

22 January 1960

Dr. A. C. Anderson
 School of Veterinary Medicine
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 Davis, California

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Dear Bud:

I received this week three copies of an undated, unsigned, 5-page document titled "Experimental Design for the Strontium-90 and Radium-226 Experiment". Although there was no transmittal letter I am guessing that perhaps this is the revised version of the pertinent parts of the tentative minutes of the 22-23 June 1959 meeting at Davis which you circulated for comment in August 1959, and that you would like to have comments on the present draft.

Rather than commenting point by point on the new draft, I am enclosing another copy of my letter of 31 August 1959 which gave a number of detailed suggestions and comments, many of which seem not to have been in view when the present draft was written up. I feel that a number of the points made there should be incorporated in the minutes. Dr. Bruner's notes and mine appear to agree very well because there are a number of points of overlap with his letter to you dated 18 January 1960 with which I am in full agreement.

There is one feature of the new minutes which deviates sharply from the agreements reached at all of the previous planning sessions. This is the numbering of the dosage levels in the Sr ingestion and injection series. It had been firmly agreed to call the top level the "5 level". Your Ra injection series continues to be properly numbered from the 5 level down to the 0 level, or control. Your top Sr level should also be called the 5 level because all the dosimetric estimates have been made on a basis of approximately equivalent toxicity for the top Sr ingestion level, and the top Ra injection level, and also for the 4, 3, 2, and 1 levels. The second reason for adopting the 5 level is the desire for easy correlation with the Utah dosage ladders where the top level is called the 5 level for each of the radioactive materials used. Your top ingestion level is a 5 level because it is designed to give approximately

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which was meant approximately 14.5 months, so that the 8th and final injection would occur when the animal was just 18 months of age.

My third point is that I think you should carefully distinguish between "level", "group", and "series", perhaps more or less as I indicated in the corrected copy of your preliminary minutes which I also sent you in August. In the present minutes, page 2, item 4, the words "group" and "level" seem to be used interchangeably. I would suggest that "level" have its usual meaning of dosage level, that "group" mean the consecutive order in which the animals enter the experiment, exactly as the word is used in the Utah injection tables, and that "series" refer to the type of treatment, for example injected Ra series, ingested Sr series, etc.

A definition of "brief exposure" can be taken from page 5 of my August 1957 letter to Dr. Claus, which summarized the 14 June 1957 meeting. Thus "the human cases of internally deposited Ra are due mostly to brief exposures of the order of 3 years, with administration by either repeated intravenous injection or by roughly continuous oral ingestion. In order to imitate these exposures, the "brief exposure" of the dogs is to be a series of 8 injections over a period of 4 months (\approx 3 human years), from age 14 to 18 months. The radium dogs are to be caged from birth in the same manner as the Sr⁹⁰ dogs."

With every good wish.

Cordially yours,
ORIGINAL SIGNED BY
ROBLEY D. EVANS

Robley D. Evans
Professor of Physics

RDE:ems
enc.

cc: Dr. A.M.Brues
Dr. H.D.Bruner
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21 August 1959

Dr. A. C. Andersen
School of Veterinary Medicine
University of California
Davis, California

Subjects: Minutes of 22 and 23 June 1959 meeting at Davis

Dear Bud:

As suggested in your letter of 4 August 1959 I am returning one marked copy of the first draft of the minutes and experimental design for your experiment, as developed in the meeting in your laboratory on 22 and 23 June.

Based on the notes which I took, I would also suggest the following additions.

- page 2: II. A. add "Sex of serial sacrifice dogs to be chosen so as to leave a sex ratio as close as possible to unity in the experimental dogs for each dose level."
- page 3: II. B. 3. add "i.e., use each dam only once, for first litter, on second oestrus cycle."
- page 3: add II. C. "All dogs in control and experimental levels to be F₁ generation, and virgins."
- page 5: IV. B. add "Retention in the 0.3-level Sr⁹⁰ dogs will probably be too small to permit bremsstrahlung measurements, and will be estimated by β -ray counting on specimens from an enlarged group of 10 serial sacrifice animals."
- page 5: IV. D. Add "Build up all 6 dose levels simultaneously; of 8 dams one would supply 3-level pups, another 4-level pups, etc., and two would supply control pups."

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- page 5: IV. E. 1. add "Identify each dose level by a color-code for utensils, data sheets, and feed if possible."
- page 5: IV. E. 3. add "If errors are made in 0.05 percent of feedings, there would be about 75 errors in the experiment. All detected or suspected errors must be scrupulously recorded in an error log. The error log can be used to identify various types of error, and to develop methods for minimizing their repetition."

Comments on the Experimental Dose Levels, page 4, are as follows.

I. INGESTION. I agree with the values given in the column " $\mu\text{c Sr}^{90}/\text{g-Ca}$ in feed." Sometime in the future it may be important to recall how these numbers originated. The basic document is Chuck Mays' letter to you dated 2 June 1959. This made use of Mays' bremsstrahlung measurements on your two test dogs 581 and 582, which had been fed $1.85 \mu\text{c Sr}^{90}/\text{g Ca}$ (for 18 months?) and had retained an average of $19.5 \mu\text{c Sr}^{90}/\text{kg}$ body weight at an age of 26 months. Mays' calculations indicate that the accumulated skeletal radiation dose in rads would be the same (~ 8000 rad) in Utah 5-level Sr^{90} dogs 2.5 years post-injection and in your 5-level dogs at age 2.5 years if you fed for 18 months a diet containing about $1.5 \mu\text{c Sr}^{90}/\text{g Ca}$. Therefore the tentative dosages listed in your agenda for the 22 June 1959 meeting were reduced (about 22 percent) to the value of $1.5 \mu\text{c Sr}^{90}/\text{g Ca}$ for the 5-level, and to dosages decreasing from the 5-level in the ratios $1/3, 1/2, 1/3, 1/6, 1/6$ for the 4, 3, 2, 1, and 0.7-levels.

The estimated body burden, 2 days after the last Sr^{90} feeding, would equal the Sr^{90}/Ca ratio in the feed multiplied by the $\text{g Ca}/\text{kg}$ body weight, if the discrimination factor is unity. We have two calcium values: $14 \text{ g Ca}/\text{kg}$ used in your agenda, and $12 \text{ g Ca}/\text{kg}$ used in your minutes, from which estimates of the body burden could be calculated. These give, respectively, estimates of $21 \mu\text{c Sr}^{90}/\text{kg}$ (as used at the meeting) and $18 \mu\text{c Sr}^{90}/\text{kg}$ (as given in your minutes) for the 5-level dogs, and proportionate values for the other dose levels.

II. Sr^{90} INJECTION. The decisions on the Sr^{90} injection series were, if my notes are correct, 20 experimental dogs plus 5 serial

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sacrificed dogs, to receive a single 4-level injection of 33 $\mu\text{c Sr}^{90}/\text{kg}$ at age 18 months. It was felt that 20 experimental dogs, rather than 30, would suffice in this one experiment because the comparison 4-level Sr^{90} injection series at Utah will be only 12 dogs. The control dogs would be the 60 0-level dogs of the concurrent radium injection series, and not a special group of controls.

Mays' data on Sr^{90} retention following a single injection show 27 percent retention at 80 days. Therefore you will expect a retention of about $0.27 \times 33 = 9.0 \mu\text{c Sr}^{90}/\text{kg}$ measured 80 days post-injection.

III. Ra^{226} INJECTION. The numbers 1.25 $\mu\text{g}/\text{kg}$, etc., given in the minutes, seem to be in the wrong column. These numbers are the injected dose for each of 8 injections. For example, the 5-level dogs are to receive an injection of 1.25 $\mu\text{g Ra}/\text{kg}$ every 2 weeks, beginning when they have passed 14 months of age and ending with the 8th injection at about 18 months of age. Then a 5-level dog will have received a total of $1.25 \times 8 = 10 \mu\text{g Ra}/\text{kg}$, which is the same as single-injection dose for the 5-level Utah radium dogs.

The estimated retention of R would be based on the experience at Utah where 25 percent retention is found at 60 to 90 days post-injection. Because your radium injections will cover a time span of 14 weeks, or 98 days, we might expect the 25 percent retention value (e.g. 2.5 $\mu\text{g Ra}/\text{kg}$ for the 5-level) to occur at roughly 30 days after the 8th injection.

Please let me know if there are other points which should be reviewed, or if my notes do not agree with others on any of the design items just discussed.

With every good wish.

Cordially yours,

ORIGINAL SIGNED BY
ROBLEY D. EVANS

Robley D. Evans
Professor of Physics

RDE:pam

cc: Dr. A. M. Brues
Dr. H. D. Bruner
Dr. W. H. Langham
Dr. L. W. Tuttle

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