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TO PEAK PIONS AND X-RAYS

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INITIAL COMPARATIVE RESPONSE OF EXPERIMENTAL
TUMORS TO PEAK PIONS AND X-RAYS

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PRELIMINARY TO THE START OF HUMAN RADIOBIOLOGY AT THE CLINTON P. ANDERSON MESON PHYSICS FACILITY OF THE LOS ALAMOS SCIENTIFIC LABORATORY, COMPARISONS WERE MADE BETWEEN PHYSICAL MEASUREMENTS OF THE ABSORBED DOSE AND BIOLOGICAL EFFECTS ESTIMATED BY CELL SURVIVAL AS A FUNCTION OF DEPTH (1). FURTHERMORE, A RADIOBIOLOGICAL EFFECTIVENESS (RBE) VALUE FOR T1 CELLS HAD BEEN OBTAINED. HOWEVER, IT WAS DEEMED DESIRABLE TO EXPLORE THE RESPONSE OF AN ANIMAL TUMOR SYSTEM BEFORE TESTING THE COMPARATIVE EFFECT OF PEAK PIONS AND X-RAYS ON METASTATIC NODULES IN THE SKIN OF HUMANS, A PROGRAM NOW UNDER WAY.

A. EXPERIMENTAL DESIGN

A MAMMARY ADENOCARCINOMA WHICH HAD ARISEN SPONTANEOUSLY WAS TRANSPLANTED SUBCUTANEOUSLY INTO THE BACKS OF C_3H MICE. SINCE THE PION BEAM WAS AVAILABLE TO THE AUTHORS ON SPECIFIC DATES, THE TUMORS COULD NOT BE IRRADIATED WHEN THEY REACHED A PREDETERMINED SIZE. ACCORDINGLY, A STRATIFIED RANDOMIZATION SCHEME WAS USED TO ASSURE AN EQUAL DISTRIBUTION BY SIZE OVER THE SEVERAL X-RAY AND PION DOSAGE GROUPS. THE ANIMALS WERE HELD IN POSITION WITHOUT ANESTHESIA IN HOLDERS DESIGNED BY MR. REUBEN ARCHULETA. TUMORS SURROUNDED BY BOLUS WERE IRRADIATED BY PIONS IN THE DOWNSTREAM REGION OF THE PHYSICAL PEAK OF THE ABSORBED PION DOSE AND THEREFORE IN THE ASSUMED HIGH LINEAR ENERGY TRANSFER (LET) PORTION OF THE PEAK REGION. THE MOMENTUM OF THIS BEAM IS 171 MEV/C. DEPTH DOSE CURVES AND DISTRIBUTIONS IN DOSE FOR THIS BEAM WERE MEASURED WITH 0.1 CC. THIMBLE-TYPE TISSUE EQUIVALENT IONIZATION CHAMBERS. THE CHAMBERS WERE CALIBRATED

WITH RESPECT TO A Co^{60} SOURCE AND 250 Kv X-RAYS. DOSES GIVEN FOR THE PION EXPOSURES WERE DETERMINED BY TAKING THE RATIO OF THE CURRENTS MEASURED FOR PIONS TO THE CURRENT PER UNIT DOSE FOR Co^{60} . THEREFORE, THE VALUES SPECIFIED ARE NOT ABSOLUTE DOSES. EXTENSIVE DOSIMETRIC MEASUREMENTS AND CALCULATIONS HAVE BEEN PERFORMED AND WILL BE REPORTED ELSEWHERE (2). THE INTENSITY OF THE DOSE OF PEAK PIONS VARIED FROM THREE TO FIVE RADS PER MINUTE. THE REFERENCE RADIATION WAS 250 Kv X-RAYS DELIVERED AT A DOSE RATE OF 300 RADS PER MINUTE.

NO ANIMALS WERE LOST DURING IRRADIATION, AND ONLY ONE WAS SUBSEQUENTLY LOST. TUMORS WERE MEASURED IN THREE DIMENSIONS AND THEIR VOLUMES CALCULATED THREE TIMES A WEEK. THE DAILY FRACTIONS OF TOTAL PEAK PIONS WERE 264, 352, AND 440 RADS RESPECTIVELY. (SEE TABLE 1 FOR TOTAL DOSES.) EIGHT ANIMALS WERE IRRADIATED WITH PIONS AT EACH DOSE LEVEL FOR A TOTAL OF 24 ANIMALS. THESE WERE TREATED IN TWO SEPARATE SERIES OF FOUR ANIMALS AT EACH DOSE LEVEL DATA POINT.

THE X-RAY DOSES FOR EACH OF FIVE FRACTIONS WERE 476, 634, 794, 1055 AND 1321 X-RAY RADS (SEE TABLE 1 FOR TOTAL DOSES). AT THOSE X-RAY POINTS WITH MORE THAN FOUR ANIMALS, THE ANIMALS WERE IRRADIATED IN TWO SERIES. ONLY ONE ANIMAL DIED DURING OBSERVATION (DAILY FRACTION 634 RADS). THE DOSE LEVELS WERE SELECTED SO THAT OBSERVATION COULD BE MADE ON REGRESSION, REPRESSION, AND REGROWTH.

B. STATISTICAL ANALYSIS

THE ANALYSIS IS A MODIFIED VERSION OF THAT REPORTED BY WILCOX AND COWORKERS (3) IN THEIR EVALUATION OF POTENTIAL ANTI-CANCER AGENTS. THIS METHOD IS BASED "ON THE ASSUMPTION THAT THE (VOLUME) OF A TUMOR IS IN DIRECT PROPORTION TO THE NUMBER OF CELLS IN IT; THAT THE CELLS KILLED BY THE (TREATMENT) BECOME NON-VIABLE PROMPTLY, THOUGH THEY MAY DIVIDE A FEW TIMES AFTER TREATMENT; AND THAT THE CELLS REMAINING VIABLE DESPITE TREATMENT BEGIN TO GROW AGAIN, AFTER A RELATIVELY SHORT "LAG" IN LOG PHASE REGROWTH.

THE MOUSE MAMMARY ADENOCARCINOMA 755 IS SPECIFICALLY EXCLUDED BY WILCOX ET AL., BECAUSE SUCH TUMORS "ARE NOT IN LOG PHASE DURING MOST OF THE HOST LIFE SPAN." THE MAMMARY ADENOCARCINOMA USED IN THIS STUDY, HOWEVER, WAS NOT RELATED TO STRAIN 755. IN ALL CASES THE TUMORS DID REMAIN IN LOG PHASE FOR AT LEAST ONE WEEK FOLLOWING THE ONSET OF REGROWTH. THIS WAS SUFFICIENT TIME TO PERMIT THE ESTIMATION OF THE RATE OF LOGARITHMIC REGROWTH. A CELL IS ASSUMED TO SURVIVE IF THE CELL WAS STILL PRESENT AND VIABLE AT THE COMPLETION OF TREATMENT. THE PROBABILITY OF CELL SURVIVAL THEN IS GIVEN BY S

WHERE $S = P_1 \times P_2$

AND P_1 = PROBABILITY OF CELL STILL BEING PRESENT AT THE COMPLETION OF THERAPY.

P_2 = PROBABILITY OF CELL BEING VIABLE GIVEN THAT THE CELL IS PRESENT AT THE COMPLETION OF THERAPY.

THE PROBABILITY P_1 WAS ESTIMATED BY THE AMOUNT OF REDUCTION IN TUMOR VOLUME DURING TREATMENT. THE PROBABILITY P_2 WAS ESTIMATED

USING THE MODEL OF WILCOX ET AL.:

$$N(t) = N_A e^{gt} + N_D e^{-at}$$

WHERE $N(t)$ = THE TOTAL NUMBER OF CELLS AT TIME t
(WHERE $t = 0$ AT THE COMPLETION OF THERAPY).

N_A = THE NUMBER OF VIABLE CELLS AT THE
COMPLETION OF THERAPY.

g = THE RATE OF LOGARITHMIC GROWTH OF THE
VIABLE CELLS.

N_D = THE NUMBER OF NON-VIABLE CELLS AT THE
COMPLETION OF THERAPY.

a = THE RATE OF LOGARITHMIC REGRESSION OF THE
NON-VIABLE CELLS FOLLOWING TREATMENT.

AFTER THE CONSTANTS WERE ESTIMATED FROM THE DATA, THE PROBABILITY
 P_2 WAS COMPUTED BY

$$P_2 = N_A / (N_A + N_D)$$

THE RESULTS ARE SHOWN IN TABLE 1. A STRAIGHT LINE REGRES-
SION WAS FIT TO THE NATURAL LOG OF S FOR THE PION AND THE X-RAY
DATA AND USED TO ESTIMATE THE LETHAL DOSE (LD_{99}) (SEE TABLE 2
AND FIGURE 1). FROM THIS AN RBE OF 1.67 WAS COMPUTED, WITH A
STANDARD DEVIATION FOR THE FIT OF 0.148. AN APPROXIMATE 99
PERCENT CONFIDENCE INTERVAL FOR THE COMPUTED RBE IS THEN 1.29
TO 2.05. THIS ANALYSIS DOES NOT TAKE INTO ACCOUNT UNCERTAINTIES
ASSOCIATED WITH THE PION AND X-RAY DOSES DELIVERED. FOR EXAMPLE,
THE UNCERTAINTY IN THE ABSOLUTE PION DOSE WAS NOT CONSIDERED.

THE RBE OF 1.67 ± 0.148 , THUS ESTABLISHED, WAS USED IN
CONSIDERING DOSES FOR THE HUMAN RADIOBIOLOGY EXPERIMENTS.

ONE NOTATION OF CLINICAL INTEREST WAS THE OBSERVATION THAT
THE NODULES TREATED BY PIONS SOFTENED AFTER THE SECOND TREATMENT

DAY AS COMPARED WITH X-RAY-TREATED TUMOR NODULES, EVEN THOUGH COMPARATIVELY HIGHER DOSES OF X-RAY WERE GIVEN TO SOME.

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TABLE 1
COMPARISON OF PION AND X-RAY DOSES WITH PROBABILITY OF CELL SURVIVAL

<u>MODALITY</u>	<u>DAILY FRACTION (RADS)</u>	<u>TOTAL DOSE (RADS)</u>	<u>SAMPLE SIZE</u>	<u>S (PROBABILITY OF CELL SURVIVAL)</u>
PION	264	1320	8	.2033
PION	352	1760	8	.0557
PION	440	2200	8	.0126
X-RAY	476	2330	4	.0700
X-RAY	634	3170	3	.0277
X-RAY	794	3970	6	.0043
X-RAY	1055	5275	8	.0023
X-RAY	1321	6605	4	.0008

TABLE 2				
PION AND X-RAY REGRESSION PARAMETERS				
	<u>INTERCEPT</u>	<u>REGRESSION</u>	<u>LD</u>	<u>STD. DEV. (LD)</u>
			<u>.99</u>	<u>.99</u>
PION	2.6695	-.00319	2280	32.45
X-RAY	-.7038	-.00103	3802	40.39

FIGURE 1

CAPTIONS:

FIGURE 1. SURVIVAL OF CELLS AS A FUNCTION OF DOSE IN RADS PER DAY, DELIVERED IN FIVE FRACTIONS. FROM THESE CURVES, AN RBE OF 1.67 ± 0.148 WAS ESTABLISHED FOR PEAK PIONS, IN RELATION TO 250 Kv X-RAYS.

TABLE 1. PROBABILITY OF CELL SURVIVAL WITH CUMULATIVE DOSES OF PEAK PIONS AND X-RAYS AS DERIVED THROUGH A MODIFIED VERSION OF ANALYSIS REPORTED BY WILCOX ET AL. (3).

TABLE 2. COMPUTATION OF LETHAL DOSE ($LD_{.99}$) FROM DATA PRESENTED IN TABLE 1. A STRAIGHT LINE REGRESSION WAS FIT TO THE NATURAL LOG OF S (PROBABILITY OF CELL SURVIVAL) FOR THE PION AND X-RAY DATA AND USED TO ESTIMATE THE LETHAL DOSE ($LD_{.99}$).