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RADIATION EFFECTS IN MAN: MANIFESTATIONS AND THERAPEUTIC EFFORTS

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**RADIATION EFFECTS IN MAN:
MANIFESTATIONS AND THERAPEUTIC EFFORTS
(Report Period – May 1, 1968 through April 30, 1969)**

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INTRODUCTION

This report summarizes our work on Radiation Effects in Man for the period of May 1, 1968 through April 30, 1969. Report DASA 1844 summarized our total efforts from February , 1960 through April 30, 1966. The work of the year immediately preceeding the current report is summarized in DASA 2168. Other earlier reports from this Laboratory include DASA 1422, DASA 1633 and DASA 2179, which may also be consulted.

The goal of our program has been to obtain new information regarding the pathophysiologic, psychologic, immunologic, hematologic, and biochemical effects of total and partial body irradiation in human beings. The patients who are irradiated, all of whom have inoperable, metastatic carcinoma but are in relatively good health, provide us with the opportunity to study multiple facets of the effects of radiation in man rather than in experimental animal. As we and many other laboratories have discovered, extrapolation of results from laboratory animals to man can be fraught with error. We have continued our search for a suitable biological dosimeter in human beings. The data contained in this report suggest several potential biological dosimeters previously considered to be of some value have not fulfilled this expectation.

Biochemical and psychological studies have extended the findings of our previous report in depth and scope. Success has finally been obtained in autologous marrow infusion which will permit us to employ higher doses of radiation in the coming year. Several new biological dosimeters are under evaluation. The only change in physical dosimetry has been the addition of partial body radiation from sternum to pubis for selected patients.

These studies were performed in conformation with the "recommendations guiding doctors in clinical research" as stated in the Declaration of Helsinki of the World Medical Association (1964).

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Research was conducted according to the principles enunciated in the "Guide for Laboratory Animal Facilities and Care", prepared by the National Academy of Sciences - National Research Council.

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I. CLINICAL STUDIES:

A. Relation of Symptoms to Dose

Sixty-four patients have now been fully evaluated, before and after partial or whole body irradiation. The presence or absence of nausea and vomiting are most helpful guidelines in the early determination of a patient's radiation dose. A recent report (1) states that these symptoms are mild or absent in doses below 100 rads and appear regularly at about 200 rads. The value of our data (Table I, Figure I) concerning patient's symptoms lies in the accurate dosimetry available for each patient receiving whole or partial body irradiation, obviating the need for rough dose estimates.

After one hundred rads of whole body irradiation one-third of our patients experienced nausea and vomiting. These symptoms were often of the same severity and duration as in patients receiving an absorbed dose twice as great. Also, one-third of the patient groups given 200 rads of whole body irradiation remained asymptomatic. Dose response-relationships were independent of previous radiotherapy. Thus, patients who remained symptom-free after radiation exposure may also require monitoring of blood counts for up to a month.

TABLE I. Symptoms of Patients Related to Whole Body Radiating Dose

(No symptoms occurred with doses up to 66 rads)

	100 RADS WBR		150 RADS		200 RADS	
	NUMBER OF PATIENTS	NUMBER PREVIOUSLY IRRADIATED	NUMBER OF PATIENTS	NUMBER PREVIOUSLY IRRADIATED	NUMBER OF PATIENTS	NUMBER PREVIOUSLY IRRADIATED
NO SYMPTOMS	12	7	5	3	2	1
ANOREXIA ALONE	0	0	1	1	1	0
NAUSEA ALONE	2	2	0	0	1	0
NAUSEA AND VOMITING	4	2	10	6	4	3
TOTAL PATIENTS	18	11	16	10	9	4

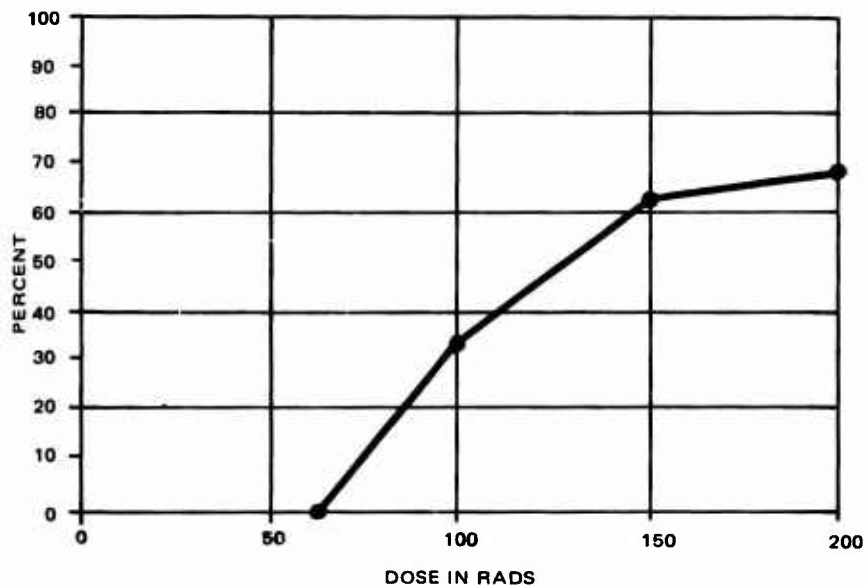


FIGURE 1. Percent of Patients with Nausea and Vomiting After Whole Body Radiation

B. Monocyte and Lymphocyte Counts After Radiation

The same publication previously cited (1) suggests that the absolute monocyte count obtained shortly after radiation might be of value as a biologic dosimeter, as has been found in rodents (2). The accompanying chart (Table II) shows the sequential absolute monocyte counts in eight patients who have received 200 rads whole body radiation. The normal monocyte count range (95% confidence limits) is 140 to 860 per cubic millimeter (3). There appears to be a trend, although not uniform, (cf, patient number 024) for a drift downward of the monocyte count paralleling the neutrophil count, but acute changes are never observed in the monocyte count. This relationship of monocyte and neutrophil counts is not surprising in view of suggestive evidence that the monocyte arises from the promyelocyte (4). Thus our data negate the value of the monocyte as a biologic dosimeter following acute radiation exposure.

Note that there is not always a significant drop in the absolute lymphocyte count after 200 rads whole body radiation either (Table III). (The standard deviation for any one count is plus or minus twenty percent).

TABLE II. Absolute Monocyte Counts of Patients with 200 Rads Total Body Radiation

(Normal: wintrobe, Hematology, Ed. 6, p. 260 — 95% confidence limits are 140 — 860/mm³) (cells per cu. mm.)

DAY	018	020	021	023	024	053	077	078
- 1	740	1050	1250	892	118	1404	372	750
Rx	—	—	—	—	—	1573	489	503
+ 1	460	1020	1378	1083	606	976	1060	525
+2	1224	1010	780	1276	676	1009	215	274
+3	627	1176	711	838	864	318	206	240
+5	368	700	1092	867	550	657	453	258
+8	612	—	1152	1076	324	1140	829	459
+12	845	—	871	547	256	427	1407	520
+15	583	119	969	—	196	165	128	561
+18	297	—	546	1176	224	111	213	284
+21	207	—	—	402	96	114	226	90
+24	210	—	170	—	128	26	—	105
+27	108	—	—	—	—	—	—	45
+30	132	—	—	287	—	expired	expired	136
+33	120	—	—	484	80	—	—	—
+36	—	—	expired	657	67	—	—	396
+40	713	—	—	781	300	—	—	418
+54	—	648	—	—	—	—	—	—
+59	—	—	—	—	—	—	—	916

TABLE III. Absolute Lymphocyte Counts of Patients Receiving 200 Rads of Whole Body Radiation

(cells per cu. mm.)

PATIENT NUMBER	24 HRS. PRE	24 HRS. POST	48 HRS. POST	72 HRS. POST
018	1644	782	816	684
020	1313	1226	1162	1029
021	1625	1060	975	632
023	1131	903	730	1078
024	1711	880	984	1080
053	1404	1220	1199	1060
077	558	280	286	412
078	800	263	238	280
087	979	581	220	480
091	910	658	264	170
093	2001	2220	—	1140

C. Marrow Transplantation and Storage

We feel that before further experiments are undertaken with revived human marrow following freezing to minus 83° centigrade, we must perfect the technique of autotransplantation using fresh marrow of nearly 100% viability. The minimum dose of marrow required for an auto- or isotransplant has been estimated at 1.1×10^7 cells per kilogram body weight (5) to 1×10^8 cells per kilogram (6). We have obtained 450 cc. of fresh marrow from the ilia of our patients employing a Vim-Silverman, Conrad-Crosby, or Kernick needle, and 50 cc. of marrow from the sternum using a Bierman needle. Each aspiration must be limited to less than 10 cc. or the marrow becomes diluted by too much peripheral blood, which probably has only 1% of the stem cells of bone marrow per unit volume (7). A marrow isotransplant has been performed on a 54 kilogram female after 200 rads whole body radiation. The nadir of this patient's leukocyte count, 2100 per cubic millimeter, was greater than 3.5 standard deviations above the mean nadir (850 per cubic millimeter) of our previous 9 patients given 200 rads of whole body radiation. We are thus reasonably certain that we have achieved a technique for successful marrow transplantation. With improvements employed on our next patient we were able to remove for autotransplantation (prior to whole body radiation) 38×10^9 marrow cells. The subject was an 80 year old woman whose marrow would be expected to be moderately hypocellular. It thus appears that many of the technical problems relating to marrow autotransfusion have been resolved.

D. Serum Iron

Serum iron levels are being measured before and sequentially after whole body radiation in an attempt to correlate the rapidity and magnitude of the rise of serum iron level after whole body radiation with the radiation dose, as well as with the fall in the reticulocyte count. The changes in the reticulocyte count and serum iron reflect the decrease in erythropoiesis due to radiation damage to the erythroblast compartment of the marrow.

There is a diurnal variation of serum iron in about 70% of the population which may range up to 60% from morning till evening (8). We have therefore measured the serum iron at the same time of day for each determination. Although our data do show a radiation effect, the fact that the serum iron level varied widely and randomly even when checked at the same time on different days (9) makes this guideline of radiation dose less than ideal. Our current but preliminary data show no consistent early change in serum iron although a rise is often noted as the reticulocyte count drops. Several more patients will be studied in greater detail for this parameter before a final impression as to the value of the serum iron as a biologic dosimeter is formed.

E. Etiocholanolone

Etiocholanolone is a naturally occurring steroid metabolite of testosterone, delta-four-androstene-3, 17 dione, dehydroepiandrosterone, and certain other steroids of gonadal and adrenocortical origin (10). Etiocholanolone is the cis isomer of androsterone. This steroid hormone has been shown to be a potent stimulus to leukocytosis in man, and the increment in circulating leukocytes is composed principally of the mature, and to a lesser extent immature, neutrophilic granulocytes released from the bone marrow (11). The quantitative relationship between the dose of etiocholanolone administered and the number of granulocytes mobilized into the circulation has been carefully elucidated by Dr. Harry Kimball and others at the National Institutes of Health, (op. cit). At a dose of 0.10 milligram per kilogram of etiocholanolone the average maximum change in granulocyte count in men was 5,850 per cubic millimeter $\pm$ 770 (1 s.d.) and in women 6,700 $\pm$ 1,400. (1 s.d.) There is good evidence that this increment of the peripheral blood count is due to mobilization of granulocytes from the bone marrow reserve and is not the result of redistribution of cells which are already in the extramedullary pool (12). The minimum normal response to an intramuscular injection of 0.10 milligrams of etiocholanolone per kilogram body weight is an increment of 2,600 granulocytes per cubic millimeter within 24 hours.

Only one report of the use of etiocholanolone to evaluate marrow reserves after radiation has appeared in the literature (13). We have begun to evaluate alterations in granulocyte reserves prior to and sequentially after whole and partial body radiation. Our studies to date are only preliminary and include less than 10 patients. The average pre-radiation granulocyte increment to etiocholanolone stimulation in 8 patients with metastatic carcinoma who were not leukopenic prior to injection was 4,960 per cubic millimeter, well within two standard deviations of the normal means found by Kimball, et al. in normals (11). A patient given 150 rads partial body radiation extending from the sternal manubrium to the pubis (14) experienced a prompt inhibition of the etiocholanolone response which lasted for 10 days despite the fact that her leukocyte counts never dropped below 7,300 per cubic millimeter. In a patient given 200 rads whole body radiation, the granulocyte reserves became abnormally low one day after radiation and did not completely return to normal for 44 days, although the granulocyte reserves were clearly increasing while the leukocyte count was falling to a nadir of 2100 per cubic millimeter. Thus, the granulocyte increment after etiocholanolone injection may allow one to demonstrate radiation effect 16 to 24 hours after the exposure, before there are any alterations in the absolute leukocyte count itself. Similarly, the granulocyte increment induced by etiocholanolone may be an important prognostic sign during radiation-induced leukopenia. These studies are being actively pursued.

F. Lymphocyte Studies

The degree of post radiation lymphopenia at 48 hours has been related to the severity of radiation-induced symptoms (15). By these criteria 4 of 11 patients receiving 200 rads of whole body radiation would have been classified as having sustained "very severe" injury, 3 "severely" injured and 5 only "moderately" injured (Table III). Yet the carefully calculated dose and overall hematological responses of these patients were not different, and none of them showed evidence of the gastrointestinal syndrome.

Similarly mean "lymphocyte profile" values, which Thoma and Wald (16) had found to separate their groups II to V within two days post radiation exposure, showed wide variation in our patients, ranging from 0 to 8, which would have placed two of these patients in Thoma and Wald's Group V, giving them a virtually hopeless prognosis if they had been radiation accident victims. The advantage of accurately known dosimetry, the absolute lymphocyte count in our hands has considerable variation in patients receiving 200 rads whole body radiation, and its value as a biologic dosimeter seems considerably diminished.

Thus, in our population the value of profile scoring appears less useful than it has in the case of healthy individuals exposed accidentally to non uniform partial body radiation. When the original cases from which Wald and Thoma derived the method of profile scoring are reexamined, it is readily apparent that those subjects did not experience even the degree of uniformity of radiation of our patients. In addition they lacked the characteristic of neoplasm. Recent experience in accident cases suggests that profile scoring is valuable as a biological indicator following exposure of healthy individuals and its use should be continued.

Phytohemagglutinin (PHA) studies have just begun on the alteration in the PHA response of the post-radiation lymphocyte as measured by the uptake of the tritiated thymidine. It has been suspected that decreases in the ability of the lymphocyte undergoing blast transformation to take up tritiated thymidine following radiation (as a result of radiation injury) might be proportional to radiation dose. However, our first study has indicated no change in PHA-induced DNA synthesis after radiation.

G. Histochemical Studies

Histochemical studies are being performed to evaluate soluble, microsomal, and mitochondrial enzymes in pre- and post-radiation neutrophils, lymphocytes and monocytes. Among the enzymes to be studied are:

- Acid phosphatase
- Beta-glucuronidase
- Periodic acid Schiff reaction
- PAS-diastase
- Methyl green-pyronin

Sudan black
Peroxidase
Lactic acid dehydrogenase
Succinic acid dehydrogenase
Alkaline phosphatase
DPNH oxidase
DNA-ases

Any early dose-related enzyme changes found would be of practical importance in providing a biologic dosimeter easily applicable in the field. Electron microscopy will be employed to evaluate alterations in organelle morphology to provide more basic information in correlating functional with structural changes.

H. Chromosome Studies

Following the report of Goh and Sumner (17) we have searched in vain for a transferrable substance in the plasma of persons exposed to total body radiation which, according to the above authors, induced breaks in normal human chromosomes. We are continuing to look for such a factor however, although another laboratory has also reported not finding this transferrable substance (18).

Because of our excellent dosimetry measurements on all patients irradiated we are planning to reevaluate the radiation-induced chromosome aberrations found in these patients. These studies will provide the most accurate relationship of chromosome aberrations to radiation dose yet available, and should assist in settling in current questions on dose-response relationships of chromosome changes as a biological radiation dosimeter.

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II. BIOCHEMICAL STUDIES

The discovery by Parizek et al of a radiation-induced increase in urinary excretion of deoxycytidine (CdR) by rats have led us to investigate the possibility of using CdR-uria to estimate the degree of radiation exposure by man.

A. Urinary CdR

(a) A sensitive colorimetric technique was developed in our laboratory to analyze the quantity of CdR excreted into urines (1). It was found that urinary excretion of CdR as well as blood CdR concentration in rats were elevated about 6 hours after rats were exposed to x-ray and returned to the pre-irradiation levels 24 hours after irradiation (2). The amount of daily CdR excretion was proportional to the amount of radiation exposure up to 200 R. Approximately, a six-fold increase from an average pre-irradiation value of 0.7 mg per 24 hour urine was attained at 200 R.

(b) Man excretes a much smaller quantity of CdR in urine than does a rat. An average pre-irradiation value was found to be 0.007 mg of CdR per 24 hour urine as compared to 0.7 mg excreted by a rat. Only about a two-fold increase from an average pre-irradiation value of 7 ug was observed in several cancer patients receiving 178 to 300 rads of local, partial or total body irradiation (Table IV).

TABLE IV. CdR in the Urine of Irradiated Patients

PATIENTS			DOSE (Rads)	CdR in 24 hour urine (ug)			
Case No.	Sex/race/age	Diagnosis		Pre-irradiation average	Post irradiation (days)		
					1	2	3
—	F/W/48	Ca lung	176 local *	6.6	16.7	—	—
—	F/W/54	Ca breast	200 local **	8.5	16.5	—	—
0.92	F/W/60	Ca Breast	150 P. Neck to Pubis	5.8 ± 1.3	10.0	8.1	—
0.75	F/W/60	Ca Ovaries	200 P. Lower	5.4 ± 1.1	6.8	6.1	6.0
0.72	F/W/62	Lymphoma	300 P. lower	8.2	15.2	7.7	—
0.82	M/N/49	Ca Colon	300 P. lower	8.1 ± 1.8	16.4	5.0	—
0.79	F/W/50	Ca Breast	100 total	26.0 ± 5.2	39.0	25.0	12.3
0.81	F/W/52	Bronchogenic	100 total	4.2 ± 0.2	4.4	3.4	—
0.86	F/W/57	Bronchogenic	100 total	3.9 ± 0.9	4.5	4.0	—
0.83	F/W/78	Ca Breast	100 total	5.9	9.3	6.5	—
0.88	F/N/54	Ca lung	150 total	8.4	27.8	6.4	—
0.77	F/W/63	Ca Pharynx	200 total	6.9 ± 0.4	11.9	12.2	14.3
0.78	M/N/55	Bronchogenic	200 total	20.4 ± 4.3	33.0	31.0	—
0.87	F/W/11	Ewing's tumor	200 total	3.9 ± 1.1	5.8	4.8	—

P. — Partial

* To the anterior and posterior mediastinal ports, including the right hilus and both supraclavicular areas in a "T" portal.

** To the internal mammary chain and supraclavicular and axillary regions.

(c) Urinary CdR excretion by patients with various diseases were also investigated. One patient with lymphoepithelioma and two burn patients showed abnormally high urinary CdR excretion. In burn patients, the quantity of CdR excretion seemed to be proportional to the degree of burn. Thus it seems that the increased excretion of CdR is not specifically caused by radiation but rather can be caused by general tissue destruction.

B. CdR Metabolism

Our experimental results indicate that CdR-uria is a sensitive biological indicator for radiation dose in rats but not in man. It was thought that some differences in CdR metabolism in these two species might be partially responsible for the discrepancy in the radiosensitivity of CdR-uria.

(a) CdR-deaminase

We have now demonstrated that CdR deaminase, which is capable of converting CdR to deoxyuridine, is present in man (Tables V, VI) but was not detectable in rats. Thus CdR in man can be deaminated and metabolized further whereas CdR in rats is excreted into urine unchanged. CdR deaminase activity in serums of cancer patients before and after they were treated

TABLE V. CdR Deaminase Activity in Serum and CdR Content in Urine from Selected Human Controls

Subject			Serum CdR deaminase		CdR in 24
	Age	Sex	activity (units / mg protein)		hour urine (mg)
1.	6	M	0.46		5.7
2.	8	M	0.96		12.0
3.	9	M	1.02		13.1
4.	9	M	0.65		4.0
5.	12	F	0.71		2.4
6.	22	F	0.37		5.0
7.	23	M	0.38		8.4
8.	25	M	0.71		4.8
9.	28	F	0.94		4.0
10.	28	M	0.51		2.0
11.	29	M	0.43		6.0
12.	30	M	0.59		12.0
13.	51	M	0.98		7.5
Average			0.67 $\pm$ 0.24		6.68 $\pm$ 3.67

with gamma radiation generally showed an initial drop shortly after irradiation. The deaminase activity in rat serums was still not detectable even after they were exposed to radiation.

(b) Metabolism of isotopically labelled CdR

Our comparative study of CdR deaminase activity in rat and human suggest that CdR is metabolized differently in these two species. Studies on the differences in CdR metabolism in rats and humans are of importance because they may provide us further insights into the metabolic origin of radiation-induced urinary CdR and may lead us to obtain more sensitive biological indicators of radiation injury in man.

TABLE VI. CdR Deaminase Activity in Serum and CdR Content in Urine from Patients with Various Diseases

Patients				Serum CdR deaminase activity	CdR in 24
	Sex	Age	Diagnosis	Units / mg Protein)	hour urine (mg)
1.	M	14	Lymphoepithelioma	1.20	38.0
2.	M	30	Chondrosarcoma (shoulder)	0.54	14.0
3.	F	76	Carcinoma (bladder)	0.66	20.0
4.	F	62	Carcinoma (breast)	0.64	18.0
5.	M	61	Lymphoma	0.20	18.0
6.	F	42	Bronchopneumonia	0.43	6.1
7.	M	19	Paraplegia	0.76	3.9
8.	M	14	Myasthenia gravis	1.12	11.5
9.	F	47	Rheumatoid arthritis	0.54	10.0
10.	M	28	Diabetes mellitus	0.36	5.9
11.	M	12	Body burns (55%)	0.90	32.6
12.	M	16	Body burns (72%)	1.21	57.3
13.	F	28	Pregnant (3 months)	0.64	5.6
14.	F	17	Pregnant (8 months)	0.72	4.3

In the study using CdR specifically labelled with H-3 on the carbon-5 of the cytosine, we found (3) that irradiated rats (200 R) excreted about 21% of total radioactivity injected whereas only 13% of radioactivity was excreted by unirradiated rats (Fig. 2). Specific radioactivity of CdR isolated from the urine of irradiated rats decreased about 2 to 6 fold as compared with that of CdR in the urine of unirradiated rats, indicating the increase in the pool size of free CdR in irradiated rats (Table VII). Our preliminary results of the analyses of radioactive compounds excreted in urines indicate that the urine of irradiated rats contains a radioactive compound or compounds which chromatographically behaved differently from the radioactive compounds isolated from the urine of unirradiated rats.

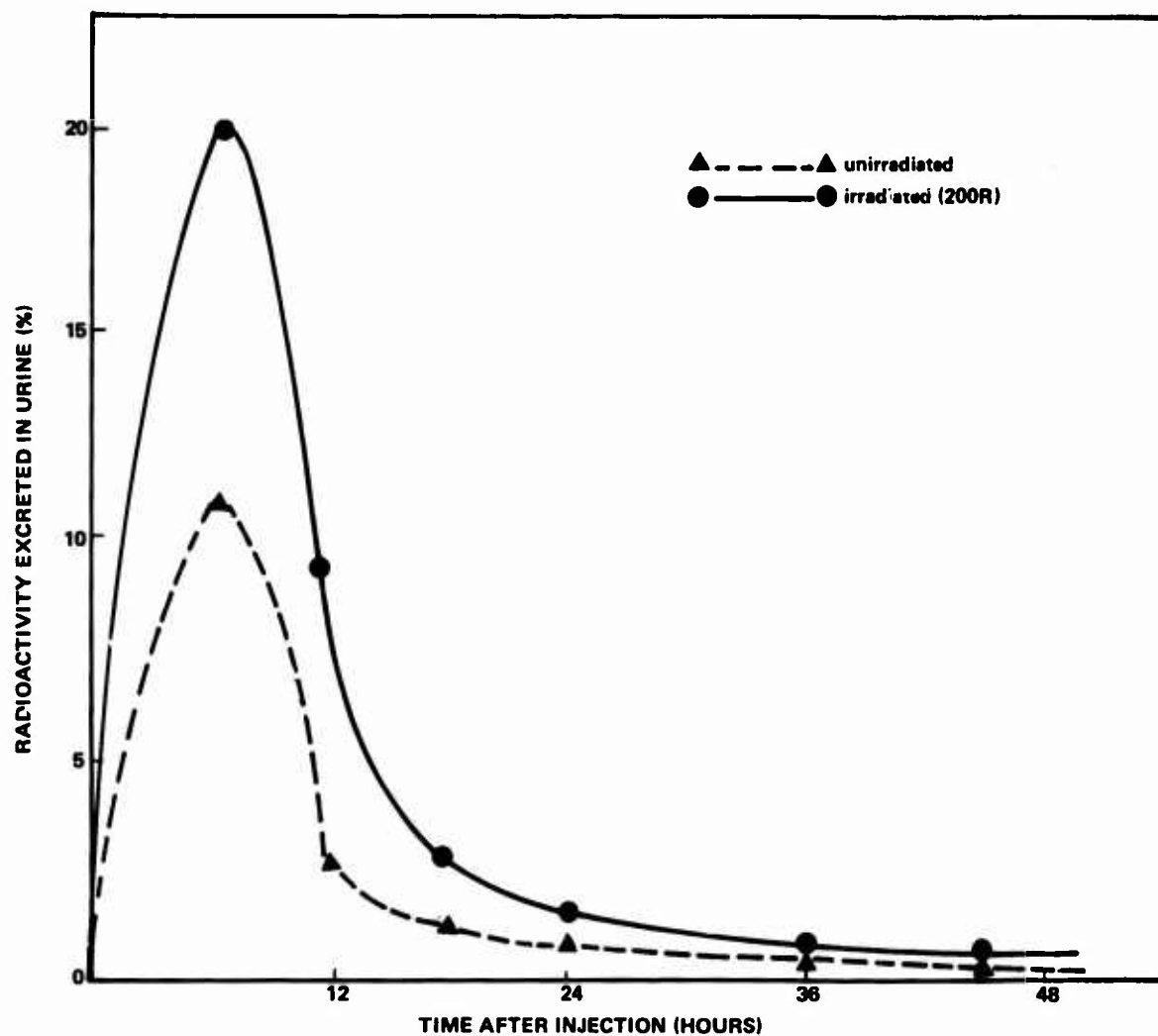


FIGURE 2. Effect of Irradiation (200R) on the Excretion of Tritiated CdR in Rats

TABLE VII. ^3H -CdR Excreted in 24 Hour Urine in Rats

Rat No.	Pre-irradiation		Post-irradiation	
	Specific Radioactivity (cpm/mg)	Total excreted (mg/day)	Specific Radioactivity (cpm/mg)	Total excreted (mg/day)
1	192,000	0.60	61,000	5.13
2	179,000	1.04	31,000	7.16
3	141,000	1.93	83,000	6.50

We have also shown that the same animal can serve as its own control in the study mentioned in (Table VIII). This result is especially helpful when human subjects are involved, because the number of individuals receiving radioactive material can be reduced.

TABLE VIII. Excretion of ^3H -Radioactivity in the Urine in Rats

Rat	^3H -Radioactivity in 24 hour urine (%)	
	First Collection	Second Collection
1	22.2	1.8
group A 2	1.5	1.8
3	21.6	1.5
4	13.1	25.8
5	1.8	27.4
group B 6	14.9	19.5
7	23.2	39.6
8	19.2	16.1
group C 9	13.6	15.5
10	7.7	6.4

First urine collection was made immediately after ^3H -5-CdR injection.

Second urine collection was made 5 days after the first collection.

Group A: exposed to 200R of x-ray before the second collection.

Group B: exposed to 200R of x-ray and ^3H -5-CdR injected before the second collection.

Group C: ^3H -5-CdR injected before the second collection.

C. Other enzyme studies

The levels of two serum enzymes, B-glucuronidase and acid phosphatase using phenolphthalein glucuronide and nitrophenyl phosphate substrates respectively were studied before and after irradiation in four cancer patients. The results so far obtained showed no significant change in pre- and post-irradiation activities. Assays of other lysosomal enzymes in blood as well as in urine are in progress at present.

D. Effects of radioprotective compounds on urinary CdR excretion

Effects of serotonin on the radiation-induced urinary excretion of CdR were studied in the hope that further insight into the mechanism of radiation injury could be obtained. It was found that injection of these chemicals into rats could suppress the radiation-induced urinary

excretion of CdR. Dose reduction factor (DRF) was derived in terms of 24 hour urinary excretion of CdR for chemically protected and non-protected rats. DRF of 1.7 and 1.5 were obtained, respectively, for serotonin and L-cysteine. These values are within 7% of DRF values reported by other investigators using LD₅₀ as the response criterion.

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III. IMMUNOLOGY

A. Immunization with T2 Bacteriophage. Four normal individuals and seven patients with metastatic malignant solid tumors were immunized with 2×10^{10} PFU (plaque forming units) T2 bacteriophage. The antibody response to this antigen was determined using the 50% neutralizing titer method as described by Hajek (1). On initial determinations, this dose of antigen seemed to elicit an adequate antibody response. However, when repeat antibody titers were performed, the results with each individual serum were not reproducible. The sera were then further tested using K value determination as described by Adams (2). These experiments revealed that phage-antibody reactions gave non-reproducible results when incubation of the phage-antibody mixture was allowed to continue beyond 80 minutes (three (3) hours of incubation was used with Hajek's method). Incubation for less than 80 minutes gave reproducible results. As the K value method is quite cumbersome for determination of multiple samples, we have now begun to use a modification of the 50% neutralizing test as described by Barlow et al (3) which employs only 60 minutes incubation. Antibody titers obtained with this test have been extremely consistent. The K value determinations also revealed that immunization with 2×10^{10} PFU of T2 bacteriophage gave peak K values which were in the range of 0.4, a low value according to the literature reports.

We have now immunized 4 more normal human volunteers. One received 2×10^{10} PFU's, two received 2×10^{11} PFU's and one 2×10^{12} PFU's. Results are incomplete at this time but immunization with 10^{11} or 10^{12} PFU T2 bacteriophage gave considerably higher antibody titers both by K value determination and by 50% neutralizing titer than those achieved previously with 10^{10} PFU's.

B. Immunization with ϕ X174 bacteriophage. Two normal human volunteers and 2 patients with metastatic carcinoma were immunized with 2×10^{10} PFU ϕ X174 bacteriophage. Both patients with metastatic carcinoma were immunized 24 hours post irradiation (1 patient received total body irradiation and the other partial body irradiation). Both patients had received T2 bacteriophage 3 weeks prior to irradiation. Five (5) other patients with metastatic tumors who had been immunized with T2 bacteriophage were not immunized with 174 because of failure to follow the protocol or of death before total body irradiation could be administered. The method for detecting antibody response was that of Hajek (1) and the results obtained were not reproducible. Determinations of K value were also done and revealed that the antibody responses obtained were quite low. However, again using a modification of Barlow et al (3) neutralization technique with 60 minutes incubation of the phage-antibody mixture, reproducible titers were obtained. The K values were low compared to those reported in the literature. In future experiments, it will be necessary to immunize each individual with at least 10^{11} PFU ϕ X174. It is planned in the near future to immunize several more normal volunteers before immunizing patients with metastatic carcinoma.

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IV. EFFECTS OF TOTAL AND PARTIAL BODY RADIATION ON COGNITIVE- INTELLECTUAL FUNCTIONING AND EMOTIONAL REACTIONS

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This report deals with 25 of the subjects on DASA Project DA-49-146-XZ-315 who received complete psychological evaluation. The procedures used in the evaluations were outlined in DASA Report 2168 and will not be reviewed here. As recommended in a previous report, additional measurement days were added for day 21 and day 35. However, not enough data have been accumulated to date to use these new measurements meaningfully, and in general longitudinal data are presented only up through day 14.

Descriptive data for new patients added in the last year are given in Table IX. The subjects of this report included 15 females and 10 males, of whom 17 were Negro; the mean age was 61. With regard to marital status, 8 were married, 8 widowed, 5 separated, 2 divorced and 2 single. These subjects ranged from 0 to 10 years of completed schooling with a mean of 6 years. On the Wechsler Adult Intelligence Scale (WAIS) their I. Q. range was from 63 to 116 with a mean I. Q. of 86.

TABLE IX. Biographic Data of 9 Radiation Patients
1968 - 1969

Study No.	Sex	Race	Age	Marital ^a Status	Site of Ca.	Type Rad. ^b	Survival Time ^c (days)	Educ. ^d	I. Q. ^e
083	F	W	78	S	Breast	T100	264	10	82
084	M	N	65	W	Lung	U300	280(A)	4	89
086	F	W	57	M	Lung	T100	20	7	95
087	F	W	11	S	Knee	T200	180(A)	5 ^f	100
088	F	N	53	W	Lung	T150	8	7	67
089	F	W	71	S	Breast	T200	17	9	101
090	F	N	80	W	Bladder	T150	4	12+	102
091	F	W	62	W	Colon	T200	42(A)	8	101
092	F	N	69	W	Colon	P150	45	9	98

a - Marital status: S = single; W = widowed; M = married.

b - Type radiation: T = total body; U = upper body; P = neck to pubic area.

c - Survival time: (A) = still alive at time of report.

d - Education: years of elementary and secondary school.

e - I. Q. was evaluated by means of selected subtests of the Wechsler Adult Intelligence Scale.

f - Still in school.

Personality Profile at Initial Interview.

The Sixteen Personality Factor Questionnaire—Form A (Cattell & Eber, 1962) was administered during the period of initial evaluation. Although this instrument is designed to be self-administered by subjects whose educational level is equivalent to that of normal high-school graduates, we have found that meaningful data can be secured from patients with less schooling and/or intelligence by administering the questionnaire orally in an interview situation. When necessary for the well-being of the patient, the testing is done over several sessions. In order to keep the testing situation consistent, the test is administered orally even in those cases where the patient appears able to undertake it on a self-administered basis.

The statements involved in Factor B—intelligence have been less amenable to this procedure than the rest of the items, and patients frequently have seemed confused at the change of set required from answering statements of attitudes and preference to items of fact. Our present policy, therefore, is to omit Factor B statements during 16 PF administration and to evaluate intelligence solely with the WAIS scores obtained during a separate testing session.

Table X presents the means and standard deviations in sten scores for 15 primary factors (Factor B—intelligence has been omitted) measured by the 16 PF and for four second-order factors for the total groups of radiation patients ($N = 21$) and for short and long survival groups. These are defined as those who lived less than 100 days after total body or partial body radiation (short survival group, $N = 10$) and those who lived 100 days or more after this treatment (long survival group, $N = 11$). Figure 3 identifies the factors measured by this test and displays the profile of the two survival groups.

Total group. While this group of terminal cancer patients conform in many respects to general population norms on the 16 PF (Cattell and Eber, 1962), they do differ in some important ways on a number of the factors: (1) They are less intelligent both as measured by earlier use of Factor B items and by continuing administration of the WAIS. (2) This group of cancer patients is more humble and accommodating, mild and conforming on Factor E ($t = 2.71$, $p < .01$, 2-tail). (3) There is a significantly greater tendency to score low on Factor F—sober, prudent, serious, taciturn ($t = 3.64$, $p < .001$, 2-tail). (4) As a group these cancer patients score significantly higher than general population norms on Factor Q_2 —self-sufficient and resourceful ($t = 3.31$, $p < .001$, 2-tail). (5) There is a highly significant tendency for this group to score well above the general population norm on Factor Q_3 which involves being controlled and socially precise ($t = 4.25$, $p < .001$, 2-tail). These factors form a cluster on second-order factor II. Thus the group as a whole is significantly more introverted than the general population.

TABLE X. Means and Standard Deviations for Sixteen Personality Factor Scores for Short and Long Survivor Groups of Cancer Patients

Factors	Short Survivors N = 10		Long Survivors N = 11		Total Group	
	Mean	S. D.	Mean	S. D.	Mean	S. D.
A	5.3	1.8	5.3	2.1	5.3	1.9
C	4.2	2.0	5.5	2.1	4.9	2.1
E	4.8	1.6	4.4	2.1	4.6 ^d	1.8
F	4.4	1.3	4.3	1.3	4.3 ^e	1.3
G	5.8	1.4	5.9	1.3	5.9	1.3
H	5.2	2.3	5.0	1.5	5.1	1.9
I	4.7	2.2	5.9	1.6	5.3	2.0
L	5.9 ^b	1.4	3.6	1.3	4.7	1.8
M	4.9	2.9	5.5	2.2	5.2	2.5
N	4.7	2.3	5.9	2.6	5.3	2.5
O	6.1 ^c	.9	4.6	2.0	5.3	1.7
Q	3.8	2.0	5.4	2.3	4.6	2.3
Q ¹	6.3	1.9	6.9	1.7	6.6 ^e	1.8
Q ²	6.9	1.9	7.8	1.8	7.4 ^e	1.8
Q ³	5.8 ^c	1.8	4.0	1.7	4.9	1.9
I	5.9 ^c	1.6	3.9	1.7	4.9	1.9
II	4.3	1.4	4.0	1.2	4.1 ^e	1.3
III	5.4	1.8	5.0	1.2	5.2	1.5
IV	4.7	1.9	5.5	2.4	5.1	2.2

a. Factors:

A: Reserved — Outgoing
C: Lower Ego Strength — Higher Ego Strength
E: Submissiveness — Dominance
F: Sober — Happy-go-lucky
G: Expedient — Conscientious
H: Shy — Venturesome
I: Tough-minded — Tender-minded
L: Trusting — Suspicious
M: Practical — Imaginative
N: Forthright — Shrewd
O: Self-assured — Apprehensive

Q₁: Conservatism — Radicalism
Q₂: Group — adherence — Self-sufficiency
Q₃: Undisciplined Self — conflict — Controlled
Q₄: Relaxed-Tense
Second — order Factors:
I: Low Anxiety — High Anxiety
II: Introversion — Extraversion
III: Tenderminded Emotionality — Alert Poise
IV: Subduedness — Independence

b. $p < .01$ 2-tail for difference between means of short and long survivors.

c. $p < .05$ 2-tail for difference between means of short and long survivors.

d. $p < .01$ for difference between means for total group of cancer patients and normative group.

e. $p < .001$ for difference between means for total group of cancer patients and normative group.



16 P F TEST PROFILE

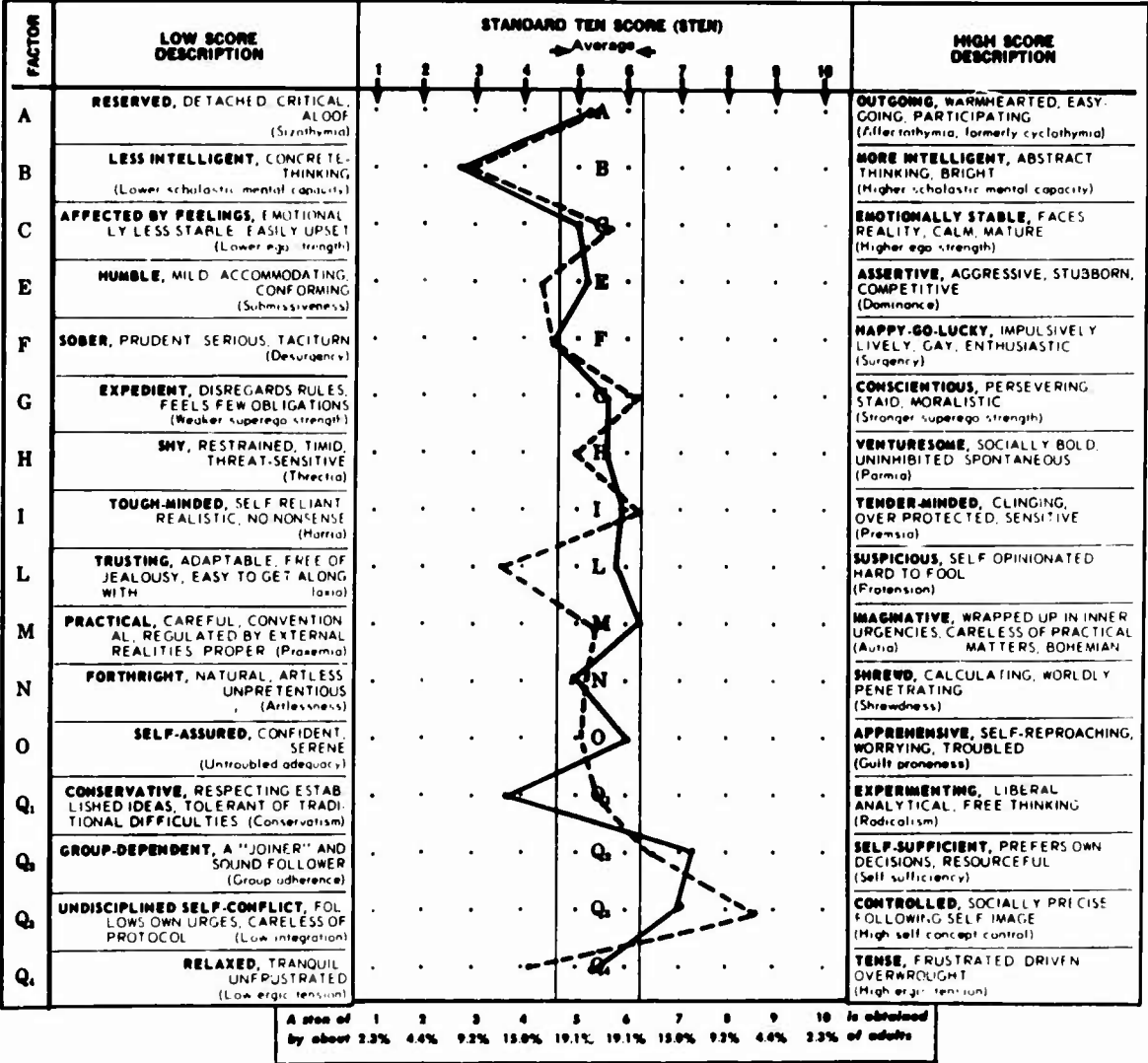


FIGURE 3. IPAT Profiles for Low and High Survival Groups

The Long and Short Survival Groups. As can be seen from Table X, the short and long survival groups also differ from each other on a number of factors. The greatest difference is to be found in Factor L where short survivors are very similar to general population norms but long survivors are significantly more trusting, adaptable, and easy to get along with than are the short survivors ($t = 3.90, p < .01$).

Both short and long survivors are within the normal range on Factor O, but long survivors are significantly more self assured and confident than are the short survivors ($t = 2.18, p \leq .05$, 2-tail).

While short survivors resemble the general population in terms of tension and frustration (Factor Q₄), long survivors are significantly more relaxed, tranquil and unfrustrated ($t = 2.36, p < .05$).

These two groups also differ significantly from each other on second-order Factor I -- anxiety. Again it should be noted, however, that the short survival group does not differ significantly from the general population. Rather it is the long survival group which exhibits markedly less anxiety than either the short survival group or the general population.

In general these results of the IPAT tend to confirm the findings reported a year ago on the basis of a smaller number of patients.

Depression Rating Scales.

Two scales are regularly utilized to assess the amount of depression of patients over the entire study period. The Wechsler Depression Rating Scale -- DRS (Wechsler, Grossen, and Busfield, 1963) and a Clinical Depression Scale devised by Gottschalk.

Figure 4 graphically presents average scores for the subscales and total scale of the DRS at each testing session according to type and amount of radiation received. The scale made up of three parts, is constructed so that a high total score indicates a high degree of depressive symptomatology. The maximum possible total score is 131 and the minimum is 28. Part A of the DRS, labeled "Patient's Attitudes and Feelings," covers items such as the patient's comments regarding his ability to meet his past and future, his assessment of his memory and ability to concentrate, guilt, fear, anxiety, manifest mood, etc. Part B is concerned with physiologic functions such as appetite, sleep, weight change, and changes in energy level. Part C "Observations by the Interviewer" includes an evaluation of motor activity, voice inflection, press of speech, quality of ideation, concentration, tension and energy level.

As noted in previous annual reports, all patients tend to show at least mild depression throughout the period of study. Those receiving partial body radiation are in general consistently lower on all subscales for each measurement period than are those receiving total body radiation. The seven patients who received total body radiation of less than 150, on the other hand, tend to be somewhat more depressed at the time of initial evaluation, and to exhibit more depression subsequent to sham and irradiation. There is a marked similarity of all three groups on day 7. The three groups do not appear to vary much from one another or

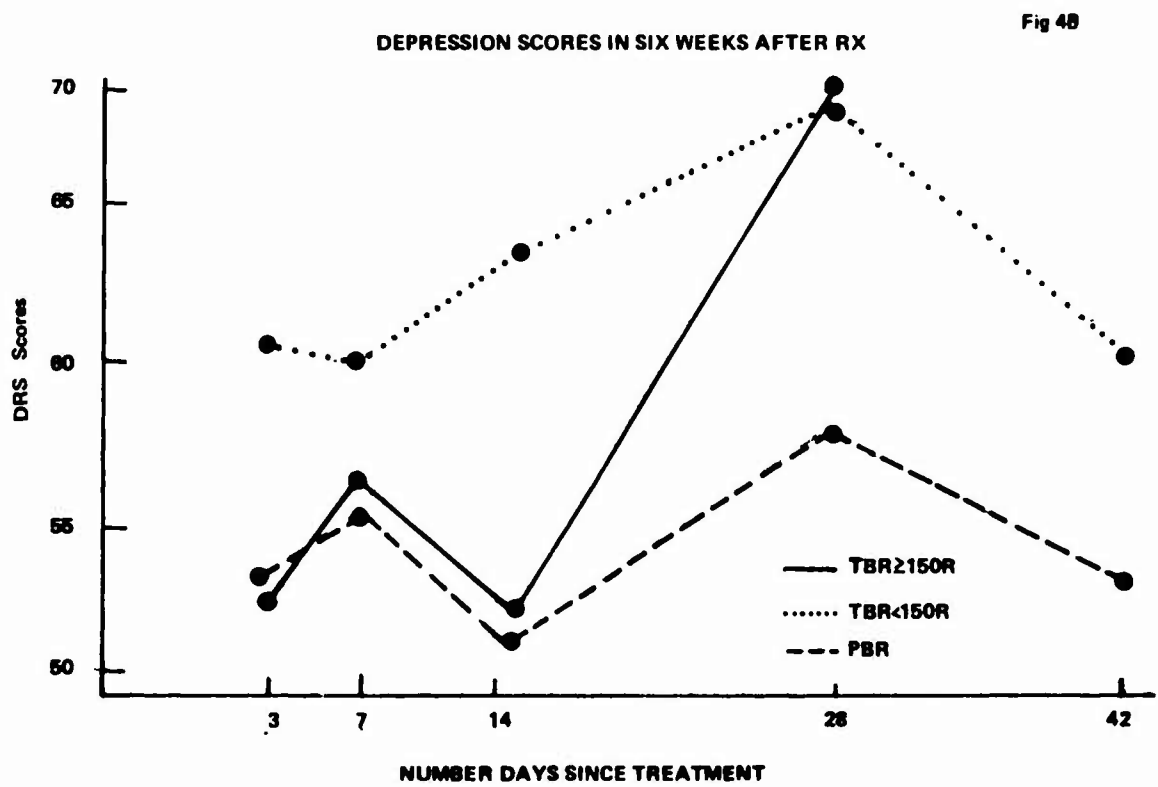
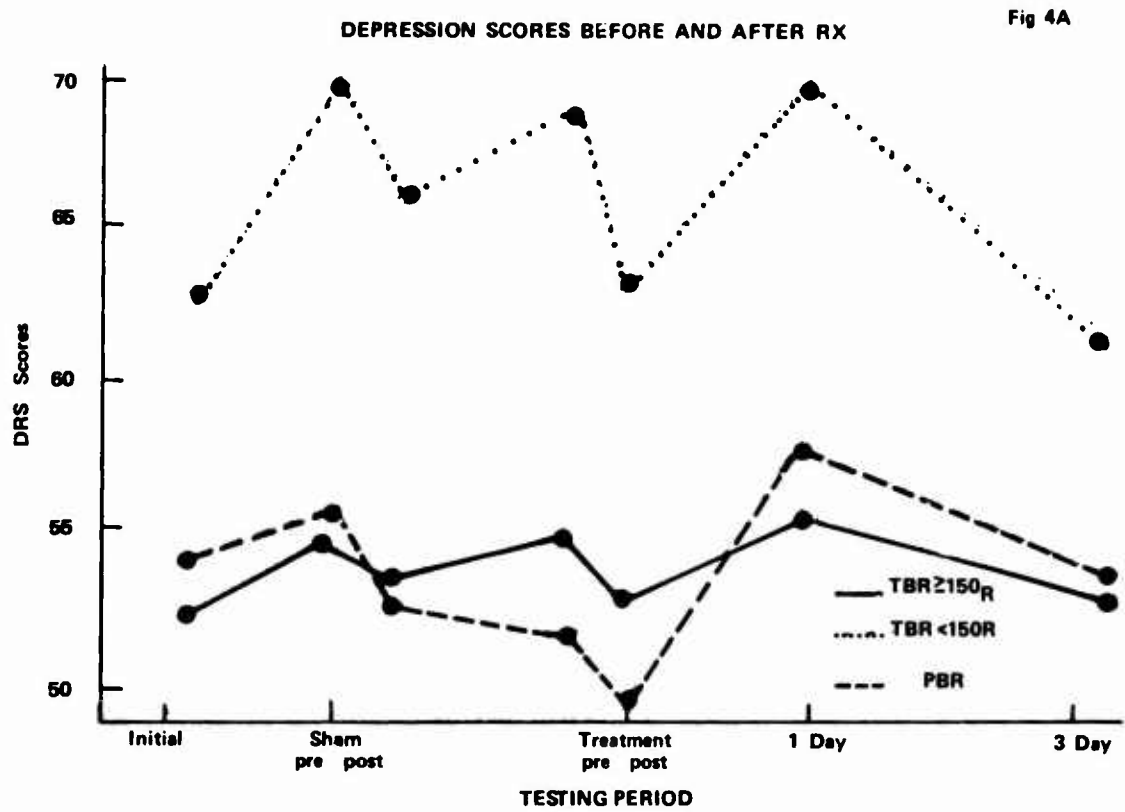


FIGURE 4. Wechsler Depression Rating Scale, Mean Scores by Type of Radiation Received

over time on Part B, "Physiologic Function." This is especially interesting, since as shown in Table XI, there is a significant rank order correlation for the total group of 25 patients between the sum of the first two measurement periods (usually initial and pre-sham) for white cell blood counts and each of the three subscales and the total scale of the DRS.

TABLE XI. Rank Order Correlations Based on Sum of First Two Measures (except for I.Q. and Survival Time)

	DRS-A	DRS-B	DRS-C	DRS-Σ	CDS	Est. I. Q.	Total Words	Anxiety	Hostility In	Ambiv. Hostility	Hostility Out	Human Relations	Schiz.	Cognitive Impair.	Hope	Health-Sickness	White Cell Count	Hemo. in gr.	Survival Time
DRS-A		.65	.80	.88	.84	.31	-.39	.11	.27	.25	.26	-.22	.23	+.30	-.23	-.08	.63	-.28	-.33
DRS-B			.52	.81	.74	.56	-.42	.24	.33	.19	.34	-.16	.25	+.39	-.30	-.04	.42	-.36	-.49
DRS-C				.91	.79	.19	-.60	.15	.44	.25	.36	-.28	.49	+.21	-.29	-.13	.67	-.42	-.34
DRS-Σ					.90	.35	-.53	.10	.38	.20	.25	-.17	.30	+.37	-.25	-.10	.59	-.41	-.36
CDS						.42	-.44	.11	.26	.35	-.37	-.29	.24	+.33	-.28	.10	.62	-.25	-.39
Est. I. Q.							-.19	.16	.13	.26	.39	-.32	.14	+.40	-.40	.25	.10	-.01	-.28
Total Words								-.11	-.36	-.14	-.30	.19	-.23	.50	.06	.22	-.26	.28	.18
Anxiety									.65	.53	.51	-.26	.35	-.06	-.20	-.00	.13	-.07	.01
Hostility In										.39	.40	-.16	.59	-.12	-.21	.05	.28	-.30	-.14
Ambiv. Hostility											.56	-.57	.21	-.01	-.44	.31	.12	.23	-.22
Hostility Out												-.75	.27	-.21	-.72	.17	.34	-.06	-.15
Human Relations													-.30	-.03	.75	-.27	-.18	.13	.23
Schizophrenic														-.34	-.38	.30	.41	-.20	-.31
Cognitive Impairment															-.07	.28	-.16	.33	-.15
Hope																+.49	-.19	-.05	.32
Health-Sickness																	.18	.17	+.53
White Cell Count																		-.49	-.29
Hemoglobin in gr.																			.23

DRS = Depression Rating Scale
CDS = Clinical Depression Scale

Figure 5 shows the mean DRS scores for the three subscales and for the total scale by survival groups, i. e., those who lived less than 100 days following total or partial body radiation and those who lived 100 days or more following treatment. On all days of evaluation, and for all subscales, those we have defined as the short survival group show higher depressive symptomatology. As the days pass following treatment this discrepancy between the two groups grows more pronounced, especially in the area of attitudes and feelings.

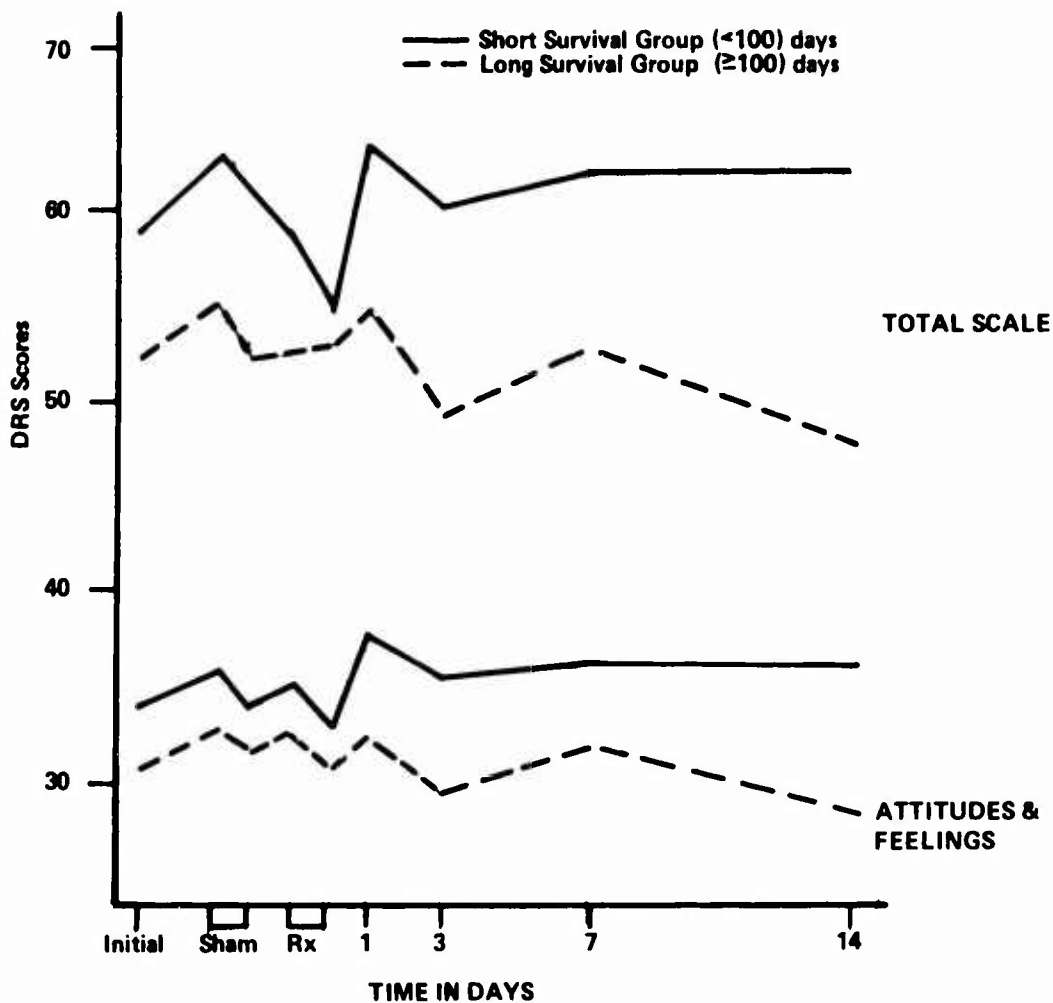


FIGURE 5. Wechsler Depression Rating Scale, Mean Scores for Survival Groups

Measures Based on Verbal Behavior.

Affect scales. A number of rating scales devised by Gottschalk and Gleser (Gottschalk and Gleser, 1969; Gottschalk, Winget and Gleser, 1969) have been applied to the verbal samples collected from subjects at each of the 13 measurement times. Figure 6 shows the average scores for the group of 25 subjects for anxiety, hostility directed outward, hostility directed inward, and ambivalently directed hostility. Average anxiety is high at the time of the initial interview and dips sharply at the time of the post-sham assessment and then level off in a downward slope. Neither hostility directed inward or ambivalently directed hostility show more than minor fluctuations, although average hostility directed inward scores at the time of sham and radiation treatment are somewhat above those of normative groups.

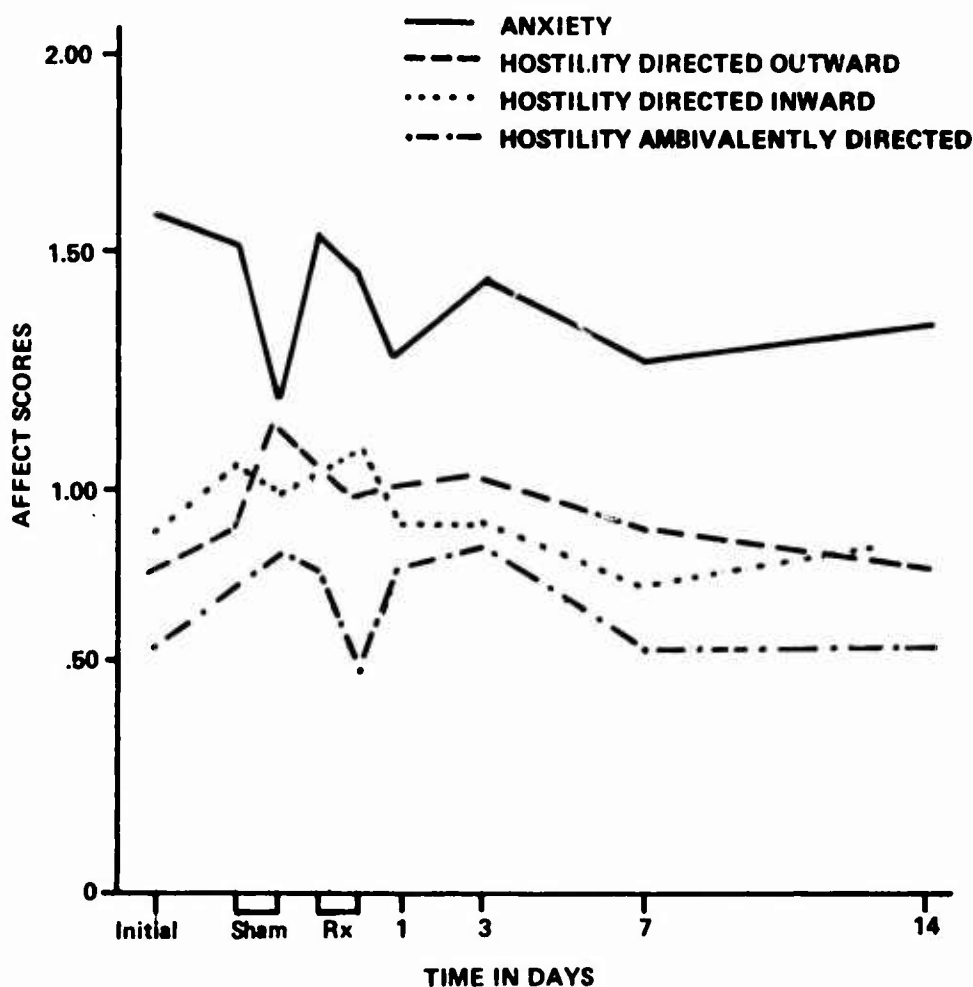


FIGURE 6. Average Affect Scores from Verbal Behavior for Total Group (N=25)

Table XI, based on the sum of the initial and pre-sham measures, shows the intercorrelation of the affect measures with some other variables. There is a high positive correlation between anxiety and hostility directed inward, hostility directed outward and ambivalently directed hostility ($r = .65, .51, \text{ and } .53$ respectively). Hostility in, as measured by content analysis of verbal behavior, also shows a significant positive correlation with subscale C of the DRS, i. e., observation by the interviewer of depressive symptoms in the patient. There is likewise a high positive correlation between hostility in and the measure of social alienation and personal disorganization (Schizophrenic Scale). Ambivalent hostility (which measures feelings that persons or situations are hostile to the self) shows a high positive correlation with hostility directed outward.

Number of words spoken. The number of words spoken in a five-minute time period in response to the standardized instructions for obtaining verbal samples was also examined. Figure 7 presents the data on the average number of words spoken by type of radiation received. If one hypothesizes that this measure in some respect is an index of one's ability to carry on an assigned activity, then it is clear that those receiving total body radiation of 150 or more not only are not less competent in this respect but show a trend toward increased output on days 7 and 14. This group, however, shows more of a dip in verbal output at the time of post-radiation and on day 3 than do either those receiving total body radiation of less than 150 or those receiving partial body radiation.

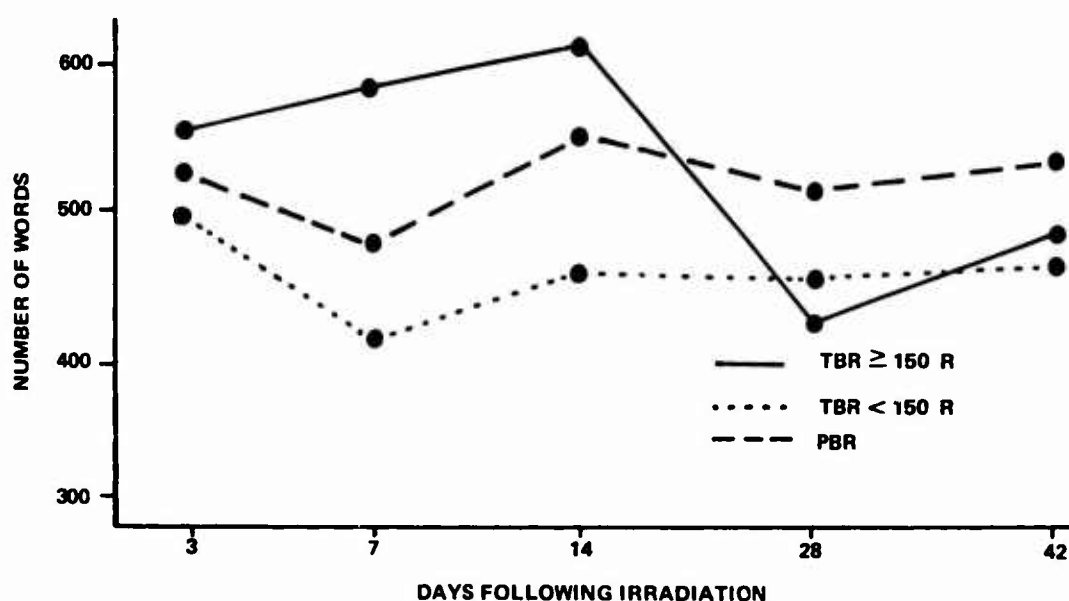


FIGURE 7. Verbal Output in the Six Weeks After Rx

The data on average number of words spoken was also analyzed by short and long survival groups and these data are presented in Figure 8. Both groups are almost identical at the time of initial evaluation but those who will subsequently become the long survival group consistently produce a higher average verbal output in five minutes at each measurement period after the initial one.

There are relatively high negative correlations (see Table XI) between verbal output at the time of the two early interviews and all of the measures of depression, and lower negative correlations between average number of words spoken and the four affect scales.

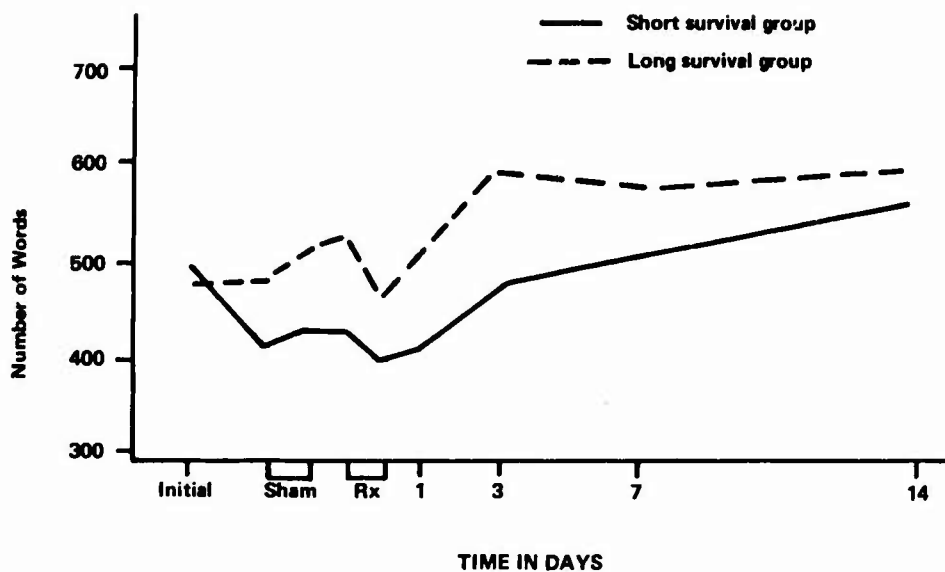


FIGURE 8. Average Number of Words Spoken by Survival Group

Human Relations, Hope, and Health-Sickness Scales. The verbal samples obtained were also independently scored for several additional scales. The Human Relations Scale, which assesses both positive and negative object relatedness, did not yield important differences either for the three different radiation type groups or for the subjects divided into short and long survival groups. Human relations was significantly negatively correlated with both ambivalent hostility and hostility directed outward. There was a very high positive correlation with hope as measured by content analysis of verbal behavior (see Table XI).

Table XI also gives the rank order correlations of the Hope Scale and the Health-Sickness. In general, hope assessed by content analysis shows modest negative correlations with the various measures of depression and with hostility directed inward and ambivalently directed hostility. There is a somewhat higher negative correlation between the Hope Scale and I. Q. as assessed by the WAIS, i. e., there is a tendency for those with lower I. Q. to express greater hopefulness in their verbal behavior at least in the early stages of their participation as study patients. There is a high positive correlation between the Hope Scale and human relations. Health-sickness and hope are also positively correlated, i. e., the subject who makes hopeful statements is also likely to verbalize attitudes of physical well-being. As a total group, these patients show a peak of hopeful attitudes at day 3, post-radiation. Except for the pre-treatment measure, the short survivors consistently manifest less hopeful attitudes on the average than those who make up the long survival group.

There are essentially no correlations between the verbal behavior measure of health-sickness and the various depression measures. Nor are the patients' verbalizations with regard to physical state related to the two hematology measures. There is a significant positive correlation between statements regarding health and physical functioning during the two initial assessment periods and ultimate survival outcome. Those who survive fewer days after treatment tend to express more statements of some type of physical malaise.

Cognitive Impairment.

The primary function of the psychological evaluation of patients on this project has been the attempt to assess the effects of partial and total body radiation on cognitive and intellectual functioning. This is a complex and multidimensional construct, susceptible to many psycho-dynamic and psychobiologic influences. Hence, some of the psychological influences—such as affective states—have been analyzed so as to understand as many influences as possible. This is especially necessary in view of the nature and extent of the physical illness of the patients who comprise our patient population for this project. The physical condition of an overwhelming proportion of the patients seen for psychological evaluation over the course of the last five years has been such that they have been unable to undertake even the most simple of performance tests with any consistency. At times this has been due to difficulties with vision, use of hands, or total physical disability which precluded sitting up in bed. In other instances the low level of basic intellectual functioning of the patient has precluded adequate task performance. We have therefore been forced to rely in large measure on the effect of radiation treatment on cognitive functioning via the content analysis of verbal behavior.

The cognitive impairment scores presented in this report continue to utilize the weighting system of earlier reports. There continues to be a negative correlation between cognitive impairment scores and scores obtained on the Wechsler Adult Intelligence Scale ($r = -.49$).

Figure 9 presents graphically the average cognitive impairment scores for three groups of patients by type of radiation received: total body radiation equal to or greater than 150, total body radiation less than 150, and partial body radiation. The shape of the curve for both the low and high dose total body radiation groups is remarkably similar through day 3 post-treatment. At day 3, the three types of radiation groups show essentially identical cognitive impairment average scores. The low total body radiation and the partial body radiation groups diverge sharply from the high total body radiation group at the time of the day 7 assessment, with the high total body radiation group manifesting a very sharp downward swing, while the other two groups tend to peak upward. By day 14 all three groups tend to peak upward. By day 14 all three groups are again very similar in average cognitive impairment scores.

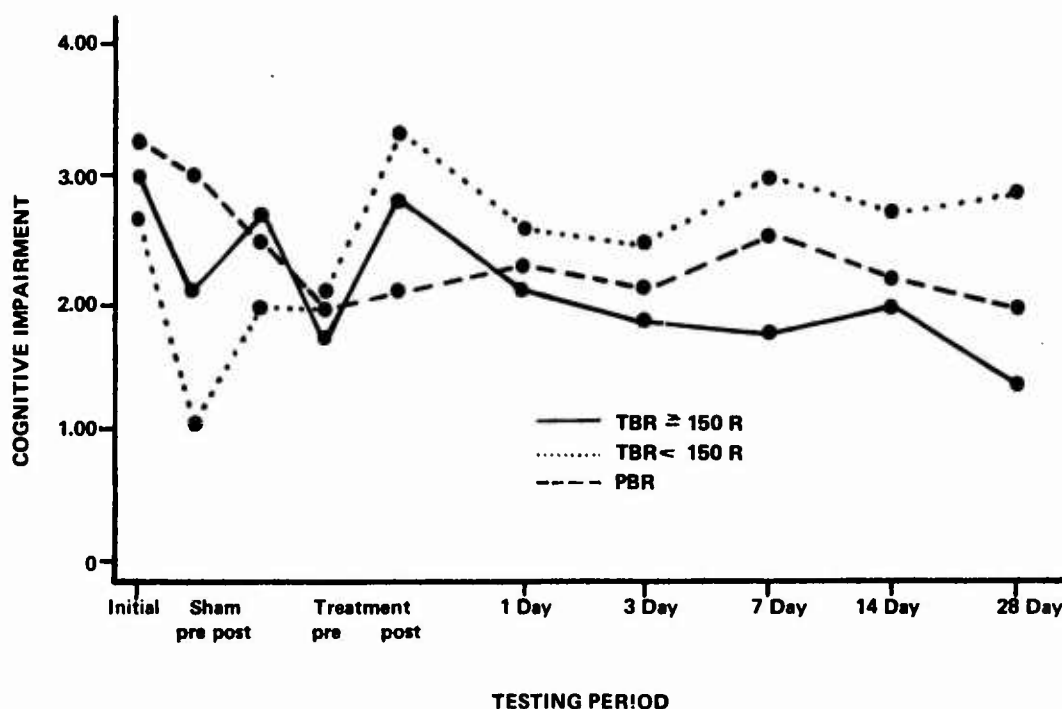


FIGURE 9. Cognitive Impairment Before and After Rx

If one examines these cognitive impairment data on the basis of survival time, the trends which were reported last year continue to be manifest. These data are presented in Figure 10. Again, both the short and long survival groups start with almost identical average cognitive impairment scores. The form of the two curves is highly consistent through day 3, with both groups showing a dip in pre-treatment scores and a subsequent rise on the post-treatment occasion. There is sharp divergence between the two groups at day 7 with those designated as long survivors deviating radically in the direction of greater cognitive impairment.

In an attempt to focus more sharply on cognitive functioning, we have also selected certain items given a positive (or zero) weight in the cognitive impairment scale and examined them more closely. These items are:

- IIA Disorientation
- IIB4 Not prepared, now knowing, not sure, forgetting
- IIIA1 Inaudible or not understandable words
- IIIA2 Incomplete sentences, clauses, phrases, blocking
- IIIA3 Illogical, bizarre, erroneous statements
- IIIB1 Repetition of words
- IIIB2 Repetition of phrases or clauses.

Each item was given a weight of one and a corrected score based on the number of words spoken in five minutes was derived.

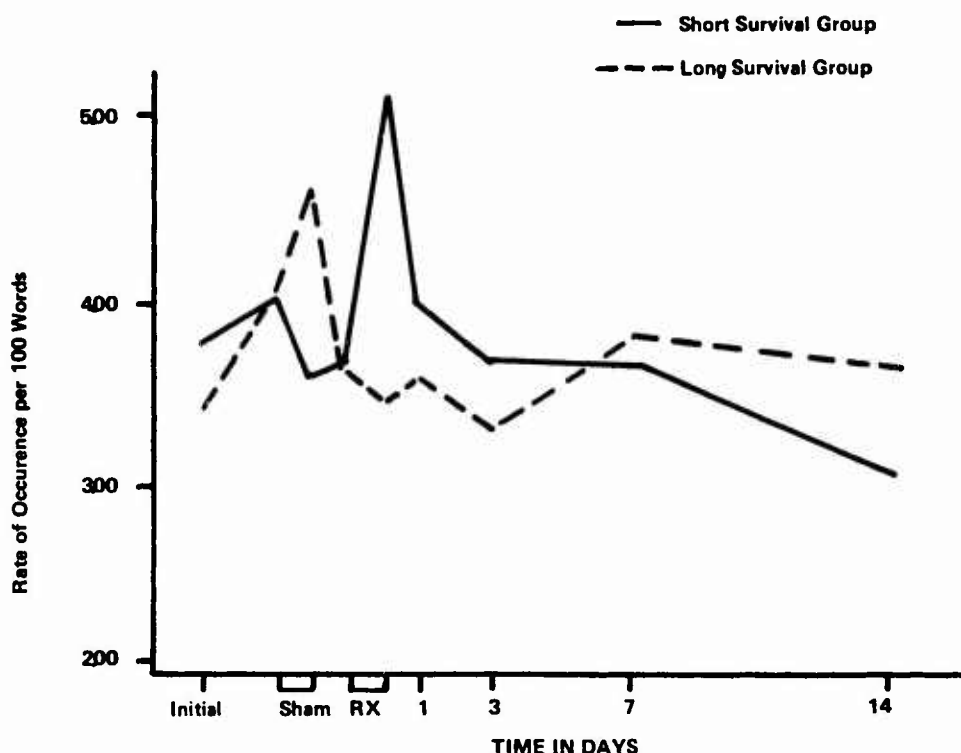


FIGURE 10. Poor Cognitive Functioning by Survival Time

These data are shown in Figures 11 and 12. Using this method, there continues to be marked pre- and post-sham variations for the groups who will subsequently receive total body radiation less than 150 rad or partial body radiation. Those who will receive total body radiation equal to or greater than 150 rad have initial values identical to those of the other two groups, but show a drop for pre- and post-sham, and then a subsequent rise for the pre-treatment, post-treatment, and day 1 measures. At day 3 the three groups are quite similar and by day 7 the picture is almost identical with that presented by the total cognitive impairment scale. One factor influencing these variations may be the total words spoken. As shown in Table XI, there is a high positive correlation for the first two measures between total number of words spoken and the cognitive impairment score, i. e., the more the patient spoke, the more likely he was to show manifestations of forgetting, repetition, confusion, illogical ideation, etc. Since in general those receiving total body radiation greater than 150 rad consistently were more verbal at each measurement period there was increased likelihood of increased cognitive impairment scores. This explanation is suspect, however, if one takes into account the survival time data, for those with the shortest survival time uniformly averaged fewer words for each occasion and also consistently averaged lower cognitive impairment scores on the total scale at each measurement period.

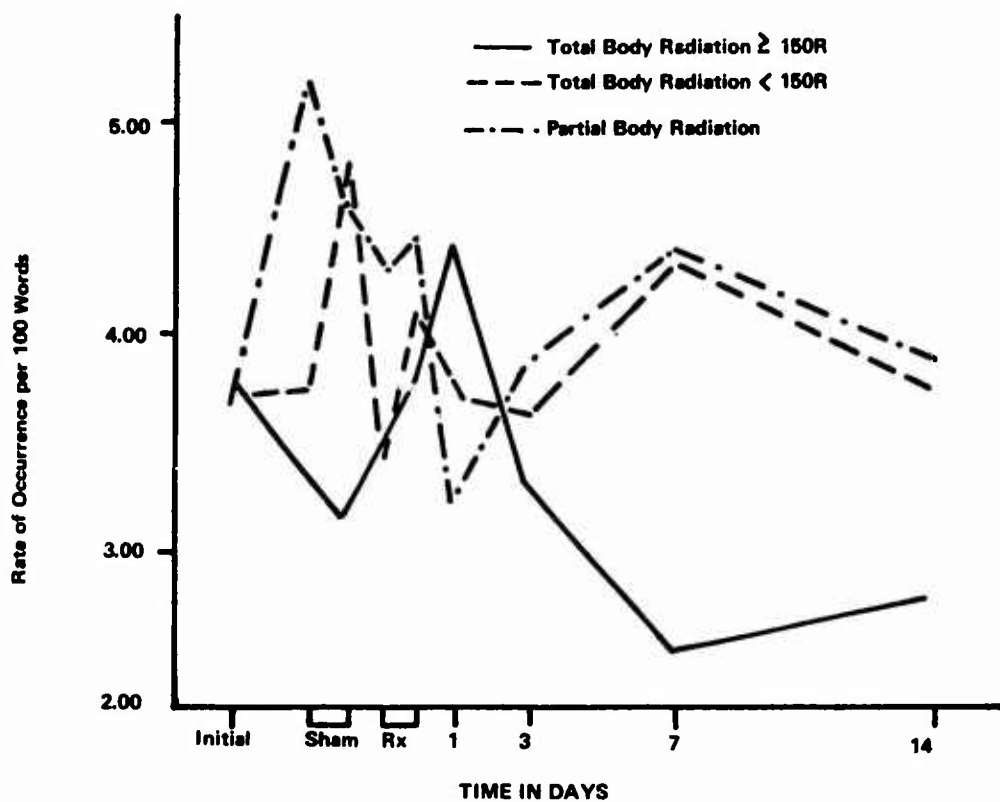


FIGURE 11. Poor Cognitive Functioning by Radiation Dose

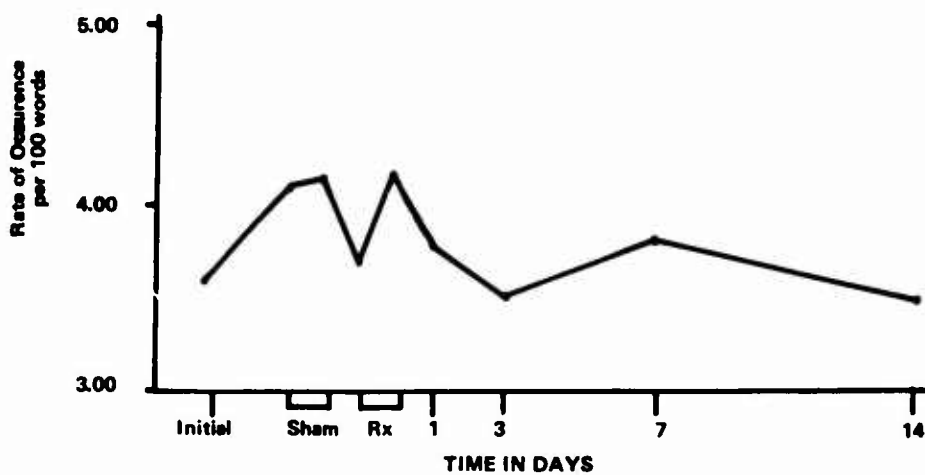


FIGURE 12. Poor Cognitive Functioning Items – Total Group

Summary

There have been two major areas of interest for those involved in the psychological evaluation of subjects on this project:

- (1) The identification and elucidation of those psychological variables which are predictive of survival time; and

(2) Intensifying the focus on variables differentiating those receiving high total body radiation from those receiving either low total body radiation or partial body radiation. In both of these areas, progress has been made as the total number of subjects for whom data are available has increased.

With regard to survival time it should be emphasized that outcome predictions are based on measures taken prior to the time the subject receives any radiation treatment. It appears that the lower the depression scores initially, and the higher the Health-Sickness scores (i. e., the fewer statements the patient makes about feelings of physical and emotional malaise), the longer the survival time. There is a tendency for higher verbal output under standardized conditions at the time of the initial measures to correlate with shorter survival time. In addition, it was noted that the anxiety score on the IPAT also related to survival time; the more anxious the subject, the lower the survival time. A multiple correlation of .79 was found between long survival time and the weighted sum of scores on Part B of the depression inventory, the health-sickness score, total number of words, and cognitive impairment. Adding the IPAT anxiety score raised the correlation to .87. The resulting multiple regression prediction needs to be cross-validated and the limitations of its use explored.

The longitudinal nature of our data collection, the use of pre- and post-treatment measures, and the employment of varying doses of radiation have all been important factors in increasing our focus on those variables differentiating high and low dose groups. Presumably if radiation affects cognitive functioning at all, the effect should be more pronounced at the higher dose levels. For all subjects, there is a tendency for cognitive impairment scores as measured by verbal behavior to decrease by the third day after radiation treatment. The average scores increase again by day 7 for all subjects but those in the high total body radiation group. In order to investigate how this finding regarding cognitive impairment might be interpreted, we also looked at those items of the Cognitive Impairment Scale which seemed most likely to represent actual disruption of cognitive processes. The same pattern with regard to the group receiving high total body radiation persisted and was even more pronounced.

Except for those subjects where nausea intervened and they were not able to accomplish the verbal behavior task, the amount of radiation used in treatments does not seem to interfere with fluency of speech, except for the measure taken immediately post-treatment. The low total body radiation group does not show this immediate post-treatment effect, but the partial radiation group does, particularly as a result of sizeable decreases by the two persons given 300. By the third day there is a sizeable difference in response between the high total body radiation and the other two groups. The latter group is somewhat below its initial value while the low total body radiation and the partial body radiation groups are above theirs.

Further data analysis will be aimed at using these trends and possibly others to obtain a multiple regression equation to predict amount and type of radiation.

V. CASE HISTORIES

STUDY NO. 083

PATIENT E. P.

CHART NO. CGH No. 445-774

This patient, a 78 year old Caucasian female, was first admitted to Cincinnati General Hospital May 12, 1966, with a right breast mass which had been present since December, 1965, and with back pain and weakness in both legs of several weeks duration. Biopsy of the right breast on May 13, 1966, revealed (Path. No. SP-1591) carcinoma. A dorsal laminectomy and biopsy (Path. No. SP 66-1732) on May 23, 1966, revealed metastatic carcinoma. X-ray therapy 2500 R minimal tumor dose was given from June 1, 1966, to June 17, 1966, to the thoracic spine. The patient was discharged to her home July 27, 1966, to be followed by Tumor Clinic.

On August 7, 1968, the patient was admitted to CGH for possible total body radiation. A liver scan on August 14, 1968, revealed some decreased activity consistent with metastases. The patient received sham irradiation on September 3, 1968, with no adverse side effects. On September 4, 1968, she received 100 rad midline absorbed tissue dose (144 R midline air exposure) of total body radiation. She vomited twice approximately 2 hours post irradiation and several times the following day. On October 7, 1968, 33 days post TBR, her white blood count suddenly dropped to 3100, due to medication (Mellaril) rather than irradiation. The medication was discontinued and her count returned to normal.

The patient was discharged on October 31, 1968, 57 days post TBR, to a nursing home to be followed by Tumor Clinic.

April 29, 1969, the patient was seen in Tumor Clinic. At that time she complained only of minimal cervical spine pain. She expired May 26, 1969, 264 days post TBR.

STUDY NO. 084
PATIENT E. C.
CHART NO. CGH NO. 354-960

This patient, a 65 year old Negro male, was admitted to CGH March 5, 1968, with a four month history of pain radiating down the ulnar aspect of his right arm, forearm and hand and weakness in his right hand. Chest x-rays on March 5, 1968, revealed bullae in both lungs and blunting of both costophrenic angles. Right apical density was compatible with Pancoast's Tumor. A right brachial arteriogram and venogram, performed March 13, 1968, were within normal limits. The patient refused a scalene node biopsy and was discharged March 20, 1968 to be followed in Chest Clinic.

The patient was again admitted April 9, 1968. A right scalene node biopsy was performed April 17, 1968 (Path. No. SP 68-1243) and diagnosed as: Metastatic Poorly Differentiated Carcinoma. Lymph Node. Co-60 teletherapy to the right lung apex was from April 23, 1968, with a total tumor dose of 4000 R.

The patient was last admitted to Cincinnati General Hospital on October 14, 1968 for possible total body radiation. The patient was shammed on November 4, 1968, and treated on November 7, 1968, with 300 rad midline absorbed tissue dose (471 R midline air exposure) of partial body radiation to the upper body. He experienced only slight nausea and anorexia following treatment.

He was discharged to his home on November 16, 1968, 9 days post PBR, to be followed by Tumor Clinic.

The patient was last seen in Tumor Clinic on August 7, 1969, complaining of anorexia and an eleven pound weight loss. Physical examination revealed considerable tightness and and fibrosis in the right supraclavicular area with drooping of the right shoulder and increased skin pigmentation.

STUDY NO. 086
PATIENT M. J.
CHART NO. CGH NO. 475-403

This patient, a 57 year old white female, was admitted to Cincinnati General Hospital on November 20, 1968, complaining of left anterior chest pain and a chronic non-productive cough with several episodes of hemoptysis during the previous eight months. Chest films on November 20, 1968, revealed left lower lobe infiltration with probable left lower lobe collapse and a large pleural effusion. A thoracentesis on November 21, 1968, was positive for malignancy. On December 12, 1968, the patient received an intrapleural injection of nitrogen mustard. A left shoulder film demonstrated a metastatic lesion of the left clavicle. On December 18, 1968, 3200 R tumor dose to the left clavicle and 3000 R tumor dose to the mediastinum was begun. Radioactive gold was instilled in the left pleural space on January 3, 1969. A tumor dose of 4000 R was administered to the retrobulbar region from January 16, 1969 to February 12, 1969.

Sham irradiation was given February 24, 1969, with no adverse side effects.

The patient was treated on February 25, 1969, with 100 rad midline tissue dose (142 R midline air exposure) of total body irradiation. She tolerated the procedure well. Her hemogram remained fairly stable until March 4, 1969, 7 days post TBR, when her hematocrit dropped to 25%. She received two units of packed red cells on March 5, 1969; however, her condition continued a steady down hill course and she expired on March 18, 1969, 20 days post TBR.

STUDY NO. 087
PATIENT D. W.
CHART NO. C. R. C. No. 193-614

This patient, a 10 year old Caucasian female, was admitted to Children's Hospital on February 17, 1969, for whole body irradiation and evaluation of her previously diagnosed Ewing's Sarcoma (Path. No. S 68-1873) of the right distal femur. She had been treated with 7000 R tumor dose to the right femur over a 49 day period from July 18, 1968 to September 8, 1968.

On March 3, 1969, approximately 500 cc of bone marrow was aspirated from the anterior and posterior iliac crests of the patient's identical twin. The patient was shammed on February 25 and 26, 1969, with no adverse side effects. She was treated on February 17, 1969, with 200 rad midline absorbed tissue dose (278 R midline air exposure) of total body irradiation. Nausea and vomiting occurred within sixty minutes; however, after eleven hours these symptoms subsided. On March 3, 1969, 4.38×10^9 of her twin sister's filtered bone marrow cells were infused. Trypan blue viability at the time of the infusion was 99%. She tolerated the procedure well with the exception of a slight elevation in temperature.

The patient's hemogram reached its lowest on March 24, 1969, 25 days post TBR. The white blood count was 2100, platelet count, 54,000, and the hematocrit, 29%. She was discharged to her home April 5, 1969, in good condition with her hemogram near normal.

The patient remains in good condition 195 days post TBR.

STUDY NO. 088
PATIENT K. D.
CHART NO. C. G. H. No. 192095

This patient, a 53 year old Negro female, was first admitted to the Cincinnati General Hospital December 2, 1968, complaining of cough, anorexia, hemoptysis and shortness of breath for a duration of three weeks. A chest film on December 2, 1968, represented a right upper lobe density and a shadow superimposed over the aortic knob. Chest fluoroscopy and barium swallow revealed esophageal varices secondary to obstructed superior vena cava and partial right upper lobe bronchus. On December 7, 1968, nitrogen mustard was given and from December 9, 1968 to January 10, 1969, a tumor dose of 4100 R, Co-60 teletherapy was administered to the supraclavicular area and mediastinum. She was discharged on December 24, 1968, to be followed in Tumor Clinic.

On March 10, 1969, the patient was readmitted due to severe pain in her right side, and difficulty in walking. Axillary lymph node biopsy (SP 69-799) on March 14, 1969, revealed: Metastatic Undifferentiated Carcinoma. An upper G. I. series on March 26, 1969, revealed probable metastatic lesions involving the mesentery of the small intestine.

The patient was shammed on April 7, 1969, with no adverse side effects. On April 9, 1969, she was treated with 150 rad midline tissue dose (244 R midline air exposure) of total body irradiation. She tolerated the procedure well; however, her condition continued steadily downhill and she expired on March 16, 1969, 7 days post TBR.

STUDY NO. 089
PATIENT E. A.
CHART NO. 226-470

This patient, a 71 year old Caucasian female, was transferred from Drake Hospital to Cincinnati General Hospital for partial to total body irradiation on April 4, 1969, with a diagnosis of metastatic carcinoma of the breast, (Path. No. unobtainable) and myasthenia gravis. Chest films on April 14, 1969, revealed extensive metastatic disease.

She was shammed on April 25, 1969, with no adverse side effects. On April 28, 1969, with no adverse side effects. On April 28, 1969, the patient was treated with 200 rad midline tissue dose (347 R midline air exposure) of partial body irradiation. She tolerated the procedure well.

On May 4, 1969, she developed a urinary tract infection which responded to antibiotic therapy. The patient continued to be lethargic with episodes of dyspnea and May 14, 1969, 16 days post PBR, she expired.

STUDY NO. 090
PATIENT M. B.
CHART NO. 368-065

This patient, an 80 year old Negro female, was admitted to Cincinnati General Hospital on April 19, 1969, complaining of anorexia, weight loss of 70 lbs, right upper quadrant pain and hemoptysis of several weeks duration. Chest x-rays on April 19, 1969, revealed bilateral nodular densities throughout both lung fields, some cavitation consistent with metastatic disease. An IVP on April 22, 1969, revealed no filling of the right kidney and ureter. Cystoscopy and biopsy of the bladder on April 26, 1969, revealed: Transition Cell Carcinoma, Bladder (SP 69-1294).

The patient was shammed on June 2, 1969, with no adverse side effects. On June 4, 1969, 500 cc of bone marrow was aspirated from the posterior and anterior iliac crests and the sternum with ease. At approximately two o'clock in the afternoon, the patient received 150 rad midline tissue dose (226 R midline air exposure of total body irradiation. She experienced only mild nausea and vomiting. Following irradiation the bone marrow containing 15.6×10^9 cells and 96% viability was infused. The patient tolerated the procedure well, no fever, chills or dyspnea were noted.

On June 9, 1969, the patient was noted to have left sided facial weakness, suggestive of a cerebrovascular accident and on June 10, 1969, 6 days post TBR, she expired.

STUDY NO. 091
PATIENT G. S.
CHART NO. 503-512

This patient, a 62 year old Caucasian female, was transferred to Cincinnati General Hospital from Drake Hospital on June 17, 1969, with adenocarcinoma of the sigmoid colon, metastatic to the liver and left humerus, diagnosed in 1967 (at Good Samaritan Hospital). A local resection of the sigmoid colon was performed with end to end anastomosis. In November, 1968, severe back and abdominal pain necessitated the patient's admission to the Good Samaritan Hospital, where she was treated with chemotherapy. Due to increased weakness and disability the patient was transferred to Drake Hospital, May 15, 1969.

The patient received sham irradiation on July 1, 1969. On July 2, 1969, approximately 500 cc of bone marrow was aspirated from both posterior and anterior iliac crests. The patient tolerated the procedure well. Following the aspiration she was treated with 200 rads (295 R midline dose in air) total body irradiation. The bone marrow which contained 4.6×10^9 cells and 98% viability, was then infused intravenously without complications. There was no significant depression of the white blood count or platelet count and she appeared protected from the otherwise severe radiation effect. The patient remained depressed but alert and oriented until she expired August 23, 1969, 52 days post TBR.

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13. ABSTRACT The goal of our program has been to obtain new information regarding the patho-physiologic, psychologic, immunologic, hematologic, and biochemical effects of total and partial body irradiation in human beings. The patients are irradiated, all of whom have inoperable, metastatic carcinoma but are in relatively good health, provide us with the opportunity to study multiple facets of the effects of radiation in man rather than in experimental animal. As we and many other laboratories have discovered, extrapolation of results from laboratory animals to man be-be fraught with error. We have continued our search for a suitable biological dosimeter in human beings. The data contained in this report will suggest several potential biological dosimeters previously considered to be of some value have not fulfilled this expectation. Biochemical and psychological studies have extended the findings of our previous report in depth and scope. Success has finally been obtained in autologous marrow infusion which will permit us to employ higher doses of radiation in the coming year. Several new biological dosimeters are under evaluation. The only change in physical dosimetry has been the addition of partial body radiation from sternum to pubis for selected patients.			

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