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Introduction:

It is already known that congenital anomalies are formed in close relations with heredity and environments, and particularly the experiments of deformity formation by use of radiation as physical factors, done by many predecessors, have greatly contributed in clearing causes of congenital anomalies. However, while the conventionally used irradiations such as X-ray, neutron beams, etc. done to pregnant women, may mean only a local irradiation on the lumbal area, it does mean a total irradiation on the embryo or the fetus.

The proton irradiation which is a high LET irradiation shows a very characteristic dosimetry called Bragg peak. By using this physical characteristic, it is said that there is a possibility of preliminarily setting a local irradiation on the fetus, which will be an interesting aspect in experimental teratology application.

By using the AVF-type cyclotron which belongs to Tohoku University, we irradiated pregnant mice at the abdominal area with proton issued from it, and could produce a new type deformity, which we are reporting hereunder.

Materials and Methods:

The animals used were C<sub>3</sub>H/He mice, male and female, of 8 to 12 weeks old. The day the copulation plug was recognized was set the zero day and the mice were fixed on a special fixation plate specially made by us for the purpose on the 10th, 11th or 12th day of pregnancy. The control of the proton beam and the experimental set up are shown in fig. 1. The 35 MeV protons were focused in the pipe onto a quartz plate and the beam emerging from the scatterer of quartz was further transported in a distance of 4.3m, then extracted out into air through Mylar foil of 200 μm thickness (beam diameter of 20cm). Furthermore, in order to measure the proton-induced proton, a plastic scintillator was placed beside the transport pipes, and the dose measurement was done by using a parallel plate ionization chamber with ionization volume of 0.1ml.

Figure 2 shows the proton dosimetry of 35 MeV. The beam dosage was about 15 rad/sec by using a beam chopper, and Bragg peak was 6.7mm depth on the acrylic plate, with the Bragg peak/plateau ratio about 5.5. In front of the proton beam

was set an acrylic plate of 15mm in thickness, whose central part was cut off in the diam. of 4cm, and 4  $C_3H/He$  mice were fixed with the interval of about 7cm on another acrylic plate of 10mm in thickness having a cut-off of about 3 cm diam. for the abdominal part, with pressure not so much as to inhibit breathing, and the irradiation was done by remote control moter driving from the control room under watching the TV camera.

For generation X-ray , tube current  $20_m A$ , tube voltage 250KV, a filter of 0.3mmCu + 1mmAl was used, taking 50cm distance between the focus and a mouse and the field of irradiation 13 X 13cm, 147.6R/sec in dose rate, while the mice fixed on the acrylic plate equally processed as in the case of proton irradiation.

The mice of 10, 11, 12 days of pregnancy fixed on the acrylic plate in 30 minutes was termed as TC group (treated control) and another group entirely untreated was termed as UC group (Untreated control group) for comparisons.

Under such irradiation conditions, groups of proton irradiations of 70 rads, 130 rads, 200 rads and of X-ray irradiation 130 R as well as TC and UC groups were prepared. The mice were given casarean section on the 18th day, their implantations were counted, the fetus taken out and examined for superficial deformity, sex and weight. The dose of the proton was used the beam absorbed dose (rad) at the plateau and the X-ray was used the surface exposure (R).

#### Results :

The experiment data are given in table 1. The comparison was done among the groups of proton, X-ray, TC and UC. In the rate of survival/implantation, significant differences were observed between TC and X-ray 130 R groups ( $P < 0.01$ ); TC and proton 130 rad group ( $P < 0.005$ ). In the mean birth weight, statistical significance was recognized in all groups. In the rate of deformity, significant differences were seen between TC and X130R ; TC and proton 130 rad ; X130R and proton 130 (all  $P < 0.0001$ ). The comparisons among proton-irradiated groups will be our future task to be undertaken after more repeated experiments. However, in photo 1, we could show certain superficial deformities in proton 130 rad group (11th day of pregnancy) which reflect apparent influences of Bragg peak, specific to local irradiations. Those appeared in areas from the upper right to the lower part of the body as multiple superficial deformities which seem to have their cause in Bragg peak influence. Those are the Mo(microphthalmia), CP(cleft palate), AG(agnathia) or Mg(micrognathia), Mm(micromelia), Od(oligodactylia), St(short tail) etc.

In the future we are planning to continue our studies in comparison of deformities by days of pregnancy, preparation of bone structural samples, and how the histological deformity was repaired.

Table 1. Experimental Study of Proton Irradiation on C<sub>3</sub>H/He Mice

Group	No. of litters	No. of implantations	Living fetuses	Prenatal deaths	Living imp. (%)	Malformed fetuses (%)	Body weight (M±SD)
Proton (70)	10	91	48 (4.8)	43	(52.7)	40 (83.3)	0.86 ± 0.20
Proton (130)	7	67	31 (4.4)	36	(46.3)	28 (90.3)	0.71 ± 0.16
Proton (200)	5	44	12 (2.4)	32	(27.3)	5 (41.7)	0.60 ± 0.17
Xray (130)	14	123	66 (4.7)	57	(53.7)	18 (27.3)	0.85 ± 0.13
T.C.	10	90	63 (6.3)	27	(70.0)	1 (1.6)	1.08 ± 0.15
U.C.	10	86	69 (6.9)	17	(80.2)	2 (2.9)	1.22 ± 0.19

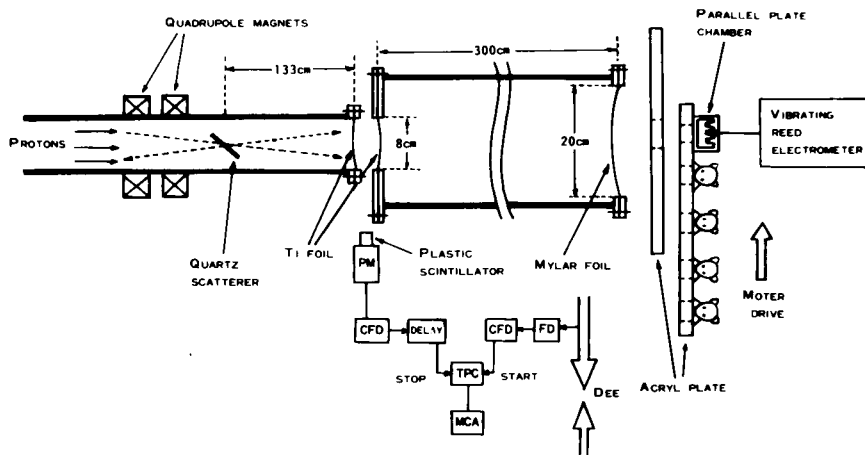


Fig. 1. Experimental setup. PM ; photomultiplier, CFD ; constant fraction discriminator. FD ; frequency divider. TPC ; time to pulse converter. MCA ; multi-channel analyzer.

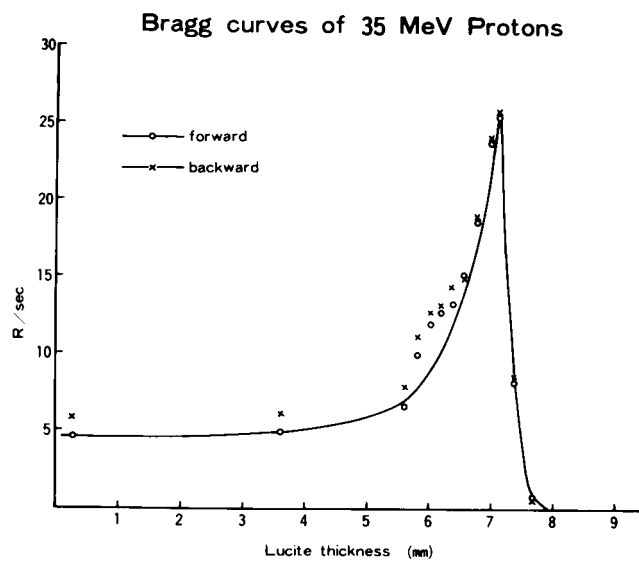


Fig. 2. Bragg curves of 35 MeV Protons.

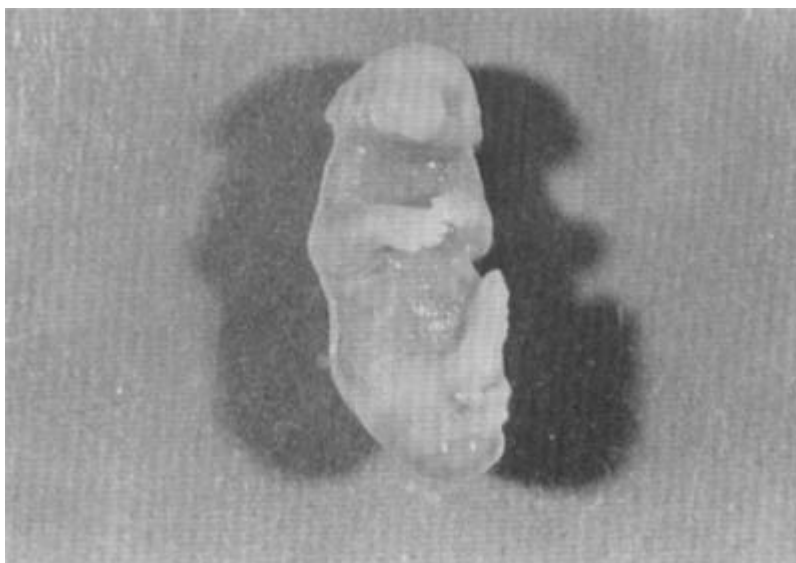


Photo 1. Malformed Mouse Irradiated Proton 130 rad (preg 11th day).  
 Bragg peak caused multiple deformities from the upper right to the  
 lower left part of the body.