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February 10, 1982

Robert B. Moseley, Jr., M.D.
Chairman, Department of
Radiology
University of New Mexico
Albuquerque, New Mexico 87131

Dear Dr. Moseley:

Enclosed, please find a draft copy of the rebuttal to pink sheets on the radiobiology part of the pion radiotherapy program.

If you need any additional information, please let me know.

Sincerely,

MRRaju

M. R. Raju, Fellow
Toxicology Group

MRR/mg

Enc. a/s

CY: M.W. Bitensky, LS-DO, MS 881
L. Rosen, MP-DO, MS 850
J.N. Bradbury, MP-3, MS 844
S. Bush, UNM/CRTC, MS 809
Dr. Francis Mahoney, N.C.I.

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CLINICAL STUDIES OF PION RADIOTHERAPY

(REBUTTAL)

Radiobiology

Some sections of critique:

"The only deficiency noted in this aspect of the program (cell culture studies) was the lack of detailed OER measurements. However, Dr. Raju is familiar with techniques to answer these questions and can add them easily."

(p. 10, 3rd paragraph)

"The concept of using two tumor systems, one well differentiated and the other poorly differentiated, is a good one. The choice of the mammary tumor, however, seemed poor. . . . ." The reviewers gained a general impression that Dr. Tokita did not have a good grasp of what he wished to accomplish with these studies. They seemed poorly conceived and the tumor models insufficiently defined to test the hypothesis."

(p. 13, 2nd paragraph)

"Dr. Raju, a competent cellular radiobiologist, has neither the training nor the time to perform the studies with the insight Dr. Van der Kogel brings to them. He states, however, that he would take over the project if Dr. van der Kogel left."

(p. 14, 2nd paragraph)

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"The biology program is now centered at LANL and under Dr. Raju's direction since Dr. Yuhas left. Dr. Raju has a good understanding of the needed data. On the other hand, LANL is not strong in the type of tissue and tumor biology required and there is little depth in this area."

(p. 15, 2nd paragraph)

These comments indicate lack of appreciation by the committee regarding the steps that have been taken to improve the quality of radiobiology programs as outlined in the proposal as well as in our presentations. Raju was asked to undertake responsibility for guiding the radiobiology program in October, 1980. Fortunately, he had his own ongoing research grants that are related to this program. He moved quickly using his own resources from his grant and the resources of the Life Sciences Division of Los Alamos National Laboratory (with full permission of the Life Sciences Division) in order to give a healthy start to the radiobiology program during the unexpected transition. Raju persuaded Dr. van der Kogel to join the effort in Late Effect studies. Raju's high standing in the field of particle radiobiology and the expertise and facilities available in the Life Sciences Division, along with the expertize in pathology at the University of New Mexico, helped to attract Dr. van der Kogel. The resources from this program are used only for late effect studies because of the importance of these studies. The expertise and facilities in the Life Sciences Division (such as

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the genetics group, headed by Dr. Ron Walters, and excellent facilities for experimental animals) have been used to strengthen the program. Contrary to the opinion expressed by the Committee, the Life Sciences Division of LANL has very strong expertise and facilities for tissue and tumor biology strengthened by flow cytometry. The radiobiology program in the past did not take advantage of this potential, but this has been fully corrected.

As clearly stated in the radiobiology presentation, the radiobiology component was mostly aimed to assist the clinical program with a minimum budget. Since OER data for pions are already available (Raju et al., B.J.R. 52, 494, 1979) and there is no practical way of using OER data in patient treatment, OER measurements were not considered as a high-priority item.

Regarding the tumor work, we intended to broaden our studies to include a number of other relevant tumor systems as we gain further experience with the existing systems. We consider Dr. Tokita, with his excellent background in radiobiology (Ph.D.) and radiotherapy training with Dr. Frank Ellis, as an excellent addition to the program.

It is unfortunate that Raju's assurance to the site reviewers to make certain the work in progress would not be allowed to founder is misquoted. Raju never said he would take over the late effects project if Dr. van der Kogel was compelled to return to The Netherlands; our plan actually was that Dr. van

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der Kogel either join our staff or return here for periodic consultation. It would have been more appropriate to commend Raju for having recruited Dr. van der Kogel for this project in such a short period of time.

3. Late Effects

a) Beam

The beam being used for localized irradiation of spinal cord, lung and kidney is being criticized for "not being close to any clinical beam" (p. 13, para 4) and again, "In no way is the size of beam used similar to that used clinically." (end of p. 13).

Rebuttal: The fan shaped beam with a 6 cm peak width as used in these studies is a clinical beam tune, being used for dynamic treatments. This beam will be used extensively in future treatments. It is stated in the proposal that the peak width of 6 cm is the smallest in use for clinical applications and will yield an upper estimate of RBE values.

The beam not being flat is inherent in the use of small fields (1.5 - 2 cm wide) not only with pions, but also with neutrons and electons. For the spinal cord this does not affect the results, as long as about 5 mm of the cord receives a uniform dose, which is the case for the beam and collimator used.

For the lung experiments the beam flatness aspect might induce an uncertainty in comparing results for X rays and pions. However, it is indeed possible to compare the results for

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different fractionation schemes and to provide guidelines for optimal clinical schemes and changes in dose per fraction.

b) Lung studies - functional endpoint

"The respiratory rate system has not been tested in these mice nor at Los Alamos altitude."

(p. 13, last para.)

Rebuttal: Changes in respiratory rate after lung irradiation have been measured in several strains of mice, and all show the same base-line respiration rate. Changes after irradiation show the same pattern in different strains.

That the lung studies have less priority than those of the CNS was stated explicitly during the site visit.

c) Carcinogenesis in vivo.

On p. 14, a long critique is given of the work on carcinogenesis in vivo. It is stated twice that "the results will be largely anecdotal."

Rebuttal: Since in the late effects studies animals will be observed for the rest of their life-span, any tumors that develop will be characterized histologically, and the incidence in the various experimental groups will be compared. This is only regarded as a by-product of the late effects studies, to get the maximum possible information out of these expensive studies. This was stated clearly during the site visit.

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Finally, the remark regarding the expectations for the pion beam:

"The proposed biologic advantage of the high LET peak pions appears to be limited; as the beam was spread to cover the target volume, the high LET component fell to about 10% of the dose from fragments and 10% from neutrons, with 80% being low LET."

(p. 1 of the pink sheets)

Rebuttal: This is by no means a new finding. These facts were documented much earlier. "Forty-five percent of the total dose at the negative pion peak was found to be due to stars." (Sullivan and Baarli, Phys. Med. Biol. 13, 434-441, 1968). "Nearly 50% of the dose at the peak of the depth-dose distribution of a pion beam is found to be due to nuclear events." (Raju et al., Phys. Med. Biol. 16, 599-610, 1971). In both cases the peaks were narrow.

The rest of the dose is low LET and it is from ionization loss of pions. It was also known that 50% of the star dose from charged particles is from protons; a large fraction of this is low LET.

Even the OER values were fairly well documented before the program in Los Alamos got started. "The OER appears to be dose dependent and has values of 1.9 and 1.5 at survival levels of 50 and 10 percent respectively. The OER of ^{60}Co gamma rays was 2.6 and 2.3 measured at 50 and 10% survival respectively."

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(Raju, Gnanapahi, Richman, Martins and Barendsen, Brit. J. Radiol. 45, 178-181, 1972).

Recent work indicated that the OER values do not significantly increase with increasing peak width, possibly because of the importance of neutron conbribution. (Raju et al., Brit. J. Radiol. 52, 494-498, 1979).

Hence, the criticism regarding the beam characteristics in different places in the pink sheets:

"The reader is reminded of the two theoretical expectations upon which the entire program was based--that the pion beam would deliver high LET radiation to tumor volume and low LET in the access area and that superior dose distribution might be achieved. Unfortunately, neither of these expectancies appears to have been met."

(p. 26, last paragraph)

"High LET component has been less than anticipated. . ."

(p. 27, line 25)

Our main point regarding the characteristics of pions is that no unexpected pion characteristics (that are disappointing) were found that we did not know before the beginning of the pion project in Los Alamos (from the experimental work at Berkeley, CERN and U.K.).

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