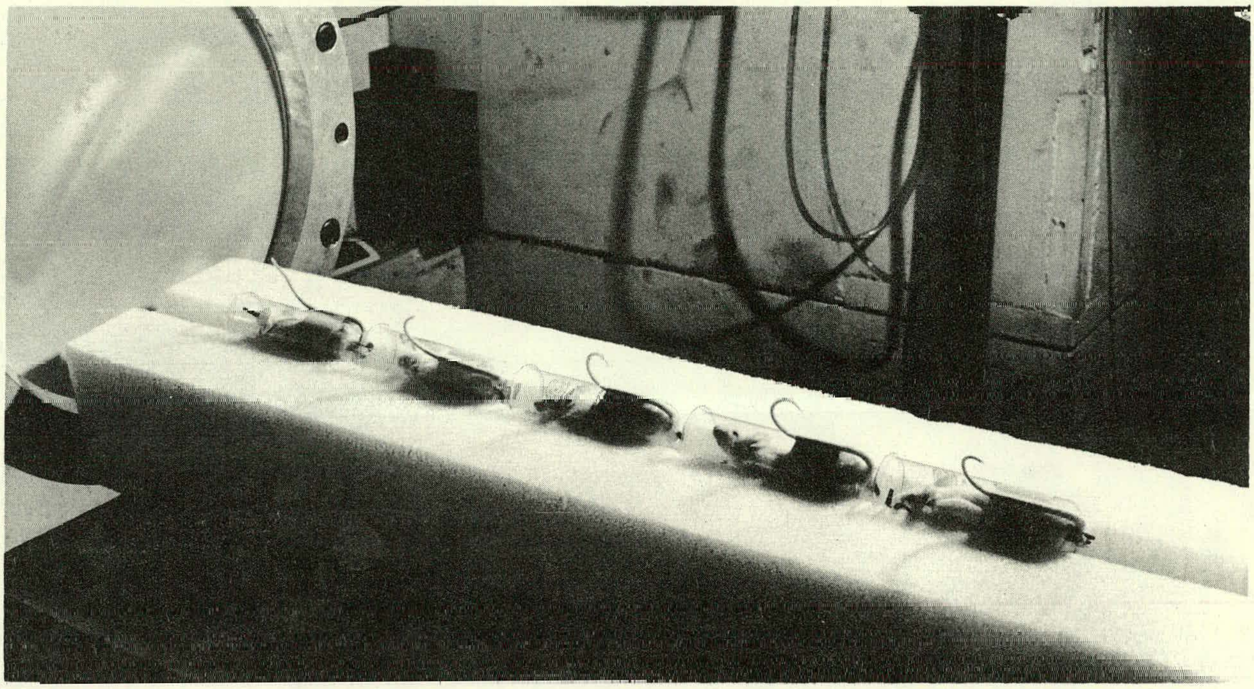

FIGURE 2

$LD_{50/30}$ Study for 2.2 BeV Protons
(Cosmotron)

Proton Dose	Deaths
1.20×10^{10}	0/30
1.56×10^{10}	0/30
1.76×10^{10}	0/30
2.44×10^{10}	0/30
2.95×10^{10}	3/30
3.03×10^{10}	0/30
3.73×10^{10}	0/30
4.94×10^{10}	13/35
5.92×10^{10}	28/30
7.56×10^{10}	30/30
9.69×10^{10}	30/30

FIGURE 3

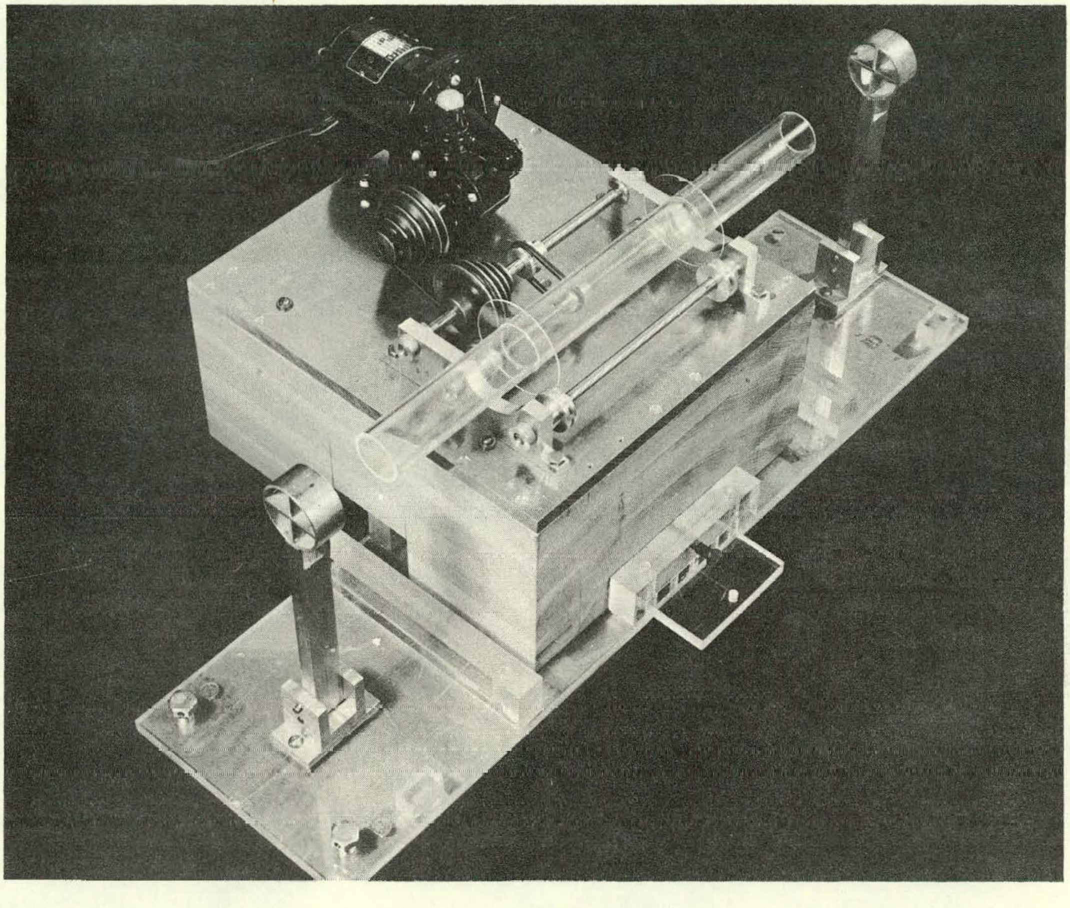

FIGURE 4

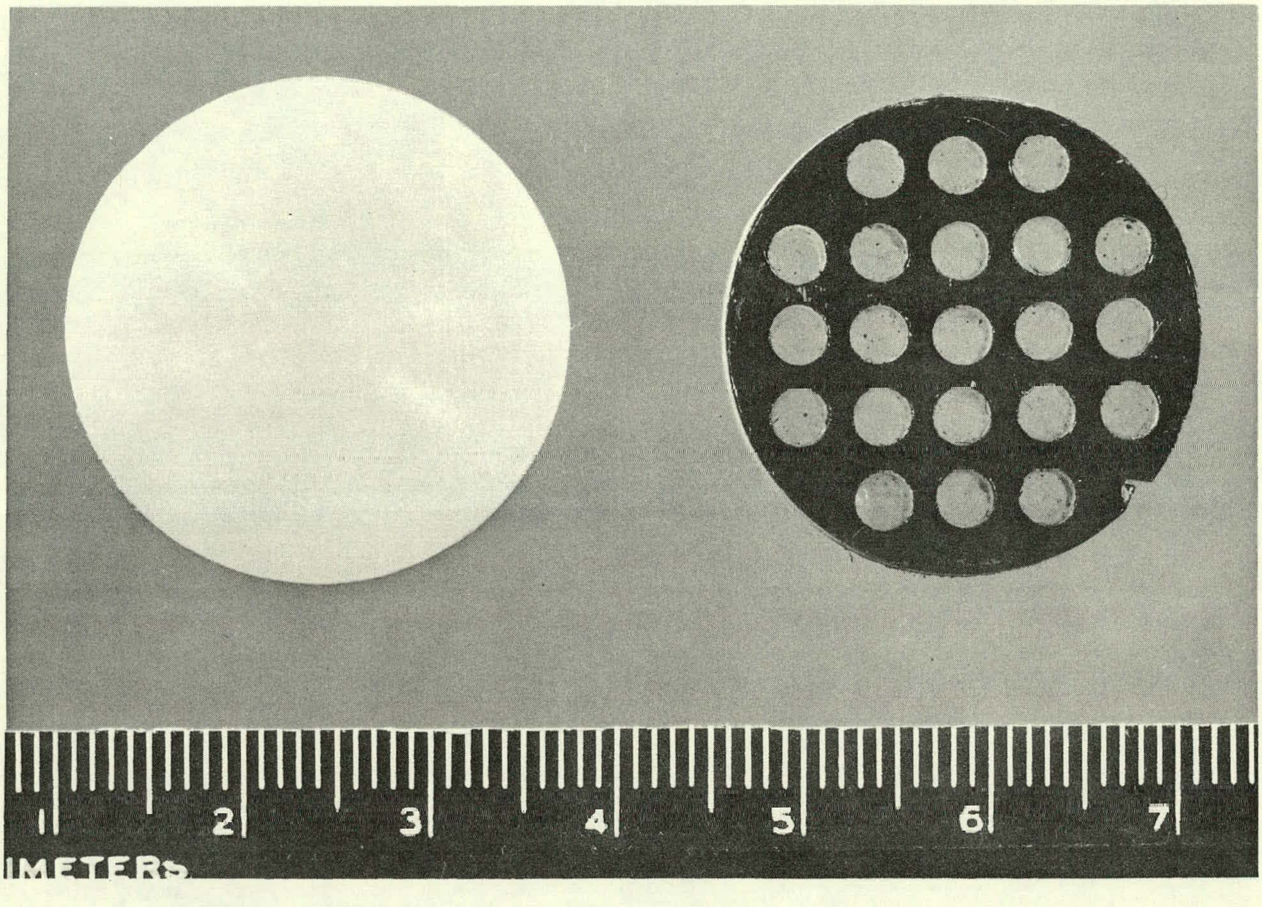

FIGURE 5

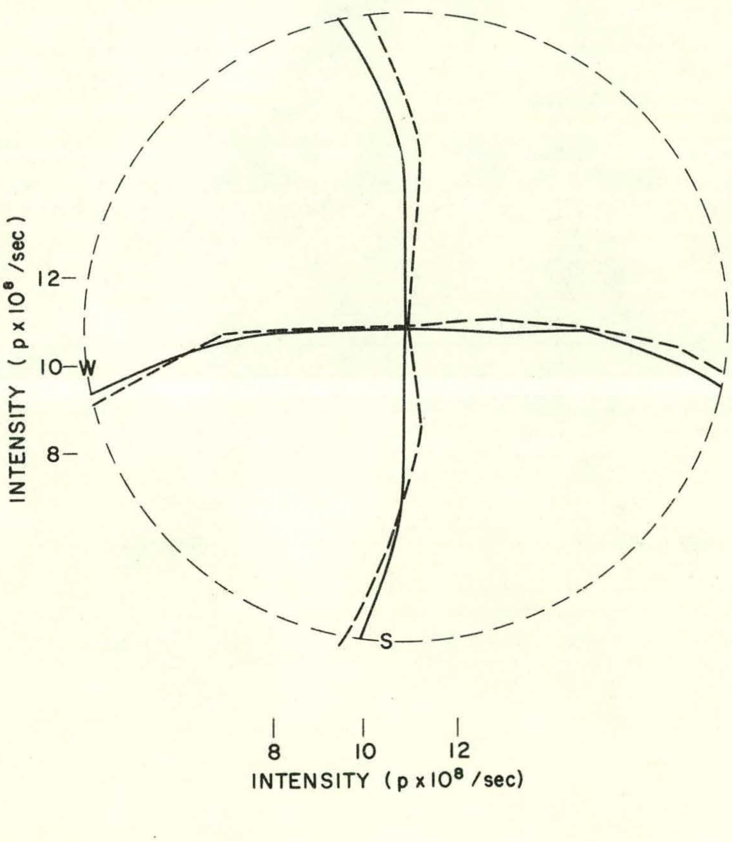

FIGURE 6

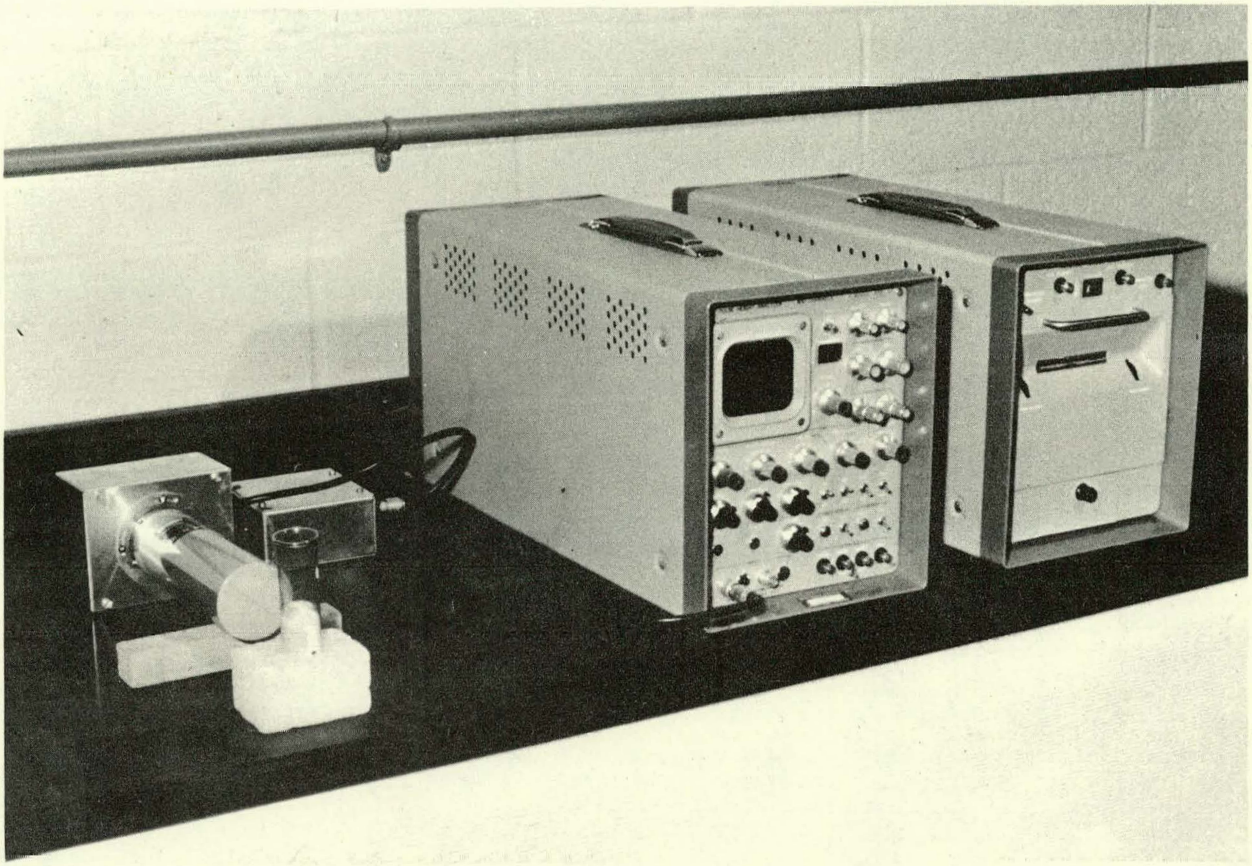

FIGURE 7

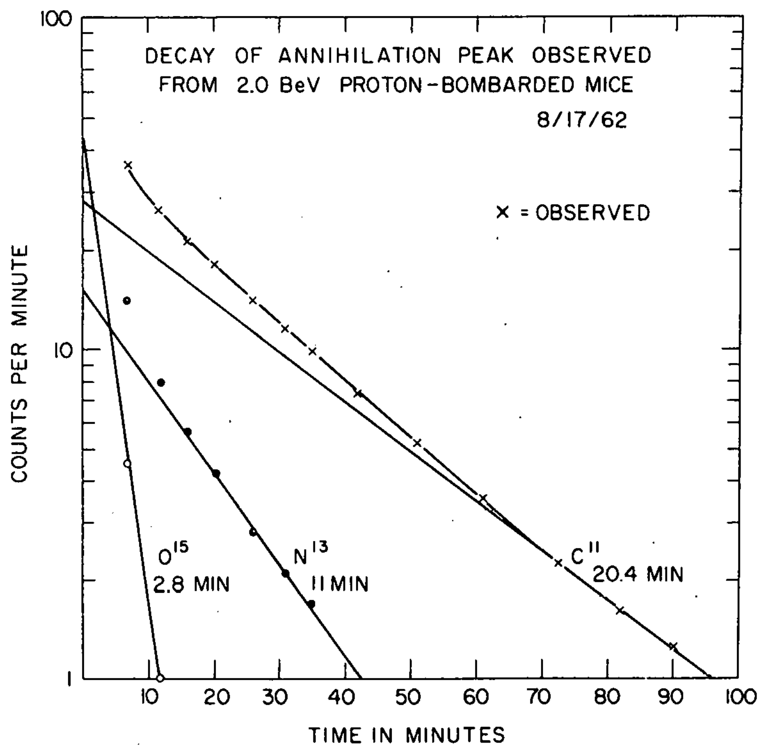
DECAY OF ANNIHILATION PEAK OBSERVED
FROM 2.0 BeV PROTON-BOMBARDED MICE
8/17/62
× = OBSERVED
COUNTS PER MINUTE
TIME IN MINUTES
O15
2.8 MIN
N13
11 MIN
C11
20.4 MIN
100
10
1
10
20
30
40
50
60
70
80
90
100

FIGURE 8