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FERMILAB NEUTRON PROTOCOL
FOR
PHASE II STUDIES

Protocol to Study Neutron Irradiation in the
treatment of non-resectable tumors of Salivary
Gland, Pancreas, Lung, and other selected sites.

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FERMILAB PHASE II, NEUTRON STUDY

1.0 Background

Initial neutron studies at several centers around the world and at the Fermilab Cancer Treatment Facility, have demonstrated the effectiveness of neutrons in a selected group of tumors and have developed reasonable preliminary data on the tolerances of various normal tissues to neutron therapy. In general, the RBE for neutrons varies with the neutron energy being somewhat less for higher energy neutrons. The Fermilab RBE is estimated to lie between 2.7 and 3.0. The Fermilab neutron beam has skin sparing aspects and depth dose distribution closely approximating that of a 4 MeV photon beam. This permits comparable treatment planning, set up techniques, and skin protection for the treatment of deep seated tumors. New information is now desired on the response of a variety of tumors that do not ordinarily respond well to low LET treatment, presumably because of poor oxygenation and/or poor re-oxygenation during fractionation. Tumors to be considered include: inoperable or recurrent salivary gland tumors, localized non-resectable carcinoma of the pancreas, non-resectable soft tissue and bone sarcomas of all varieties, malignant melanoma with definable measurable lesions not suitable for other forms of treatment, and bronchogenic carcinoma with measurable lesions, and non-resectable adenocarcinomas in various sites.

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Phase II Neutron Study

Schema

<u>Tumors</u>	<u>Neutron Dose</u>	<u>Evaluations for all Studies</u>
Salivary	2000 to	Rate of tumor regression
Pancreas	2500 rad	Fraction of patient responding
Sarcomas	in	Duration of Response
Melanoma	5-7 weeks.	Acute and normal tissue reactions
Selected Adenocarcinomas	appropriate	Late normal tissue reactions
Miscellaneous radioresistant tumors	appropriate	

In specific sites (e.g. lung, CNS) dosage will be reduced appropriately.

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2.0 Objectives

- 2.1 To further define tolerances of normal tissues in deep locations such as: gastrointestinal tract, lung, and genitourinary system.
- 2.2 To quantitate the response frequency and duration in a variety of tumors ordinarily considered non-responsive to low LET radiation.
- 2.3 To establish preliminary data on which to base further randomized Phase III studies.

3.0 Patient Selection and Eligibility Criteria

- 3.1 All patients will have histologic proof of malignancy;
- 3.2 The disease should be too advanced for conventional management of the specific type on study, or otherwise on current standard treatment methods;
- 3.3 The patient should have an estimated life expectancy of at least four months;
- 3.4 The patient should have (Karnofsky) performance status of 40% or better;
- 3.5 The patient should have disease that is measurable, either clinically or radiographically;
- 3.6 The patients must sign an informed consent indicating that they are aware of the investigational nature of the study. Consent forms must be consistent with the policy of the Fermi Laboratory and the institution from which the patients come.

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3.7 Patients that have failed prior chemotherapy must be off all chemotherapy at least one month prior to entering the study;

3.8 Patients must not have had previous irradiation to the proposed radiation target volume.

4.0 Pre-Treatment Evaluation

4.1 General evaluation--a complete history and physical examination including the documentation of all measurable disease. Special attention should be directed to the normal tissues that would be encompassed in the treatment volume.

4.2 A radiologic evaluation of all radiologically demonstrable lesions should be secured.

4.3 A general laboratory evaluation including CBC and other parameters appropriate for the tumor in question.

5.0 Registration

This is a non-randomized Phase II study designed to accumulate information on the response of a variety of resistant tumors and the tolerances of the normal tissues contiguous to these varying tumor sites. Information will be recorded as to the stage, histopathology, and performance status prior to therapy. A minimum of 10 patients in each tumor category will be entered prior to closing of the study.

6.0 Radiation Therapy Parameters

6.1 All patients will be treated with the neutrons alone or with photons mixed (2 fr. n + 3 fr. ph.) or neutron boost.

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- 6.2 Simulation and/or neutron portal films will be secured to ensure encompassing of the entire tumor and at least one cm. of normal tissue beyond the defined tumor margin.
- 6.3 Doses will be specified as minimum target volume doses. The "prescribed dose" will be, in general, 10% higher.
- 6.4 The portals chosen will be defined by the disease site and are at the discretion of the Radiation Oncologist.
- 6.5 When used alone, the neutron dose should, in general, be between 2000 and 2500 rad, over a five to seven week schedule. The number of fractions per week may be one to four. Where neutrons are used with photons a total equivalent dose should be 6600-7400 rads in six to eight weeks, assuming an RBE = 3.0.
- 6.6 Time dose modifications are permitted for patient illness, transportation, logistics, or other appropriate reasons. However, such modifications must be accurately recorded for further evaluation.
- 6.7 Documentation of the completion of therapy and the treatment chart must be maintained.

7.0 Study Parameters and Criteria of Response

- 7.1 Regression of the tumor is observed in relation to both the initial response (a function of cellular radiosensitivity and growth parameters) and the end-result (cure or recurrence). The immediate response is assessed from a series of dated volume measurement, before, during and after the course of treatment. End-results are determined

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by serial follow-up, noting the dates of maintained remission or of recurrence. From this information the following observations will be recorded:

- (1) Initial tumor volume (at first treatment);
- (2) Observed pre-treatment growth rate;
- (3) Rate of macroscopic regression following treatment;
- (4) Period of observation without recurrence (updated annually);
- (5) Time to appearance of first recorded recurrence;
- (6) Tumor volume at time of observed recurrence;
- (7) Observed post-recurrence growth rate.

7.2 Normal tissue reactions are expected to appear after a latent interval, ranging from a few days to many years and vary widely in severity. To record this information, reactions observed will be at suitable intervals and graded at each visit. As a general guide to grading reactions, the following ten-level ranking procedure has been adopted:

- 0 = No detectible reaction
- 1 = Doubtful, suspected, or threshold response
- 2 = Transient radiation effect
- 3 = Minimal long-lasting radiation reaction
- 5 = Permanent radiation injury or limited extent

6 = Extensive radiation injury but no necrosis

7 = Extensive damage with limited necrosis

8 = Massive necrosis of irradiated volume

9 = Unknown or data not available

A detailed normal tissue reaction code, applicable to specific organs and tissues on the basis of described above is appended.

8.0 General Management: Additional Treatment and Criteria for Removal from Study

8.1 Patients must have all necessary general medical supportive care including nutritional support, control of infections, blood replacement, and analgesic requirements.

8.2 Patients shall be removed from the study at any time at their request or if unacceptable side effects develop. If their functional status should deteriorate without obvious explanation preventing their out-patient attendance at the facility, they will also be removed from the study but followed to evaluate their response to whatever dose had been delivered.

0.0 Statistical Considerations

9.1 This is a non-randomized Phase II Study to develop information of the response of tumors ordinarily resistant to radiation and the effects of neutrons on tissues contingent to such tumors.

9.2 At least 10 patients in each tumor type will be entered on study.

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9.3 The currently utilized on study and evaluation forms for the neutron program will be used in this protocol.

10.0 Special Consultants

The Radiologic Physics Center Neutron Section has already intercompared the varying neutron facilities. Their input to evaluation of consistency and comparable dosimetry will be ongoing.

11.0 Patient Consent Forms

The consent form currently in use for all patients at Fermilab will be used.

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APPENDIX
DOSE-TIME FACTORS
CODING SYSTEM FOR NORMAL TISSUE REACTIONS
AND HIGH DOSE EFFECTS

A. GENERAL GUIDE

- a) The affected organ, system or tissue will be identified by the conventional anatomical code (3 digits).
- b) Specific reaction levels will be defined for each organ or system of interest, using a single-digit decimal code, numbered 0 to 9.
- c) A general guide to coding, compatible with the specific levels to be described, can be used to devise a code for any tissues not covered in the specific list.
- d) The general guide is coded as follows:
 - 0 = No detectible reaction.
 - 1 = Doubtful, suspected or threshold response.
 - 2 = Transient radiation effect.
 - 3 = Minimal long-lasting radiation reaction.
 - 4 = Permanent radiation injury of limited extent.
 - 5 = Marked radiation damage (high-dose effect).
 - 6 = Extensive radiation injury.
 - 7 = Extensive damage with limited necrosis.
 - 8 = Massive necrosis of irradiated volume.
 - 9 = Unknown or data not available.

B. SPECIFIC SYSTEMS IN WHICH WELL-DEFINED RADIATION REACTIONS ARE KNOWN TO OCCUR

I.	SKIN	Acute Reaction	Late Effects
II.	MUSCULO-SKELETAL	Bone	Joints
III.	RESPIRATORY	Lung	Larynx
IV.	VASCULAR	Peripheral Vessels	Heart and Pericardium
V.	R-E SYSTEM	Hemopoietic Marrow	Lymph Nodes
VI.	G-I TRACT	Salivary Gland	Oropharynx
		Liver	Bowel
VII.	G-U SYSTEM	Kidney	Bladder
		Testes	Ovary
VIII.	ENDOCRINES	Thyroid	
IX.	NERVOUS SYSTEM	CNS	Peripheral Nerve
		Eye	

C. SPECIFIC REACTION CODES

I. SKIN

<u>LEVEL</u>	<u>SKIN (Acute)</u>	<u>SKIN (Late)</u>
0	Nil	Nil
1	Threshold Erythema	Minimal Pigmentary Reaction
2	Erythema (1°)	Predominant Pigmentation
3	Erythema & Desquamation	Pigment Mosaics/Clones
4	Dry Desquamation Reaction (2°)	Predominant Depigmentation
5	Desquamation & Blistering	Telangiectasia
6	Moist Exudative Reaction (3°)	Combined High-Dose Effect; Atrophy
7	Small Necrotic Ulcer or Slough	Persistent Trophic Ulcer
8	Massive Acute Skin Necrosis	Ischaemic Necrosis
9	UNKNOWN	UNKNOWN

II. MUSCULO-SKELETAL SYSTEM

<u>LEVEL</u>	<u>BONE</u>	<u>JOINT</u>
0	Nil	Nil
1	Threshold Effect (e.g. scan)	Threshold Effect
2	Growth Restraint, Stunting	Transient Function Loss
3	Reduced Density, Resorption	Persistent Minimal Function Loss
4	Spontaneous Fracture	Marked Function Impairment
5	Osteitis, Local Lesion	Peri-articular Fibrosis "Frozen"
6	Extensive Aseptic Necrosis	Non-infective Degenerative Arthritis
7	Ostemomyelitis or "Osteoradionecrosis"	Joint Involvement in "Bone Necrosis"
8	Massive Necrosis of Treated Volume	Massive Necrosis Involving Joint
9	UNKNOWN	UNKNOWN

III. RESPIRATORY SYSTEM

<u>LEVEL</u>	<u>LUNG</u>	<u>LARYNX</u>
0	Nil	Nil
1	Cough, Suspected Minimal Pneumonitis	Slight Hoarseness
2	Transient Effusion or Pleuro-pneumonitis	Transient-mucositis of Larynx
3	Minimal Pleural Reaction or Fibrosis	Severe Irradiation Laryngitis
4	Limited Pleural Thickening/ Fibrosis	Membranous Reaction
5	Marked Localized Fibrosis	Transient Chondritis, No Edema
6	Extensive Significant Fibrosis	Persistent Chondritis or Edema
7	Massive Fibrosis, Crippling	Chondronecrosis, Septic Chondritis
8	Massive Necrosis Involving Lung	Massive Necrosis of Larynx
9	UNKNOWN	UNKNOWN

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IV. VASCULAR SYSTEM

<u>LEVEL</u>	<u>ARTERIES AND ARTERIOLES</u>	<u>HEART AND PERICARDIUM</u>
0	Nil	Nil
1	Asymptomatic Physiological Changes	Asymptomatic EKG Changes
2	Transient Increased Endothelial Permeability	Transient Pericardial Effusion
3	Persistent Endothelial Defect; Mild Telangiectasia	Persistent Asymptomatic Effusion
4	Minimal Endarteritis; Telangiectasia	Fibrous Pericarditis; Limited
5	Endarteritis with Ischemia	Severe Constrictive Pericarditis
6	Extensive Arteritis, Severe Ischemia	Coronary Endarteritis, Angina
7	Arterial Occlusion and Gangrene	Coronary Sclerosis or Infarct
8	Massive Necrosis of Vessels	Massive Necrosis of Heart
9	UNKNOWN	UNKNOWN

V. RETICULO-ENDOTHELIAL SYSTEM

<u>LEVEL</u>	<u>HEMOPOIETIC MARROW</u>	<u>LYMPHNODE</u>
0	Nil	Nil
1	Physiologic Changes, e.g. Fe-uptake	Physiologic Changes; e.g. Immunologic
2	Transient Depression of Function	Transient Depression of Barrier Function
3	Persistent Depletion of Blood Cell Precursors	Persistent Depletion of Lymphoid Elements
4	Marked Cellular Depletion, All Elements	Marked Cellular Depletion
5	?	?
6	Complete Fibrous Replacement of Hemopoietic Marrow	Complete Obliteration of Lymphnode; Fibrous Replacement
7	?	?
8	Massive Necrosis	Massive Necrosis
9	UNKNOWN	UNKNOWN

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VI. GASTRO-INTESTINAL TRACT

<u>LEVEL</u>	<u>STOMACH AND SMALL BOWEL</u>	<u>LIVER</u>
0	Nil	Nil
1	Transient Nausea, Hypochlorhydria, Dyspepsia	Asymptomatic Abnormal Physiologic Parameters
2	Transient Enteropathy (Diarrhea)	Transient Functional Impairment or Abnormal Scan
3	Persistent Malabsorption or Achyilia	Persistent Local Defect (Abnormal Scan)
4	Ulcer or Intermittent Obstruction	?
5	Extensive Fibrosis or Chronic Ulcer	"Radiation Hepatitis"
6	Stricture or Perforation Requiring Surgery	?
7	Limited Necrosis or Infarction	Extensive Cirrhosis, Liver Failure
8	Massive Necrosis of Bowel	Massive Necrosis of Liver
9	UNKNOWN	UNKNOWN

<u>LEVEL</u>	<u>SALIVARY GLAND (and taste sense)</u>
0	Nil
1	Transient Aberration of Taste or Salivation
2	Temporary Suppression of Salivation with Dry Mouth
3	Partial Loss of Taste; Persistent Lack of Saliva
4	Complete Loss of Taste; Non-functioning Salivary Gland
5	Complete Obliteration of Salivary Gland
6	Extensive Replacement Fibrosis
7	Necrotic Ulcer
8	Massive Necrosis
9	UNKNOWN

VI. GASTRO-INTESTINAL TRACT (Continued)

UPPER AERODIGESTIVE TRACT (oral cavity, naso-, oro-,
hypo-pharynx, larynx, trachea)

<u>LEVEL</u>	<u>ACUTE REACTION</u>	<u>LATE EFFECTS</u>
0	No Reaction	No Reaction
1	Threshold Erythema	Minimal Paleness (Atrophy)
2	Definite (1°) Erythema	Definite but Minimal Atrophy
3	Patchy Mucositis (less than 1/2 of field)	Moderate Atrophy and/or Lymphedema
4	Patchy Mucositis (more than 1/2 of field)	Minimal Fibrosis (Thickening of Submucosa)
5	Confluent Mucositis	Moderate Fibrosis
6	Confluent Mucositis with Bleeding	Extensive Fibrosis with Contracture
7	Superficial Ulceration	Partial/Superficial Necrosis
8	Deep Ulcer or Necrosis	Ischemic Deep Necrosis
9	UNKNOWN	UNKNOWN

RECTUM AND SIGMOID COLON

<u>LEVEL</u>	<u>ACUTE REACTION</u>	<u>LATE EFFECTS</u>
0	Nil	Nil
1	Transient Change of Bowel Habit	Minimal Change of Bowel Habit
2	Definite Change: Mucosa Normal	Definite Change of Bowel Habit
3	Minimal Tenesmus and/or Reddening of Mucosa	Minimal Tenesmus and/or Mucus Stools
4	Moderate Tenesmus with Mucus	Persistent Bleeding without Ulcer
5	Severe Tenesmus with Mucus	Superficial Ulcer
6	Severe Tenesmus with Bleeding	Deep Ulcer and/or Stricture
7	Intractable Hemorrhage Requiring Transfusion and/or Fecal Division	Stricture with Obstruction or Fistula
8	Necrosis	Necrosis
9	UNKNOWN	UNKNOWN

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VII. GENITO-URINARY SYSTEMS

<u>LEVEL</u>	<u>KIDNEY</u>	<u>BLADDER</u>
0	Nil	Nil
1	Suspected Minimal Nephropathy	Minimal Subjective Bladder Discomfort
2	Transient Irradiation Nephropathy	Transient Irradiation Cystitis
3	Persistent Minimal Nephropathy	Persistent Dysuria, Mucositis
4	Partial Radiation Injury of Kidney	Severe Acute Radiation Cystitis
5	Chronic Radiation Nephritis	Telangiectasia or Bleeding
6	Radiation Fibrosis (unilateral) with Malignant Hypertension	Fibrosis, Contracted Bladder
7	Bilateral Radiation Nephritis	Fistula (e.g. vesico-vaginal, due to radiation)
8	Necrosis of Kidney	Massive Necrosis of Bladder
9	UNKNOWN	UNKNWON

<u>LEVEL</u>	<u>OVARY</u>	<u>TESTIS</u>
0	Nil	Nil
1	Sterility/Oligomenorrhea, ? Radiation Induced	Sterility or Transient Oligospermia
2	Temporary Amenorrhea	Temporary Partial Azospermia
3	Prolonged Amenorrhea; no Systemic Symptoms	Persistent Sterility or Oligospermia
4	?	Complete Permanent Azospermia
5	Complete Functional Oblation	?
6	Atrophy and Fibrosis, Complete	Testicular Atrophy with Impotence.
7	?	Severe Radiation Fibrosis of Scrotal Contents
8	?	Necrosis of Scrotum
9	UNKNOWN	UNKNOWN

VIII. ENDOCRINE GLANDS

<u>LEVEL</u>	<u>THYROID</u>
0	Nil
1	Suspected Malfunction
2	Diminished Iodine Uptake (scan)
3	Mild Hypothyroidism
4	Thyroiditis
5	Myxedema
6	?
7	Fibrous Replacement of Gland
8	Necrosis of Thyroid Gland
9	UNKNOWN

IX. NERVOUS SYSTEM

<u>LEVEL</u>	<u>SPINAL CORD</u>	<u>PERIPHERAL NERVES</u>
0	Nil	Nil
1	Subjective CNS Reaction	Subjective Reaction
2	Transient Myelopathy (L'llermitte)	Transient Neuropathy
3	Significant Sensory Loss	Significant Sensory Loss
4	Significant Motor Loss	Significant Motor Loss
5	Segmental or Regional Paresis	Limited Motor Nerve Palsy
6	Complete Paraplegia/Hemiplegia/ Transection of Cord	Complete Anaesthesia or Paralysis of Nerve Trunk
7	Massive Gliosis, Fibrosis or Infarct	Fibrosis of Nerve Trunk
8	Necrosis of Spinal Cord	Necrosis of Nerve
9	UNKNOWN	UNKNOWN