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MINUTES OF MEETING TO DISCUSS STATISTICAL PROBLEMS

OF THE

BIOMEDICAL PROGRAM

ARGONNE NATIONAL LABORATORY, SITE B, 6 MARCH 1950

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Present:

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DATE
*Ltr. DNA Varello to DOE, OC dated 9/14/87
J. Diaz 11/22/8.

1. The general plan of the mouse LD Study (2.4.1.1) was presented. It consists, essentially, of the exposure of mice, in suitable containers to the ionizing radiations of an atom bomb. The objective is to obtain a lethal dose curve for LAF_1 mice exposed to a bomb of known kiloton nage. The lethal agent can be expressed in terms of distance, or in terms of radiation r, measured in air, or in depth dose, etc.

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The atom bomb radiation dose required for the LD_x of this species can then b e compared with the dose required when laboratory radiations are used.

1.1 There was no discussion of the strain of mice to be used. The selection of LAF_1 had been based on its extensive use in lethal dose studies at the National Institute of Health.

1.2 There was considerable discussion of the age-distribution of the animals. It was pointed out that ideally a representative population containing all ages would most nearly approximate the conditions of the use of atom bombs in warfare. However, the extrapolation from mice to men is not desirable. What is desired is the comparison of 3-4 MEV gamma radiation, with gamma and x-radiation of energies usually used in experimental medicine. Such a comparison will be useful in evaluating experimental therapy, etc. For this limited goal, it is proper to work with a restricted age group. There is little variation in the LD_{50} versus age in mice in the age group 8-10 week to 1 year. The proposed test conditions specify mice 8-12 weeks old; Therefore they will be satisfactory.

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1.3 Lethal Dose Study:

Number of animals required was discussed. This problem has two parts: number of points desired for construction of LD_x curve; and number of animals per point.

1.3.1 It was agreed that it would be desirable to ascertain the LD_x in r ± about 5%. For this strain of mice, the LD_{50} with 2 million volt x-ray is about 750 r. Therefore, if the points were separated by distances equivalent to about 25 r, the requisite degree of accuracy could be attained. It was agreed that the mouse exposure stations in the region where the LD_{50} could be expected, should be placed about 25 r apart. This separation should be used between estimated 550 r and 900 r, to allow for variations in bomb efficiency. The closer and the farther stations would be more widely separated. To cover all possible contingencies, it was recommended that 29 stations should be used in the range 200 r to 1400 r, anticipated dose. The error in estimate of the bomb's output of energy was taken as ± 20%.

1.3.2 In the discussion of number of animals per station, it was recommended that the level of accuracy should be 95% probability. For this, 30 animals of each sex per station are required. It was the unanimous opinion of the Consultants that little would be gained by using larger numbers of animals for the LD_x study. Therefore, the total number of mice for the LD_x study is 1740.

1.4 Survivor Study:

1.4.1 The late (i.e. chronic) effects of atom bomb radiation should be studied, and comparisons should be made between such late effects after exposure to sub-lethal amounts of laboratory radiation. The minimal objectives of such a study are: a) the effect of atom bomb radiation on longevity; b) the incidence of tumors, etc., in survivors; c) the incidence of cataracts. The important survivors to study are those exposed to varying amounts of radiation less than the LD_{50}. It was agreed that for the purposes of such a study, the animals should be placed in groups whose dose varied by 100 r increments, viz: LD_{50} to LD_{50} - 100 r to LD_{50} - 200 r; etc. It was agreed that little information of value could be anticipated, reasonably, in the case of animals receiving less than 200 r, estimated dose. The number of animals which should be available in each such group to permit an adequate study of longevity, tumor incidence, etc., was agreed to be about 500. The basis for this estimate was as follows: assume a normal incidence of tumors in the strain of 0.1, and a minimum incidence in the irradiated survivors of 0.2. To obtain a standard error of 0.02, approximately 900 animals would be required.

Our current container design will accomodate about 200. It was agreed that 800 was a good enough number for the survivor study. The number of mice required to accomplish this, in excess of those to be exposed for the LD_x study was estimated to be about 4200. ~ 4800?

1.4.2 The statistical treatment of the data on the survivors was discussed, but there was not complete agreement. Life table type of study and cumulative mortality curves were suggested, as well as several other theoretical treatments. It appeared that this matter should be considered further.

1.4.3 Operational aspects: No firm agreements have been made in the Biomedical Program for the execution of the study of survivors. It is estimated that about 5000 animals will survive, ideally. In addition to these, there should be one group (800) of untreated controls of the same age; and two groups of treated controls, one irradiated with an LD_{50} dose of 250 kV x-rays, and one with some lower dose, say, LD_5 or LD_{10}. This would mean 400 / 760 = 1160 mice. The total mice for survival study is then 5960, or 6000 in round numbers. It was the consensus of opinion that these animals should be studied in one institution, especial care being taken to prevent epizootic disease.

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Complete pathologic study of all decedents, and the observation of an established protocol is imperative.

It should be noted that a study of this sort will require about two and one-half years, and would cost an estimated $75,000.00. Planning of such a study should be completed in the near future, since if it cannot be done in a thoroughly satisfactory manner, the number of mice to be exposed can be reduced considerably.

1.5 Controls:

1.5.1 For the LD_x study, it was agreed that the plan to test the LD_{50} using 250 KV x-ray with the mice on Eniwetok was necessary. The LD curve should also be determined with this radiation on the control mice at NRDL.

1.5.2 Randomization: It was stated categorically that the mice for each exposure station (i.e. each point on the LD curve) should be placed in a random manner, preferably by the use of random numbers. Studies of this sort are especially prone to develop systematic bias, and the extra effort to avoid it is not sufficient to justify neglect of true random sampling of the mouse colony.

2.0 The desirability of a study of LD_x using the swine and dogs was discussed. It was agreed that such a study should be done, since the extrapolation from swine or dogs to man is relatively valid. Brucer stated that swine are more nearly like man than any other laboratory animals. The general opinion was that dogs should also be used for a lethal dose study because of their general use in experimental medicine. It was apparent that a vote would have favored the use of both species rather than either alone.

The general situation of the large animal plans was reviewed: 120 of each species should be available at shot time. Originally, it had been planned to use 60 of each species for a serial sacrifice study on each of two weapons tests. However, for a number of reasons it is now thought desirable to use all the large animals for one shot, the characteristics of which are fairly certain. The question was asked which study would be preferred (i.e. LD or sacrifice) if only one could be done. There was fairly even division of opinion, and the consensus was that both should be done if possible.

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2.1 LD_x Study: The question was asked concerning the least number of animals to provide a valid LD curve. The level of accuracy desired was stated as follows: It will be satisfactory if the LD_x (LD_{90}, LD_{50}, LD_{10-5}) in terms of distance from a bomb of specified kilo-tonnage can be known within 100-200 yards. In the range where LD_{50} is liable to occur, this distance is equal to about 100 r. The best estimate for LD_{50} for swine is about 450 r, and for dogs about 250 r of 3-4 MEV gamma radiation. On the basis of the foregoing, the following recommendations were made by the statistical consultants: Use 10 animals per point. Less than 6 per point would give unreliable results. Four stations, or points are the least that could be used: these should bracket ELD_{10} and ELD_{90}. A very satisfactory study would result from eight well placed stations, and six would not be too bad. The final recommendation was 10 per station, and 8 stations. Actually, when the stations were plotted, the 8th would have to be in the water, so 7 are planned. The proposed location of the stations is as follows: 600 r, 525 r, 400 r, 300 r, 225 r, and 175 r. It should be noted that the LD_{50} for man, on the basis of Japanese data is about 200 r.

There was general agreement that this type of study was desirable, and that it had practical importance for civil defense and military medicine. It was the consensus of opinion, also, that pathologic studies should be made on the animals that died. Control studies of the same type, i.e., 10 animals per dose, for 6 doses of 2 million volt, and other types of radiation sources should be done.

2.2 Serial Sacrifice Study: Since it was obvious that a lethal dose study would reduce the number of large animals available for serial sacrifice, the question was asked concerning the number of animals which should be sacrificed at each time interval. The obvious answer is the more the better. It was pointed out that this sort of opinion cannot have a true statistical basis. It was the consensus of belief, however, that a trained pathologist would learn as much from two animals of each species per period of time, as he would from three or four. It was recommended that a realistic number for the serial sacrifice study was two animals of each species per period.

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It was recommended that a realistic number for the serial sacrifice study was two animals of each species per period. It was recommended that all these animals be exposed to the same dose of radiation, one that would be at least the LD_{50-90}. The recommended dose was about 550 r.

It is apparent that control studies should be done to determine accurately the most suitable dimensions of the periods: i.e. hours, days, etc.

Respectfully submitted,

CARMEN V. LARKIN, M.D.
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Joint Task Force #3

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