

MEMORANDUM

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REPOSITORY Records Holding Area Bldg. 494

COLLECTION Protocols - Clinical

BOX No. 4

FOLDER Human Protocols 1950-1963

TO: Committee on use of radioactive isotopes in humans

FROM: Dr. J. S. Robertson *JSR*

SUBJECT: Total Body Irradiation Therapy (Na²⁴)
H-45

1. Project

Total body irradiation with X-rays has been shown to be a useful addition to the management of advanced, generalized cancer (1). A comparison of the effectiveness of the radiation from internally distributed sources is of interest, and there is a possibility that such radiation will be more effective than therapy with X-rays. The tolerance of human beings to therapeutic doses of radiation from internal sources has not been established and observations pertinent to this phase of the problem are an important prelude to full scale therapeutic trials. It is therefore proposed that the studies outlined below be undertaken for the purpose of evaluating the feasibility of using whole body irradiation from internally distributed sources as a mode of therapy in advanced cancer.

2. History of total body irradiation

Medinger and Craver (2) have reviewed the early uses of total body irradiation. "The basic principles of the method of total body irradiation were first described in the form of an "X-ray bath" by Dessauer (3) in 1907 but were not applied until 1923 when Chaoul and Lange (4) reported favorable results in 12 cases of Hodgkin's disease treated with small doses of roentgen rays to the entire body. Although Teschendorf's (5) results of treatment of leukemia and Hodgkin's disease by total body irradiation were first reported in 1927, he is given credit for having introduced this method of therapy in Europe."

On the basis of their own experience involving 270 cases, mostly with lymphomatoid diseases, using the Heublein (6) method, Medinger and Craver (2) report that 300 r of 185 Kv X-rays given over 10 days appears to be the upper limit of safe dosage. They used continuous irradiation with 185 Kv, 1 ma, filtered with 5.5 mm Cu and with a working distance of 3 meters. At 0.86 r/hr, for example, 100 r was delivered in 6 days.

Craver (7) later (1947) reported a study of 6 patients having advanced metastatic cancer and who were exposed to up to 300 r of 180 Kv X-rays delivered in either 20 or 30 days. "In no case did there occur any deterioration in the blood count that might not reasonably be ascribed to the progress or complications of the malignancy. In the 3 cases followed for longer than 6 months there was no deterioration in general health not reasonably entirely attributable to the progress of the disease. In no instance was there observed any suggestion of stimulation of growth of neoplasm by the whole-body exposure to radiation." In a personal communication to Dr. Nickson, Dr. Craver said that some of the patients in this series were still alive 20 to 22 years later without known harmful effects relating to the radiation.

From a series of 30 patients treated with large doses of X-radiation, den Hoed, et. al., (8) report 4 cases with serious complications involving injury of myelopoiesis with agranulocytosis. These cases received 475 to 1800 r.

There is an extensive literature on the use of whole body irradiation in the treatment of polycythemia vera; a couple of references (9, 10) are included without comment.

Mallet (11) reports a series, primarily of lymphoma and leukemia patients treated with total body radiation with good results. Daily doses of 25 to 50 r. of 200 Kv X-ray filtered with 0.5 mm Cu were used, and total doses were 300 to 400 r.

Hempelmann et. al. (12) describe the acute radiation effects suffered as consequences of two nuclear accidents at the Los Alamos Scientific Laboratory. Although the patients in this series received a mixture of several kinds of radiation, the data was used to support the conclusion that 100 r. of 200 Kv X-rays could be delivered to the entire body of a normal subject without causing serious symptoms.

Loeffler et. al. (13) compare the effects in 4 cases with carcinomas irradiated with 50 to 150 r. of 2 million volt X-rays with the effects of nitrogen mustard and triethylene melamine. The irradiated patients did not show appreciable hematologic depression.

As Collins and Loeffler (1) point out, "from the different techniques, using varying formulas of intensity, dose and time, it is difficult to assess the tolerance to whole body irradiation." In discussing their own results (1), "The response of the patients' disease can only be considered as indicative that total body irradiation in single doses up to 200 r. has therapeutic possibilities. The tolerated dose is beyond that necessary or desirable for leukemia, but it is in the effective range for lymphosarcoma and multiple myeloma."

In general, the therapeutic doses of isotopes such as I - 131 and P - 32 are chosen on the basis of their concentration in and therefore selective irradiation of certain special tissues; the whole body dose of radiation is usually too small to serve as a basis for the evaluation of the tolerance to internal radiation. There is every reason, however, to expect the tolerance level to be roughly comparable to that for X-rays.

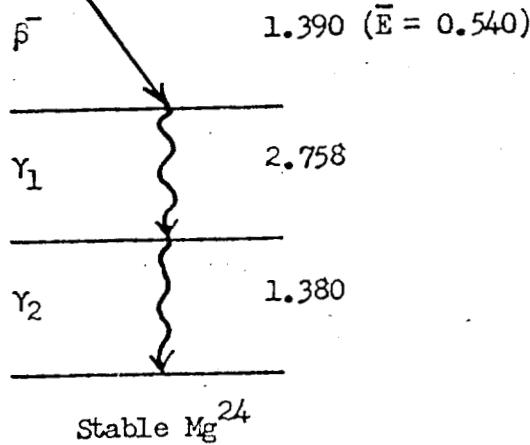
3. Method

For whole body irradiation an isotope which becomes uniformly distributed throughout the body is required. It is also necessary that the material administered does not produce untoward pharmacological effects and that the isotope have a suitable half time. Discussion among the people who will participate in this study led to a selection of sodium - 24 as best fitting the criteria of acceptability. Other isotopes considered were chlorine 38, tritium and fluorine 18. The presently attainable specific activity for Cl³⁸ is not quite high enough for administration of the proposed doses without danger of pharmacological effects. Present production methods for F¹⁸ are inadequate. Tritium would give the most uniform dose but it was decided to start with an isotope having a shorter effective half-life.

4. Physical Characteristics of Sodium 24.

Half-Life: 14.97 hours = 0.625 days

Decay scheme: $^{15}_{\text{Na}}^{24}$



Activation

A^S = saturation activity in Curies/gram

0.46 = Na^{23} (n γ) Na^{24} cross section in barns

3×10^{12} = neutron flux in n/cm² · sec

6.02×10^{23} = atoms/mole

23 = atomic weight of Na

3.7×10^{10} = disintegrations/curie · sec.

$$A^S = \frac{(6.02 \times 10^{23}) (0.46 \times 10^{-24}) (3 \times 10^{12})}{(3.7 \times 10^{10}) (23)} = 0.97 \text{ c/gram of Na}^{23}$$

Beta dose

D_{β} = Beta dose in rep, integrated to infinite time

0.540 = Average beta energy in Mev

0.625 = Half-life in days

0.625/0.693 = Average life in days (to get integral)

$$D_{\beta} = (3.7 \times 10^4 \times 8.64 \times 10^4) (.540) (1.6 \times 10^{-6}) \left(\frac{1}{93}\right) \left(\frac{0.625}{0.693}\right)$$

$$\left(\frac{\text{disintegrations}}{\text{sec./day}}\right) \quad \left(\frac{\text{mev}}{\text{dis}}\right) \quad \left(\frac{\text{erg}}{\text{mev}}\right) \quad \left(\frac{\text{gram rep}}{\text{erg}}\right) \quad (\text{days})$$

= 26.8 rep for 1 mc/kg at time zero

Gamma dose

D_{γ} = Gamma dose in rep for infinite time

0.0191 = $r/\mu\text{c}\cdot\text{hr}$ at 1 cm. from point source

200 = geometry factor $\int_V \frac{e^{-\mu R}}{R^2} dV$ for center of trunk

in 70 kg adult assuming homogenous distribution of Na^{24}

15/.693 = Average life in hours

$$D_{\gamma} = (0.0191) (200) (15/.693) = 82.5 \text{ rep for 1 mc/kg at time zero}$$

$$\left(\frac{r}{\mu\text{c}\cdot\text{hr.}}\right) (\text{grams}) \quad (\text{hr.})$$

Total dose

$$D = D_{\beta} + D_{\gamma} = 109 \text{ rep for 1 mc./kg. at time zero}$$

Therefore 1.38 mc./kg. delivers 150 rep to the center of the body. The center is specified because at the surface the gamma dose is only about half its value at the center, so the total at the skin will be about 68 rep when that in the center is 109 rep. The geometry factor for the extremities is also smaller than that for the trunk, so the dose to them will be correspondingly reduced.

5. Material

The selection of patients is a difficult part of the project, requiring the selection of patients unsuitable for treatment by established procedures, yet in good enough general condition that they will survive long enough for the effects of the irradiation to be studied.

The patients for the proposed studies will be selected by the Radiology Department staff at the Memorial Center, New York City, on the basis of the following criteria:

- a. The patients will have malignant disease and all non-experimental approaches to therapy (local irradiation, surgery, chemotherapy) will have been ruled out because of failure or contraindications. Each patient will have had formal consultations with the Department of Surgery and the Department of Chemical Therapy of the Memorial Center and it will have been stated in writing that the patient is not a candidate for any form of treatment in those departments.
- b. A life span of 6 months or more will be predicted, and benefit to the patient from the radiation can be expected.
- c. Normal nutritional pattern.
- d. Normal liver profile studies (bilirubin, total protein, A-G ratio, alkaline phosphatase, prothrombin time, transeminase, thymol turbidity, cephalin flocculation).
- e. Normally functioning renal tract.
- f. The patient must be maintaining his nutrition by mouth and be expected to maintain this throughout the period of observation.

The irradiation and the studies outlined in this proposal will be conducted at the Brookhaven National Laboratory Medical Center.

6. Baseline Studies.

Studies during the period of a week or so prior to irradiation will include:

- a. Frequent blood cell and platelet counts, hemoglobin and hematocrit.
- b. Plasma sodium, potassium, chloride, carbon dioxide and pH.
- c. Exchangeable sodium, potassium and water, using tracer quantities of Na^{24} , K^{42} , and H_2O .
- d. Oxygen consumption rate, RQ.
- e. Bone-marrow examination.
- f. A slit-lamp eye examination.
- g. A 24-hour urinalysis.
- h. Cr^{51} red cell mass and initiate survival study possibly combined Ashby and/or auto labelling.

7. Dose.

Radioactive sodium, as $(Na^{24})_2CO_3$, will be given intravenously in doses calculated to deliver up to 150 rep total body irradiation. The first few patients will receive half this dose and subsequent patients will receive larger doses deemed to be safe on the basis of accumulated experience.

The following dosage schedule will be used:

<u>To deliver</u>	<u>Inject</u>
75 rep	0.69 mc/kg
100	0.92
125	1.15
150	1.38

Thus, to give a 70kg patient 150 rep will require 96.6 mc of Na^{24} . At the B.N.L. research reactor this activity can be obtained by activation of 100 mg. of Na, or 230 mg. of Na_2CO_3 .

If there is no loss of radioactivity by excretion, the radiation dose will accumulate on the following schedule:

<u>Time</u>	<u>Fraction of infinite-time dose</u>	<u>Rep from 1.38 mc/kg</u>
1 h	0.045	6.7
4.8 h	0.200	30
6 h	0.243	36
12 h	0.427	64
15 h	0.500	75
21.2 h	0.625	94
24 h	0.672	101
30 h	0.750	112
2 d	0.893	134
3 d	0.964	145
4 d	0.988	148
5 d	0.996	149
∞	1.000	150

8. Evaluation and post-treatment studies.

a. Biochemical. Experimental work in animals and, in a lesser degree, in patients indicates that for the dose levels in question little change has been noted heretofore. It seems worthwhile, in order to nail down this point as firmly as possible, to look at short range perturbations in time of the commoner electrolytes and pH of the blood. Included would be a long range evaluation of alterations in total exchangeable potassium. It should be noted that evidence of shift in exchangeable potassium has been noted following doses of the order of 150 r. This evidence is still tentative, but in our opinion, warrants follow-up. Therefore,

after administration of the Na^{24} , bloods will be drawn for the blood chemistry studies for which base line studies were made (plasma sodium, potassium, chloride, carbon dioxide and pH) at intervals to be decided on. The following schedule is tentatively suggested: After 20, 50, 62.5, 75, and 85 per cent of the total radiation dose has been received by the patient.

Exchangeable Na, K and water studies will be made at about four days after the administration of the dose. About 0.01 of the injected Na^{24} will still be in the body at this time; corrections may be necessary for the tracer studies, but should not preclude them.

b. Hematological. Studies performed before irradiation will be repeated at appropriate intervals. If significant platelet depression occurs, appropriate coagulation studies will be performed. Studies will be continued until signs of the acute effects of the irradiation appears to have become unimportant.

9. Radiation dose determinations.

The dose estimates given in this proposal are based on calculations. The chief assumption, that of uniform distribution throughout the body, is open to question, but is as good for sodium as for any other proposed isotope. The rate of exchange of the sodium in the bones with that in the circulation is relatively slow and has a negligible effect on the dose calculations.

Vigorous efforts to obtain determinations of the radiation dose by physical measurements will be made. The techniques to be used have not been agreed upon, but a suggestion being considered is the use of Seivert ionization chambers introduced into the esophagus or other divisions of the gastro-intestinal tract.

As is shown in the dose calculations, the gamma dose will not be uniform throughout the body. It may be necessary to give the center of the body more than 150 r in order to achieve a total-body effect comparable to 150 r delivered by other means.

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11. Summary.

A proposal for studies involving the use of Na²⁴ to deliver whole-body irradiation in selected patients with malignant disease is presented. Permission to deliver up to 150 rep by this method is requested.

12. Approval by the isotope committee:

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