

OFFICE MEMORANDUM

TO : Members of LASL Human Studies Committee
Paul L. Flynn, Donald F. Petersen, Rosemary
Griffith, Harry F. Schulte, David Law

DATE: July 31, 1974 712214

FROM : Robert S. Grier, M.D. RSG.

SUBJECT : Human Studies Committee

SYMBOL : H-2

Enclosed are copies of Dr. Kligerman's protocol for beginning of pion therapy at the Meson Facility, also a consent form. Would you please review these and I will be getting in touch with you so that hopefully we can have a meeting of the Committee in the middle or latter part of the week of August 5th.

RSG/hk

Enclosures

*name with letter David Law
UH Hospital
all 11/11*

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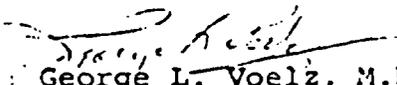
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OFFICE MEMORANDUM

TO : Robert S. Grier, M.D., Chairman
Human Studies Committee

DATE: June 13, 1974

FROM : 
George L. Voelz, M.D., Health Division Leader

SUBJECT :

SYMBOL : H

I have attached a letter I recently received from Dr. Kligerman which describes the current proposal for protocols on treatment of various tumors at LAMPF. I have the protocols at H-DO for review. Since they are fairly voluminous I have not undertaken to copy them but they are available for our use. The Human Studies Committee should be aware of these protocols and make recommendations on their use at LASL facilities.

It is my understanding that some preliminary human radiobiology studies will be made with the LAMPF beam starting possibly in the fall of 1974. These would be lower dose exposures on patients with skin or subcutaneous nodules that could be observed for skin and radiation effects. I do not have a description of these experiments at the present time. We may wish to have Kligerman invited to the next Human Studies Committee meeting to review these plans.

GLV/mjt

Encl. as stated

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THE UNIVERSITY OF NEW MEXICO ALBUQUERQUE, NEW MEXICO 87131
CANCER RESEARCH AND TREATMENT CENTER
MORTON M. KLIGERMAN, M.D., DIRECTOR (A) TELEPHONE 505 277 5411

May 24, 1974

George L. Voelz, M.D.
Health Research Laboratory
H-DO
Los Alamos Scientific Laboratory
P.O. Box 1663
Los Alamos, New Mexico 87544

Dear George:

I am sending you a copy of each of the 14 Phase III protocols for pi meson radiation therapy developed by the Cancer Research and Treatment Center. These protocols will be implemented approximately January 1976 after appropriate biology and pilot clinical studies have been completed. Some 15 institutions throughout the United States, but mainly in the Southwest, have expressed interest in entering patients into these protocols. Control patients will be treated at the participating institutions, while experimental patients will be treated at the LAMPF biomedical facility.

The pion protocols are for the following sites: bladder, brain, hypopharynx, oral cavity, oropharynx, extremities (osteogenic sarcoma), pancreas, prostate, rectum or rectosigmoid, stomach, thoracic esophagus, superior sulcus, and uterine cervix.

The protocols were developed using input of a committee of some 15 radiation therapists from throughout the nation (the Committee on Human Trials of Pion Radiation Therapy, UNM/LASL), and have recently been adopted as the protocols of record by the North American Particle Therapy Committee. Thus, they will be implemented in modified form at all pi meson facilities. At a meeting of our Human Trials Committee in March, Dr. Frederick George of the University of Southern California, who is spending this year at NCI as extramural program director for radiation therapy, commented that our model consent form approved by the group at that meeting, was the first that NCI has seen that is completely responsive to DHEW requirements.

Copies of the consent forms developed for the protocols, based on the model form, are enclosed as well. The protocols and consent forms have been approved by the University of New Mexico Human Research Review Committee, for implementation at the Cancer Research and Treatment Center, Bernalillo County Medical Center, and the Veterans Administration Hospital. They are now being forwarded to Lovelace-Batsan Medical Center and the Los Alamos Medical Center for review and approval.

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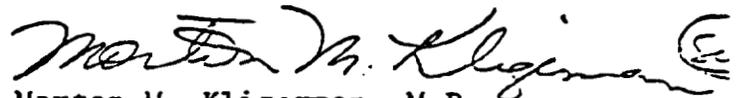
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George L. Voelz, M.D.
Page 2
May 24, 1974

I hope you will find the protocols and consent forms satisfactory. Please remember that the protocols will undergo continuing refinement until clinical trials actually begin. Please let me know if you have any questions about any of these materials.

Sincerely,


Morton M. Kligerman, M.D.

MMK:ps

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EVALUATION OF RADIOBIOLOGICAL EFFECTS OF
NEGATIVE PI MESONS ON
SKIN AND SUPERFICIAL METASTATIC NODULES
OF THE SKIN AND CERVICAL LYMPH NODES

Protocol for Human Radiobiology Studies of
Pi Meson Radiation Therapy at
University of New Mexico/Los Alamos Scientific Laboratory

Morton M. Kligerman, M. D., Director
Cancer Research and Treatment Center
University of New Mexico
Albuquerque, New Mexico 87131

July 1974

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1.0 Summary of the Study

This study will evaluate the radiobiological effects of negative pi mesons on skin and superficial metastatic nodules of the skin and cervical lymph nodes, as an initial step in gathering sufficient human data to begin pilot studies and ultimately Phase III clinical trials of pion radiation therapy at the Clinton P. Anderson Meson Physics Facility in Los Alamos.

The patient population will include patients with multiple superficial or cervical lymphatic metastatic nodules resulting from any type of solid tumor. Multiple nodules within a patient will be randomly allocated to receive either conventional radiation therapy or pi meson therapy. To avoid the possibility of extreme effects during these initial human tumor nodule experiments, doses established for this study will be well within tolerance of normal tissues in our best current experience with conventional therapy. The first series will be based on a conventional dose rate of 4000 rads in nine days, and the next series on a conventional dose rate of 52000 rads, five fractions a week, in 19 days. Patients will receive 50 percent of these doses until effects are assessed. Then the doses will be escalated to 62 percent and 74 percent, depending on results.

Primary endpoints of the study will include regression rate of nodules (area and modified volume), incidence and time of recurrence, changes in ultrastructure and cell kinetics, degree of skin erythema, and incidence of long-term effects. Results of the study will be used to establish a precise radiobiological effectiveness (RBE) value for pi mesons on human skin, tumor nodules, and underlying connective tissue, relative to the RBE of conventional 250 KVP x-rays.

2.0 Introduction and Objectives

2.1 Rationale. This study will evaluate the radiobiological effects of negative pi mesons on skin and superficial metastatic nodules of the skin and cervical lymph nodes, as an initial step in gathering sufficient human data to begin pilot studies and ultimately Phase III clinical trials of pion radiation therapy at the Clinton P. Anderson Meson Physics Facility in Los Alamos. Results will be used to establish a precise radiobiological effectiveness (RBE) value for pi mesons on human skin, tumor nodules and underlying connective tissue, relative to the RBE of conventional 250 KVP x-rays.

Preclinical studies for pion radiation therapy are now underway at Los Alamos. The studies are being conducted under a grant (CA-14052) from the National Cancer Institute to the University of New Mexico Cancer Research and Treatment Center,

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the major portion of which is allocated to Los Alamos Scientific Laboratory. The director of the Cancer Center is also assistant director of radiation therapy at LASL. A separate grant (CA-16127) from NCI to the UNM Cancer Center is providing funds for the human radiobiology studies described in this protocol.

Pions became available in the biomedical channel at Los Alamos on February 6, 1974. After initial tuning and dosimetry, preliminary biological studies were begun in June 1974. Pre-clinical studies with the pion beam were started with cell cultures and will progress to animal studies, with effects of the pion beam on spleen, intestine, skin, kidney, spinal cord, brain, lung, and colon to be observed. Results are being compared with results obtained using 250 KVP x-rays as the control. These studies are expected to continue through May 1976, with the final series to consist of actual treatment of tumors occurring spontaneously in dogs.

However, it is not necessary that all those tests be completed before studies of pion effects on human tissue can start. To provide guidance to the director of the UNM Cancer Center, an ad hoc committee on human radiobiology met in Denver on August 22, 1973. Attendees were Dr. Malcolm Bagshaw, Stanford University; Dr. Seymour Levitt, University of Minnesota; Dr. Rodney Withers, M. D. Anderson Hospital; Dr. D. F. Petersen, Los Alamos Scientific Laboratory; Dr. Paul Todd, Pennsylvania State University (currently on sabbatical at LASL); and Dr. Morton M. Kligerman, UNM Cancer Center director, who chaired the session. The group discussed (1) preliminary studies to be performed prior to human radiobiology studies, (2) dose rate, (3) fractionation schedule, (4) total dose and time period, (5) types of lesions as test systems, and (6) ethics (consent forms and the Declaration of Helsinki).

This protocol was developed using the ad hoc committee's deliberations as a guide. The group decided that human radiobiology should be undertaken as rapidly as possible. Rather than setting a definite schedule before such studies are to be undertaken, it was decided that the human radiobiology program leading to clinical trials should be instituted as soon as investigators believe sufficient laboratory data is available.

The group concluded that the minimum dose rate for human radiobiology studies should be 10 rads per minute in the pion stopping region at the tumor-bearing volume.

Consideration was given to a schedule that would provide optimum opportunity for repopulation of normal cells. It was pointed out that peak pions have a definite shoulder, an indication of the ability of cells to repair sublethal damage. However, the group agreed that this shoulder would

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be less than in conventional radiation. Therefore, the working assumption of the group was that maximum opportunity for preservation of normal tissues would occur with five fractions a week. It was decided this fractionation scheme should be the principal dose schedule during human radiobiology studies, as it was believed this would prove to be the ideal fractionation scheme for clinical trials.

- .. The total dose and time period should be comparable to 7,000 rads in seven weeks of low-LET radiation, modified by the radiobiological effectiveness (RBE) factor. This dose was selected because it is a common schedule for large-volume lesions and because it would provide a reasonable period of time to observe acute effects. It was appreciated that the magnitude of late effects on tumors may not directly follow the degree of acute effects. This may be especially true with late effects on connective tissue, in which case a shorter overall time period of treatment may be less damaging.

* * * * *

This protocol represents a first step toward achieving the type of data prescribed by the ad hoc committee. It was decided that the initial studies should depart somewhat from the committee's recommendations for two reasons:

- a. The practical considerations of the projected on and off schedules of the LASL accelerator until November 1974, and
- b. The need to acquire a substantial amount of data within a relatively short time-frame.

This protocol is designed to take advantage of the early pion beam schedule for the biomedical facility and to acquire data over a period of time with more gradually accelerated dose rates than were originally conceived. As it will be some time before the LASL accelerator can be placed on an eight-week schedule, followed by a down-time of four weeks, we believe the current schedule more useful in the early stages, since an eight/four schedule would permit only five experimental series per year. Thus, it was decided to start human radiobiology studies with the shorter on-time schedules now planned at LASL so a greater number of preliminary experiments could be conducted before the seven-week, five fractions per week definitive treatment schedule is undertaken.

2.2 Objectives. The primary objective of this study is to collect the initial human radiobiology data required before more definitive human radiobiology studies can begin. Patients with multiple superficial metastatic nodules will be eligible for participation in the study. Endpoints to be observed are:

- a. Tumor nodule regression rate (in area and modi-

fied volume).

- b. Incidence and time of recurrence of tumor nodules.
- c. Cellular changes in tumor nodules and surrounding and underlying normal tissue, as determined by examination of biopsy specimens of nodules and underlying connective tissue by light microscopy, electron microscopy, and flow microfluorometry (to determine changes in DNA content).
- d. Acute effects on normal surrounding skin, as determined by the Bewley clinical method employing randomly assigned impartial observers, and as determined by quantitative infrared radiation measurements.
- e. Eventually, incidence of long-term effects on normal surrounding skin and underlying connective tissue.

The purpose of these observations will be to determine the degree of regression and cellular changes in superficial metastatic tumor nodules attributable to pion radiation therapy and to establish an RBE value for pions on human tumor, skin, and underlying connective tissue.

To avoid the possibility of extreme effects during these initial human tumor nodule experiments, doses established for this study will be well within tolerance of normal tissues in our best current experience with conventional therapy. The first series of patients will be given pion radiation to the nodules at 50 percent of the curative dose of conventional 250 KVP irradiation, assuming an RBE of 2.2. The assumed RBE value will be altered depending on the outcome of preliminary biology studies. As early as effects can be measured, the fraction of curative conventional doses will be escalated from 50 percent in 12 percent increments, i. e., to 62 percent and 74 percent of curative doses. In each case, a low-LET control (250 KVP) is included, with clinical and quantitative evaluation of erythema, nodule regression, and cell kinetic parameters. The dose for the first series will be based on a conventional dose rate of 4000 rads in nine days. The next series in this protocol will be based on a conventional dose rate of 5200 rads in 19 days. The fractionation scheme will be increased in increments to four weeks, five weeks, and seven weeks, five fractions a week, as adequate data is collected. Depending on results, the dose may ultimately be escalated to 86, 95, and 97 percent of curative conventional doses.

3.0 Eligibility of Patients

3.1 General condition of eligibility. Any patient with multiple superficial or cervical lymphatic metastatic nodules resulting from any type of solid tumor is eligible

for this study.

3.2 Conditions for patient eligibility. In addition to the above general condition, the following conditions must be met before a patient can be admitted to the study:

- a. Biopsy proof of disease type.
- b. Previous performance of any type of potentially curative therapy (surgery, irradiation, or chemotherapy) will not be cause for exclusion from the study, except as specified under 3.3 below.
- c. Reasonable expectation of completing the study treatment and the required follow-up examination (including travel to and treatment at Los Alamos, as well as required follow-up examinations at the study center in Albuquerque).
- d. Agreement of the patient and his physician to the conditions of the study.
- e. Agreement of the patient's physician to relinquish management of the patient's treatment to the study team.
- f. Understanding by the patient of the provisions of the study, and completion of the required investigational treatment consent form. (Patients must be 21 years of age and legally and mentally competent to give consent for themselves.)

3.3 Conditions for patient ineligibility. The following conditions are cause for exclusion of the patient from the study:

- a. Previous definitive radiotherapy in the area of the superficial nodules.
- b. Ongoing chemotherapy, which, in the opinion of the study team, might compromise the evaluation of results.
- c. Active, uncontrollable infection in the area of contemplated irradiation.
- d. Medical, psychological, or other contraindication to the the contemplated irradiation.

4.0 Treatment

4.1 Pretreatment evaluation. The following will be performed at the study center for patients admitted to the study.

- a. Medical history:

- (1) Age
- (2) Sex
- (3) Race
- (4) Date (month and year) of definite diagnosis of disease
- (5) Description of development of nodules and symptoms and signs
- (6) Other illnesses
- (7) Medications currently used
- (8) Previous therapy

b. Physical examination:

- (1) Height
- (2) Weight
- (3) Temperature
- (4) Performance status (Karnofsky function assessment)
- (5) Drawing of area of superficial and/or cervical nodules with centimeter dimensions and color photographs
- (6) Assessment of degree of coloration of unirradiated skin overlying and surrounding tumor nodules by clinical observation and thermographic measurements, as a reference for later assessing degree of erythema.

c. Laboratory tests:

- (1) Complete blood count
- (2) Platelet count
- (3) Urinalysis

d. Imaging procedures: Chest x-ray.

4.2 Admission to study. Patients will be provisionally entered to the study when the eligibility criteria are met. The pretreatment evaluation will be performed at the study center, after which the patient is formally admitted to the protocol. Copies of all necessary forms, medical records, and photographs will be retained by the study center. Steps for entering patients in the study are as follows:

- a. Initial evaluation and completion of eligibility form. (A copy will be forwarded to the study center.)
- b. Completion of the patient consent form. (A copy will be forwarded to the study center.)
- c. Notification of the study center for assignment of study code number and scheduling of pion radiotherapy.
- d. Completion of pretreatment evaluation at the study center.

4.3 Treatment application. The schedule for this protocol permits the investigators to make optimum use of the planned accelerator schedule of nine days on and five days off, with one 19-day period of continuous operation, between August 10 and October 30. Four nine-day periods and one 19-day period of operation are planned, as shown in the operating schedule depicted in Figure 1.

Peak pion doses administered to patients during the nine-day schedules will be fractions of a curative dose of conventional radiation therapy of 4000 rads, nine fractions, in nine days, modified by the RBE factor. Doses administered during the 19-day schedule will be fractions of a curative dose of conventional radiation therapy of 5200 rads, five fractions a week, in 19 days, as shown in Figure 2. The peak pion doses for each series will be radiobiologically equivalent to the following conventional radiation dose schedules:

- a. Series 1: 2000 rads, nine fractions, in nine days.
- b. Series 2: 2480 rads, nine fractions, in nine days.
- c. Series 3: 2960 rads, nine fractions, in nine days.
- d. Series 4: 2960 rads, nine fractions, in nine days (same as Series 3).
- e. Series 5: 2600 rads, five fractions a week, in 19 days.
3224 rads, five fractions a week, in 19 days.
3848 rads, five fractions a week, in 19 days.

The above doses are those to be used for the 250 KVP control series. The doses for peak pions will be obtained by dividing those doses by the RBE for peak pions (currently assumed to be approximately 2.2, but this value will be modified as warranted by results of preliminary biology experiments). A minimum of nine nodules for each nine-day series and a minimum of 18 nodules for the 19-day series will be required to test the pion treatment regimen. An equal number of nodules will be required for each series for irradiation with equivalent doses of 250 KVP x-rays as the control. Each patient will have nodules treated with both pion and 250 KVP x-rays, so that each patient serves as his own control.

Patients will receive treatment as outpatients at LAMPF and will stay in Los Alamos for approximately 30 days following the end of their series of exposures so that acute effects can be assessed. Outpatient housing will be provided through

an agreement between the UNM Cancer Research and Treatment Center with the Los Alamos Medical Center, and inpatient facilities of the Los Alamos Medical Center will be available should they be required.

Radiation may be interrupted or discontinued for other causes, when required (as determined by the study team). However, data concerning those patients whose treatment is interrupted or discontinued may be excluded from the study if warranted.

5.0 Randomization

The multiple nodules within a patient will be randomly allocated to receive either conventional radiation therapy or pi meson therapy. The randomization in Series 1 through 4 will be such that half the nodules within a patient will receive conventional therapy, and the remaining half of the nodules will receive pi meson therapy. For Series 5, the randomization scheme will occur within a patient equally often.

6.0 Endpoints

Primary endpoints will be related to erythema, regression rate, and cell kinetics. In addition, an RBE value for underlying connective tissue will be established. Specific endpoints and procedures for collecting the necessary quantifying data are:

6.1 Regression rate

- a. Area. To measure regression in area, each irradiated nodule will be measured daily at its widest vertical and horizontal point, and the area estimated using the following formula:

$$\text{Area} = \frac{\pi}{4} \times (\text{widest vertical distance}) \times (\text{widest horizontal distance})$$

- b. Volume. To measure regression in volume, daily measurements will be taken using a rubber diaphragm water system. It is appreciated that this will measure only that portion of the tumor which is not sub-surface.

6.2 Incidence and time of recurrence. Incidence of recurrence of irradiated tumor nodules will be observed and recorded while patients are on study in Los Alamos and will be continued at participating institutions. Time between end of treatment and recurrence will be recorded.

6.3 Changes in ultrastructure and cell kinetics. Specimens of tumor nodules, surrounding irradiated normal skin, and underlying connective tissue will be taken by biopsy at appropriate intervals. The specimens will be examined by light microscopy and electron microscopy to determine

changes in cellular morphology. The potential exists, as demonstrated by neutron therapy trials, that the late changes in connective tissue do not correlate well with acute changes, as one is accustomed to seeing with conventional radiation. Identification of ultrastructural changes may be helpful in anticipating such late effects. The specimens will also be examined by flow microfluorometric techniques to determine changes in DNA content and to identify relationships between cellular damage due to irradiation and the various phases of the cell reproductive cycle for tumor tissue and for surrounding and underlying normal tissues.

6.4 Degree of skin erythema. Observations will be made daily to determine if a pattern of erythema development occurs. Suitable intervals for observations will then be determined. Observations will be of two types: (a) clinical, and (b) thermographic.

- a. Clinical observations. Subjective clinical evaluation of treatment sites will follow the "degrees of skin reaction" reported by Bewley et al. (1963), in which independent observers score the skin reaction on a scale of 0 to 5 by assigning the following values: 0, no visible reaction; 1, slight erythema; 2, erythema; 3, marked erythema; 4, moist desquamation of less than half the field; and 5, moist desquamation of more than half the field. Since dose levels will start at 50 percent of a curative conventional dose (or only 2000 rads, nine fractions, in nine days) and will be escalated successively by 12 percentage points to 62 and 74 percent of curative dose, injury to the patient due to moist desquamation or necrosis will be avoided. Subsequently, doses will be increased by small intervals (six and three percentage points) to tolerance.
- b. Thermographic measurements. Thermographic measurements will take advantage of quantitative and qualitative measurement of infrared wave lengths emanating from treatment sites and surrounding normal skin. Responses will be standardized against a constant infrared source to permit correction for pigmentation developing during the course of treatment, and results will be expressed numerically by electronic conversion of the input infrared wavelengths to a visible color scale. Thus, display will provide a direct, visible spectrum color rendition of the treatment site which can be evaluated visually with respect to both size and intensity of reaction and in terms of numerical output read on a scale of 1 to 100, which is informative both by difference from examination to examination and in absolute terms related to the input infrared spectrum.

6.5 Incidence of long-term effects. Patients will be ob-

served at monthly intervals for the first year, and at intervals of three months for the next two years to assess long-term radiation effects. Experience with neutron radiation therapy at the Texas A & M University cyclotron facility showed that most late effects had appeared by 13 months. Severe fibrosis could develop between six to eight months. Occasionally it occurred at four months with overlapping fields and very high doses. Because of the initial low doses and the cell kinetics studies planned for this protocol, it is anticipated that the occurrence of extreme long-term effects will be prevented.

7.0 Number of Patients Required

To provide a minimum of 18 modules for study during each nine-day period of exposure, it is estimated that a minimum of five patients with multiple nodules will be required per series. For the four periods of nine days each, a total of 20 patients will be needed. A total of 10 patients are estimated to be required to provide a minimum of 36 nodules for study during the single 19-day period of continuous operation, for a study total of 30 patients. Half the nodules in each series will be treated with peak pions, and the remainder will be treated with 250 KVP x-rays.

Biopsy material to be collected during the study will be taken at different intervals from different patients. Thus, it is expected that no patient will have more than one nodule biopsy during or after treatment to provide tissue for the cell kinetic and ultrastructure studies.

8.0 Additional Therapy

Wherever possible, unless deemed advisable by the study team and/or the patient's responsible physician, treatment of irradiated nodules (e. g., surgery, additional radiation therapy, or chemotherapy) should not be instituted prior to 100 days after the start of radiation exposure under this study. In the event that surgery or a biopsy is performed, the excised tissue or biopsy specimen should be carefully examined by a pathologist at the Albuquerque study center.

Any therapeutic measures deemed medically advisable in managing the patient's disease may be instituted while the patient is on the study or afterward, although data from a patient whose radiotherapy is interrupted may be deleted from the study.

9.0 Study Parameters

Parameters to be recorded throughout the study include:

- a. Degree and time of regression and regrowth
- b. Assessment of acute radiation effects

c. Assessment of long-term radiation effects.

10.0 Follow-up Schedules

The purpose of follow-up examinations is to assess acute and long-term effects of irradiation. The first day of radiation exposure is considered Day 1. Follow-up examinations will be reported monthly for the first year after Day 1, and every three months for the next 24 months.

.. If a study patient cannot return to the Albuquerque study center for follow-up examinations, arrangements will be made to have him examined at another participating institution or by his private physician and a report of this examination will be submitted. The following information will be recorded on the follow-up form at each visit:

- a. Brief interim history
- b. Drawing of area of superficial and/or cervical nodules with centimeter dimensions, and color photographs
- c. Description of any changes in irradiated area (particularly those related to recurrence or to long-term radiation effects, such as fibrosis or necrosis)
- d. Biopsy (when indicated for recurrence, with the date of recurrence fixed as closely as possible)

Patients admitted to this study will be examined at least annually at the study center in Albuquerque. Deaths of study patients will be reported to the study center.

11.0 Pathology

11.1 Biopsy specimens. Biopsy specimens will be examined by pathologists at the study center prior to entry of the patient in the study, and periodically thereafter as biopsies are obtained to examine radiation or recurrence.

11.2 Autopsies. It is not necessary that autopsies be performed on all study patients. However, when a post-mortem study is performed it should include, if possible, a description of tissues irradiated under this study, with a report and representative microscopic slides forwarded to the study center for review by the study pathologist.

12.0 Records

Two copies of each study form must be submitted to the study center. Data will be recorded on standard forms to be supplied to participating institutions for storage, retrieval, and analysis at the study center:

- a. Photocopy of patient consent form

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- b. Patient eligibility form
- c. Pretreatment evaluation form
- d. Study entrance form
- e. Treatment summary form:
 - (1) Treatment schedule (including dose rate and copies of port films and isodose curves)
 - (2) Evaluation of treatment
 - (a) Daily measurements of area and volume of irradiated nodules
 - (b) Clinical erythema assessment
 - (c) Thermographic measurements
 - (3) Complications during therapy
- f. Follow-up form:
 - (1) Incidence and time of recurrence
 - (2) Assessment of acute effects
 - (3) Assessment of long-term effects
- g. Pathology forms (submitted to the study center pathologist as applicable):
 - (1) Biopsy reports (on acceptance for study and as biopsies are taken to assess acute and/or long-term effects of irradiation or tumor recurrence)
 - (2) Death reports (submitted with 30 days of patient death):
 - (a) Date and place of death
 - (b) Cause of death
 - (c) Clinical description of irradiated area at death (if possible)
 - (d) Microscopic examination of irradiated area at death (if autopsy is performed)

Forms a through d should be submitted to the study center upon acceptance of the patient into the protocol. Form e should be completed by the study center within 30 days after the end of treatment. Form f should be submitted within 30 days after each follow-up examination, and as rapidly as possible if long-term radiation effects are observed. Pathology forms are to be submitted as noted above.

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The necessary study forms to support data collection and analysis are currently being designed under the direction of the senior statistician assigned to the study team. The forms will be precoded to facilitate computerized data analysis.

13.0 Patient Consent and Peer Judgment

All institutional, Food and Drug Administration, and National Cancer Institute regulations requiring submission to the institutional human experimentation committee and the use of procedures for obtaining and recording informed consent will be followed. A patient may be removed from the study if the study is not in the best interest of the patient. A patient may withdraw voluntarily from the study at any time, as will be indicated in the consent form.

14.0 References

Bewley, D. K.; Fowler, J. F.; Morgan, R. L.; Silvester, J. A.; Turner, B. A.; and Tomlinson, R. H. Experiments on the skin of pigs with fast neutrons and 8 MeV x-ray including some effects of dose fractionation. Brit. J. Radiology 136:107-115, 1963.

Start Date	10 Aug	19 Aug	24 Aug	2 Sept	7 Sept	16 Sept	21 Sept	30 Sept	12 Oct	31 Oct
Days On	9		9		9		9		19	
Days Off		5		5		5		10		
No. of Nodules	18		18		18		18		36	Long down
% of Conventional Curative Dose*	50%		62%		74%		74%		50% 62% 74%	

* For 9-day schedule = 4000 rads for 9 days (9 fractions)

For 19-day schedule = 5200 rads for 19 days (15 fractions)

Figure 1. Protocol Operating Schedule

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Curative Conventional Dose Rate

No. of Days	No. of Fractions	Total No. of Rads.	50%	62%	74%	86%	93%	97%
9	9	4000	2000*	2480*	2960*	3440	3720	3880
19	5/wk	5200	2600*	3224*	3848*	4472	4836	5044
26	5/wk	5700	2850	3534	4218	4902	5301	5529
33	5/wk	6200	3100	3844	4588	5332	5766	6014
40	5/wk	6600	3300	4092	4884	5676	6138	6402
47	5/wk	7000	3500	4340	5180	6020	6510	6790

* Dose rates applicable to this protocol.

Figure 2. Dose Delivery Schedule for Human Skin and Superficial Metastatic Nodules of the Skin and Cervical Lymph Nodes.

Pion Protocol: Metastatic Nodules of Skin and Cervical Lymph Nodes

Name of Institution

Address of Institution

PATIENT CONSENT FORM FOR PARTICIPATION IN A
STUDY TO EVALUATE EFFECTS OF NEGATIVE PI MESON
RADIATION ON SKIN AND SUPERFICIAL METASTATIC
NODULES OF THE SKIN AND CERVICAL LYMPH NODES

Purpose of the Study

Your physician has determined that you may be an eligible patient for participation in a study to compare the effects of negative pi meson radiation with the effects of conventional x-rays on superficial metastatic nodules of the skin and cervical lymph nodes and normal surrounding skin. The study is being conducted using equipment at the Clinton P. Anderson Meson Physics Facility in Los Alamos. Pi meson radiation is a new treatment form. Researchers believe it may offer additional advantages over conventional therapy, although this must be established.

Tests of pi meson radiation on human tissue are just beginning. Although limited biology experiments have been conducted since 1965 at Berkeley, California, pi meson radiation has not been produced in doses suitably large for medical use until the equipment at Los Alamos was constructed. Some preliminary biology tests, using the Los Alamos equipment, have been conducted, but this is the first series of tests on human beings. No attempt will be made in this series of tests to cure your disease; pi meson radiation does not have the potential for curing cancer after it has spread to several areas of the body. What is being attempted is to determine the differences between relatively low doses of pi meson radiation and conventional x-rays in the ways they affect human tumor tissue close to the skin surface and normal surrounding skin. This will help provide a basis for designing more extensive tests and ultimately tests which will determine whether pi mesons are more advantageous than conventional x-rays in curing cancer in humans. Thus, your participation may help others who contract some forms of the disease in the future.

Procedures to be Followed

If you choose to enter the study, you must agree to spend the required amount of time at the University of New Mexico Cancer Research and Treatment Center in Albuquerque for some preliminary tests and the required amount of time in Los Alamos for treatment. You must also agree to return to the UNM Cancer Center for the required follow-up examinations.

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You will receive radiation treatments at the Los Alamos Scientific Laboratory Clinton P. Anderson Meson Physics Facility, for a period of nine/nineteen days and will need to remain in Los Alamos for 30 days after the treatments end so that physicians can assess the short-term radiation effects. Some nodules will be treated with pi meson radiation, and some will be treated with conventional x-rays, so that differences in the two types of radiation can be determined. Treatments will be given daily for nine days, or five days a week for three weeks, depending on the series to which you are assigned. A small amount of tissue from one or more of the treated areas may be excised so it can be examined under a microscope.

While you are taking part in the study, your physician is still responsible for your treatment and can change your treatment or remove you from the study at any time if he believes it to be in your best interest. Your well-being is his primary concern. While you are taking part in the study in Los Alamos, your treatment will be managed in close cooperation with your physician, although he may not be administering the treatment himself.

Potential Benefits

The potential advantage of pi meson therapy is that it may be effective in treating patients who require more than standard management. At this early stage, it will not give you any long-term benefits, although it should cause those nodules which are treated to shrink in size. The conventional radiation administered should also cause shrinkage of an approximately similar amount. The test is designed to try to match the effects of the pi mesons as closely as possible with those of conventional x-rays, and then to compare differences in dose levels required to produce essentially the same kinds of effects. The shrinkage caused by this irradiation may be only temporary, however.

Possible Discomforts and Risks

We do not have complete information on the risk you may encounter due to pi meson radiation. Preliminary biology tests indicate the procedure will not be unduly harmful, and low doses are being given in these early studies to avoid the possibility of excessive discomfort or risk. Pi meson radiation and conventional radiation administered to areas with metastatic skin nodules could result in some or all of the following types of discomfort and risk:

1. Skin reaction in the treatment area (for example, redness and peeling, possibly with ulceration).
2. Loss of hair in the treatment area.
3. Loss of muscle tissue in the treatment area.
4. Damage to nerves of the extremities with weakness or paralysis and sensory deficit.
5. Thickening of the tissues under the skin.
6. Pain and swelling of normal tissues in the treatment area.

Pi meson and conventional radiation administered to metastatic nodules in the region of the head and neck could result in some or all of the following additional types of discomfort and risk:

1. Difficulty in swallowing and sore throat.
2. Temporary or chronic ulcers of the lining of the mouth or throat.

The incidence of these is known and has been established in conventional radiation. What is not known is the incidence of these or other effects which may occur with pi meson radiotherapy.

Patient Costs

Cost of your transportation to Albuquerque and of tests performed at the UNM Cancer Center to evaluate your condition before treatment will be paid by research funds. The cost of your transportation to and from Los Alamos, room and board while you are in Los Alamos receiving treatment, and other medical expenses resulting from radiation treatment in Los Alamos will be paid by research funds, since the meson facility is a national facility supported by research funding.

In addition, the cost of your transportation to and from Albuquerque for an annual physical examination, and associated non-routine medical expenses for the examination, will be supported by research funds.

If questions arise concerning reimbursable costs, the _____
(Name of State)
Professional Standards Review Organization will serve as an arbiter.

Your Rights as a Patient

Federal law requires that you signify your willingness to participate in this study. Your physician will explain the study to you in detail so that you understand it to your satisfaction. Please ask him any questions you may have.

You have the right to refuse to participate in the study. If you choose to participate, you can still withdraw voluntarily at any time. In addition, your physician can remove you from the study at any time if he believes it is in your best interest. Furthermore, be assured that your doctor will treat you to the best of his ability if you choose not to enter the study. Your decision not to enter the study will in no way adversely affect your right to receive whatever treatment he deems necessary.

The director of the pi meson radiation therapy program has the final responsibility for accepting or rejecting patients for pi meson radiation therapy, and can reject anyone he feels would not be an appropriate patient for the study.

* * * * *

Patient's Name: _____

Address: _____

Hospital/Clinic: _____

Hospital/Clinic I. D. Number: _____

Social Security Number: _____

Study Number: _____

I, _____, hereby expressly consent to participate in the study to evaluate effects of negative pi meson radiation on skin and superficial metastatic nodules of the skin and cervical lymph nodes. I have read the above description of the study, and Dr. _____ has explained to me personally the details concerning it. My questions concerning the study have been answered and I fully understand the procedures to be performed and the probable results, including the risk of the occurrence of complications described above.

I agree to be entered into the study. No guarantees or assurances have been given to me by anyone regarding the results that may be obtained, and I understand that this study offers no potential for curing my disease or for prolonging my life. I further understand that I may withdraw from participation in the study at any time. I also understand that the director of the pi meson radiation therapy program has the final responsibility to accept or reject me for this study if for any reason he feels I would not be an appropriate patient.

Date: _____ Time: _____ Signed: _____
(Patient)

Witness

Witness

cc: Patient
Clinic Chart
Radiation Oncology Folder
Patient's Physician
Cancer Research and Treatment Center, University of
New Mexico, Albuquerque, New Mexico

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