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CYTOLOGIC-BIOCHEMICAL RADIATION DOSIMETERS IN MAN

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ABSTRACT

The result of radiation interacting with living tissue is the deposition of energy therein. This energy triggers numerous chemical reactions within the molecules of the target tissues. We have measured in man the results of some of these reactions at doses up to 300 rads: chromosome aberrations; alterations in the kinetics of specific human cell populations; changes in 37 biochemical constituents of serum and/or urine.

The utilization of chromosomes as a biological dosimeter is partially perfected but there are numerous discrepancies in data between different laboratories. Etiocholanolone can be used to evaluate marrow injury before the white cell count falls below 5000 per cu. mm. Most biochemical dosimeters evaluated gave negative or inconsistent results. However, salivary amylase is a promising indicator of human radiation injury from doses as low as 100 rads.

Damage due to ionizing radiation in biological systems is the result of deposition of energy within the tissue of the animal irradiated. Since the victims of the explosion of a nuclear weapon may receive injury from blast and burn as well as radiation, and all three modalities involve the transfer of energy to tissue, the importance of finding a radiation-specific dosimeter cannot be overestimated. However, one might expect a priori that biochemical changes might be relatively non-specific. Our Laboratory has looked at a wide variety of pathophysiologic changes induced by irradiating human beings with whole or partial body radiation. These have included the alterations resulting from the irradiation of nucleic-acid nucleoprotein complexes as reflected in chromosome morphology; changes induced by the steroid metabolite etiocholanolone on granulocyte reserves; abnormalities in the level of several serum and urine enzymes; glycoproteins, and iron. These studies were all performed in ambulatory human subjects who clearly understood the experimental nature of this study according to the Declaration of Helsinki. Several of the subjects were tumor free and essentially normal (following radiation-induced tumor regression) receiving prophylactic whole body radiation. The rest had metastatic carcinomas which were inoperable and not amenable to conventional chemotherapy. Nevertheless, these patients were all clinically stable, many of them working daily. The radiation technique employed in these patients as well as our chromosome culture method will be found in the Appendices A and B.

CHROMOSOME ABERRATIONS

The use of chromosome aberrations as a biological radiation dosimeter began with the classical experiments of Saks (1, 2, 3) and of Lea and Catcheside (4) on the quantitative relation between the change in yield of radiation-induced chromosome aberrations and increasing dose. Although these studies were performed thirty years ago, this use of chromosome aberrations remains a highly controversial area. There are today cytogeneticists who believe that the kinetics of dose-response studied in these early experiments are inapplicable to man, because the earlier work involved plant nuclei having large chromosomes and low chromosome numbers (5), while man has 46 chromosomes (6) of small individual volume.

To justify the use of any dosimeter one must be able to reproduce the calibration curve between the dose of radiation and the response of the test system. Furthermore, one must be able to employ

the dosimeter to ascertain to what extent the test system has been exposed to radiation. That is, one would like to know whether the biological system to be examined has received an homogeneous dose of radiation distributed uniformly or an inhomogeneous dose interacting with all or part of that system. Continuing disagreement about the calibration of human lymphocyte response to radiation and the problem of distinguishing whole from partial body radiation with this system do not permit utilization of radiation-induced chromosome aberration dose-response curves in a rigorous fashion to date. However, there have been several instances where chromosome analysis has been useful in proving that high doses indicated by radiation badges were in fact not received by the individuals wearing them (7,8). Furthermore, chromosome aberrations caused by radiation in man are not affected by ambient temperature and pressure as are physical dosimeters (for which corrections can usually be made).

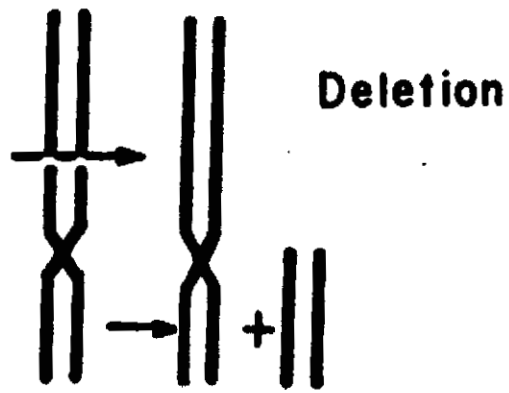
Study of radiation effects on mammalian cells is complicated by the fact that radiation sensitivity of cells varies with the stage of their cell cycle. Repair time of chromosome breaks has been found to be 90 minutes in the G_1 (post mitotic pre--synthetic phase) and S (DNA synthesis) phase but 60 minutes in late S and G_2 (post- synthetic pre-mitotic phase) (9). Furthermore, there is inter-species variation in radiation-induced chromosome aberration curves (10), with the extrapolation from animals to man somewhat hazardous. This variation is probably related to differences in chromosome number and volume between species examined. One would like to use primates in this research, but ideally one must find an animal which has the same chromosome number and configuration as man in order to be confident of the extrapolation.

An important breakthrough occurred when it was found that human lymphocytes could be stimulated to divide <u>in vitro</u> (11) where the mitosis could be arrested with colchicine and then analyzed under the microscope. Furthermore, 99.9% of human lymphocytes are in the G_1 growth phase (12) and this is a period of uniform radiation sensitivity (13). Thus numerous investigators have employed this system to obtain dose-response curves (5, 14-24). These curves were usually derived from <u>in vitro</u> studies. The relationship of <u>in vivo</u> to <u>in vitro</u> experiments will be discussed below.

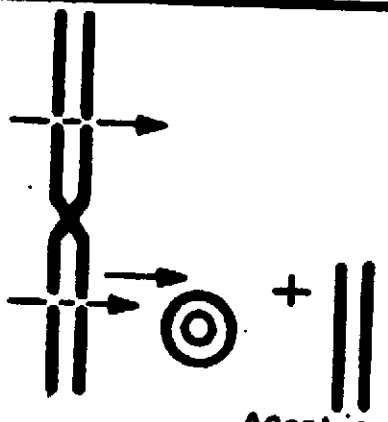
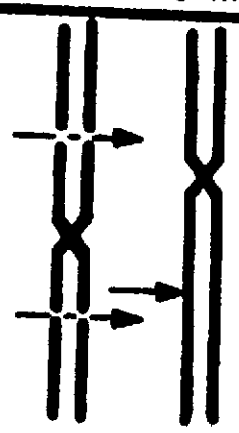
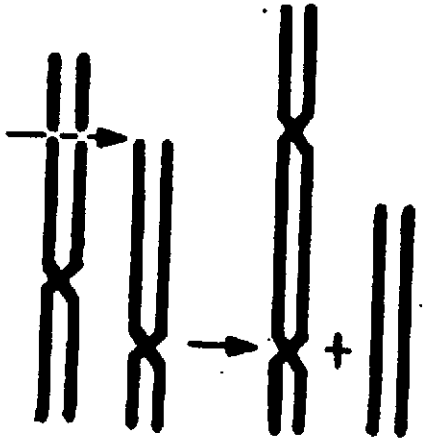
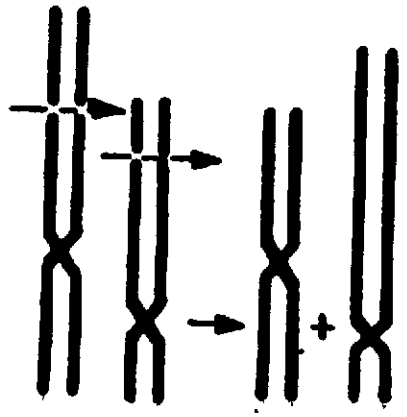
But which "response" should be studied? As noted above, radiation causes chromosome breakage in nucleoprotein or polynucleotide chains (25) which may or may not be followed by recombination between broken ends (1-3). An alternative mechanism has been proposed by Revell, the so-called "exchange-first" hypothesis (26). The aberrations produced (if broken ends do not rejoin perfectly) are of two types, chromatid and chromosome aberrations. Increments in the latter, which occur when chromosomes are in the G_1 pre-DNA synthesis phase, are the types observed in the lymphocyte system with which we are concerned. Breakage and recombination occurring in G_1 will be duplicated during the S phase so that both chromatids of a chromosome will show the abnormalities when viewed in metaphase. Therefore, abnormalities in just one of a pair of chromatids are unrelated to radiation in the system. Figures 1 and 2 indicate the common chromosome aberrations. Chromosomes with more than two centromeres have been observed. The dicentric and ring forms are far easier to score than the more subtle translocation and inversion types where slight changes in centromere position may be the only hint of preceding breakage. Furthermore, in one study the sum of all aberrations apart from dicentrics made up 60 to 70% of the dicentric yield (27). With each dicentric one should also identify an acentric fragment which would be lost after one division. Its presence is evidence that one is indeed observing the first post-phytohemagglutinin induced mitosis. Thus one may use far less experienced laboratory personnel for the chomosome analysis and it can be performed far more rapidly than a search for symmetric aberrations would allow. Since virtually all of the lymphocytes containing the chromosome aberration are not dividing it may be expected that even the unstable dicentric and ring aberrations may persist for a considerable period if the cells containing them are not activated by an endogenous mitogen (28), and if they are long-lived lymphocytes as opposed to the lymphocyte population with a brief life span (29,30).

Figure 1

CHROMOSOME - TYPE ABERRATIONS



CHROMOSOME - TYPE ABERRATIONS

	Asymmetric Aberrations (leaves acentric fragments)	Symmetric Aberrations (more subtle morphologic change)
INTRA-CHANGE	 Ring + Acentric Fragment	 Inversion
INTER-CHANGE	 Dicentric + Acentric Fragment	 Translocation

For the purpose of dosimetry however, lymphocyte cultures should be made as soon as possible. There does not appear to be a difference in aberration yield over 24 hours post-irradiation (5,7,31). After 48 to 72 hours the lymphocyte count in an irradiated human has usually fallen so low that finding enough mitoses to count (50 to 200) is more difficult. However, Bender has stated that "aberration levels measured in peripheral leukocytes remained relatively constant for the first three or four weeks after radiation" (22). The kinetics of this biological dosimeter bear careful consideration because of the current controversies surrounding the dose-response relationship. The rings and dicentrics we measure are each formed from two separate breaks in one or two chromosomes respectively. (Figure 2). These aberrations, when induced by sparsely ionizing x-rays or gamma rays should therefore usually require two separate photons to interact with the environment of the chromosome, and thus the aberration frequency should increase with the square of the radiation dose, while aberrations requiring but a single interaction should increase in linear relationship to the radiation dose. Only an occasional, well-placed single photon should lead to two separate chromosome breaks. Radiation containing particles with high linear energy transfer (L.E.T.) such as neutrons produce a much larger volume of ionizations per particle, and therefore for high L.E.T. radiation dicentrics and rings increase as a linear function of dose (32). In other words, the neutron and other particles with high linear energy transfer generally produce more than one chromosome break per neutron. However, for sparsely ionizing radiation, one might anticipate the yield of rings and dicentrics to be represented by the quadratic equation $Y = c + aD + bD^n$ where Y is the yield of dicentrics and rings after 48 hours of culture, c is the spontaneous frequency for rings and dicentrics (approximately one in 5000 normal cells), a the coefficient of aberration for a single photon inducing rings and dicentrics, b the coefficient for two hit exchanges, D the dose of radiation in rads and n equal to approximately 2 (33). Or if one believes that two separate ionizing events are always necessary for the production of dicentrics and rings, and since these abnormalities are essentially absent in a

"normal" population, one may try to fit the observed data to $Y = bD^n$ assuming n will be close to 2. Tables 1 and 2 summarize available data for cells analyzed after 44 to 52 hours of culture time for rings plus dicentrics or dicentrics alone (since the ratio of dicentrics to rings is usually about 5 to 1). Studies performed on cells cultured for longer periods of time (for example, reference 14) are excluded despite their historical and scientific significance. (See paragraph 2 below).

The discrepancies in these results are striking. How can they be explained? We may offer several reasons for the variations in data.

1. There remains uncertainty if the chromosome response to sparsely-ionizing radiation (x-ray and gamma ray) follows linear, quadratic, or power-law (dose-squared) kinetics, so that there cannot yet be agreement on a calibration curve after 8 years of experimentation. The data may be fitted by several experimental models.

2. Technical differences do not appear to be at the heart of the matter if lymphocytes are cultured for no more than 52 hours before fixation, at a time when they are in the first mitotic division (13). Waiting longer will lead to errors in counting by loss of some dicentric and ring chromosomes during second mitotic division and the formation of "artefactual" dicentrics from chromatid anomalies which self replicate prior to the second mitotic division. Mitotic delay, which theoretically could decrease the number of dicentrics observed at 50 rads, does not seem to be a problem <u>in vitro</u> at doses up to 500 rad (13,36). Temperature variations of as little as 1 degree centigrade may have marked effects on influencing the rate of cell response to phytohemagglutin (37). Two laboratories whose most recent results diverge widely used identical techniques, however (17, 19). One must obviously be

Table 1

COEFFICIENTS FOR THE EQUATION
$Y = c + aD + bD^n$
FOR RINGS AND DICENTRICS
(Quadratic Formula)

a (rad^{-1}) x 10^{-3}	b (rad^{-2}) x 10^{-6}	n	Radiation Rate (rads per min)	Type of Radiation	Ref.
3.42 ± 0.17	3.51 ± .68	2 (assumed)	17.5 - 230.5	250 kVp xrays	5
2.50 ± 0.74	1.35 ± 2.24	2 (assumed)	98 - 200	250 kVp xrays	17
1.78 ± 0.20	2.30 ± 0.53	2 (assumed)	19 - 292	1.2 meV gamma rays (^{60}Co) *in vitro*	17
0.52 ± 0.13	1.72 ± 0.27	2 (assumed)	0.04 - 0.55	1.2 meV gamma rays (^{60}Co) *in vitro*	17

Table 2
COEFFICIENTS FOR THE EQUATION
$Y = bD^n$ FOR DICENTRICS
AND RINGS

b (rad^{-2}) x 10^{-6}	n	Radiation Rate (Rads per min)	Type of Radiation	Ref
1350 ± 280	1.17 ± 0.04	17.5 - 230.5	200 kVp xrays in vitro	5
0.992 - 1.686	1.97	67	250 kVp xrays partial body radiation in vivo	7
12.74 ± 0.15	2.15 ± 0.07	50 R* per min.	250 kVp in vitro	19
5.7 ± 0.5	2 (assumed)	100-200	1.9 meV xrays in vitro	24
---- ***	0.92 ± 0.4	1	2 meV xrays whole body radiation	7
30	1.82	100	250 kVp xrays in vitro	34**
10	1.87	100-200	1.9 meV xrays in vitro	24 as fitted by 34
1200	1.17	17.5- 230.5	250 kVp xrays in vitro	5 as fitted by 34
520	1.13 ± 0.61	1	2 meV xrays whole body radiation	35
42.2	1.88 ± 0.54	1	2 meV xrays whole body irradiation same patients as above, cells taken 24 hrs. after irradiation	35
57 ± 36.4	1.52 ± 0.10	0.04 - 0.55	1.2 meV gamma rays (^{60}Co) in vitro	17
665 ± 240	1.24 ± 0.06	19 - 292	1.2 meV gamma rays (^{60}Co)	17
1170 ± 1540	1.16 ± 0.23	98 - 200	250 kVp xrays in vitro	17
8.50	1.94	-----***	1.5-1.9 meV xrays in vitro	38
25.5	1.78	-----***	1.2 meV gamma rays (^{60}Co) in vitro	38
81.14	1.66	-----***	200 kVp xrays in vitro	38
16.9	1.24	-----***	14 meV neutrons in vitro	38

* Roentgens air dose
** Dicentrics only
*** Information not given

careful of observer bias in analyzing slides and so one should count only dicentrics in cells which also contain an acentric fragment as noted above, indicating that one is indeed observing the first post-radiation mitosis. If one counts more subtle aberrations such as breaks, translocations, and inversions, there is much greater danger of erroneous subjective interpretation. Data on gamma or x-irradiated cultures (5, 17, 34) give lower power functions and higher coefficients for rings and dicentrics than data on irradiated whole blood (24).

3. Lymphocytes are inhomogeneous with respect to function and life span, only about 20% of them having a life span of 72 to 96 hours, many living much longer (30,39,40). Thus, one might hypothesize this as a cause of significant variation between donor lymphocyte aberrations in response to radiation injury and to stimulation by phytohemagglutinin. However, the variation in response between individual blood donors does seem quite small in vitro (14,27) and in vivo (31) when cultures are begun within 24 hours of irradiation. Thus, although there may be significant differences in varieties of lymphocyte populations between individuals, these populations all seem to respond similarly to radiation injury.

4. Dose rates vary widely in the experiments noted in the table. Our own dose rate is rather low, 3.5 to 6 rads per minute. The aberration yield was clearly lower with dose rates of 0.04 to 0.55 rads per minute than with rates of 17.5 to 230.5 rads per minute in a recent series of experiments (5, 27) employing the same techniques in all cultures. The yield in the range from 17.5 to 230.5 rads per minute was essentially identical (5).

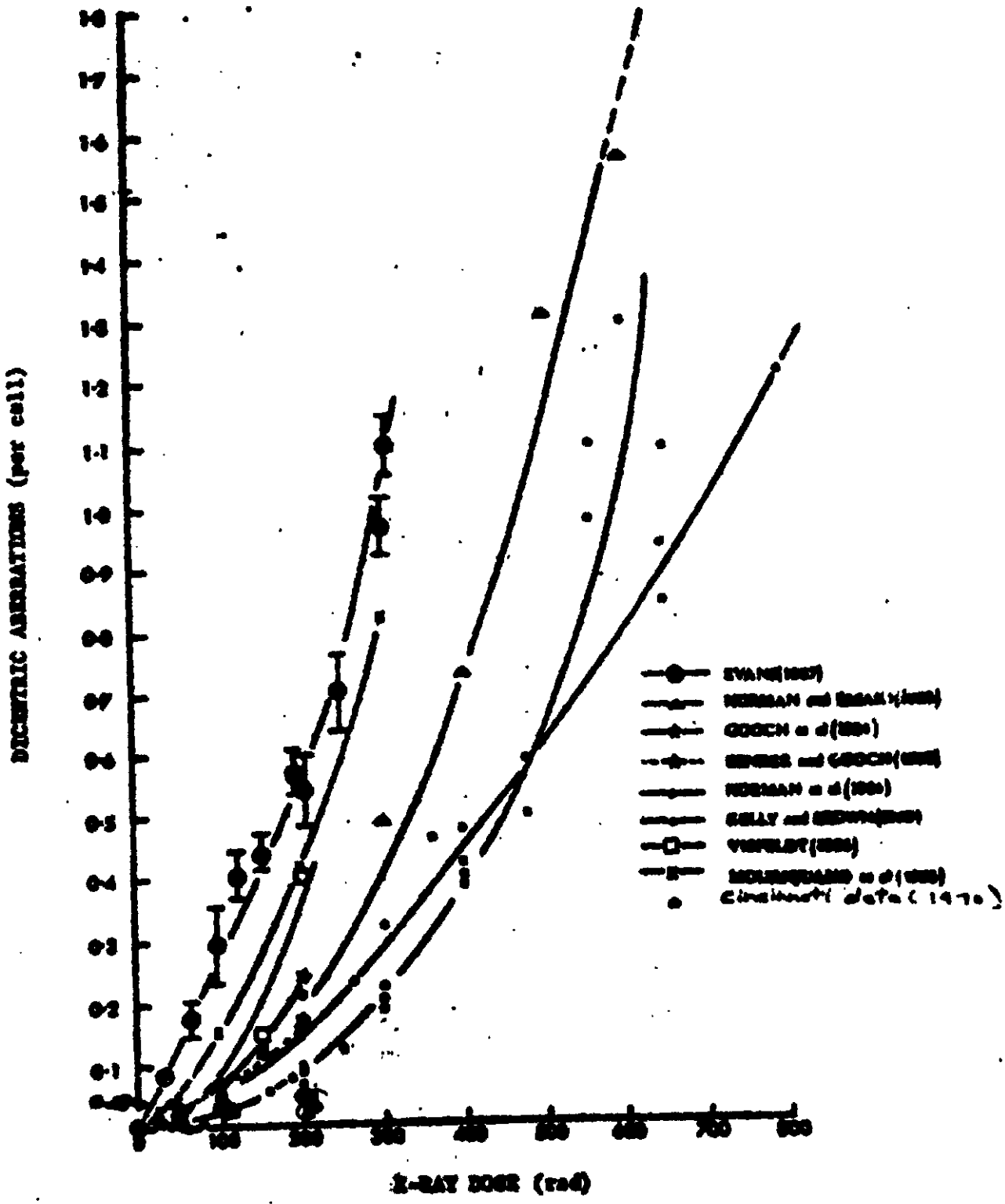
5. The relative biological effect (R.B.E.) varies because different modalities of radiation transfer different amounts of energy to the cells irradiated. Therefore, different calibration curves would seem necessary for high and low energy gamma or x-rays and for neutrons. It is generally agreed that neutrons give a linear dose response because of their high linear energy transfer. The R.B.E. of 14.1 million electron volt neutrons compared to 250 kVp x-rays has been set at 1.9 (41) while for 0.7 MeV neutrons an average value of 3 to 3.5 was found by a different laboratory (23,32). R.B.E. of Cobalt-60 gamma rays was found to be 0.8 (17) when compared to 250 kVp x-rays. The problem of chromosome biologic dosimetry with mixed radiation from reactors or nuclear weaponry thus becomes increasingly complex.

6. Because fewer chromosome aberrations after irradiation are found in an hypoxic environment (42), people with relatively low arterial oxygen saturation might have more radio-resistant chromosomes than those with normal arterial oxygen tension.

7. Another problem with the chromosome system is that of saturation of available sites where breaks can occur at higher radiation doses (24,43,44). Thus, at doses over 500 rads in vitro the dose-response kinetics have indicated saturation in dicentric and centric ring yields (24).

8. Most of the calibration curves published to date have been from in vitro studies with few exceptions, and the in vivo radiation has been with doses of 50 rads or under (7,35). Many use a culture time which we now know is too long, that is 72 to 90 hours (45). Our own preliminary data from one patient given whole body irradiation of 100 rads and three at 200 rads are illustrated in the following Figures 3 and 4. In vivo we find a much lower aberration response than has been seen in vitro. (Our patients all have metastatic, inoperable carcinoma and are clinically stable although they are hematologically normal except for

Figure 3



The Effects of Increasing X-Ray Doses on the Number of Dicentric Chromosome Aberrations in Human Peripheral Blood Lymphocytes. (Courtesy Peter C. Hewlett; Original remarks are cited in Ref. [illegible]

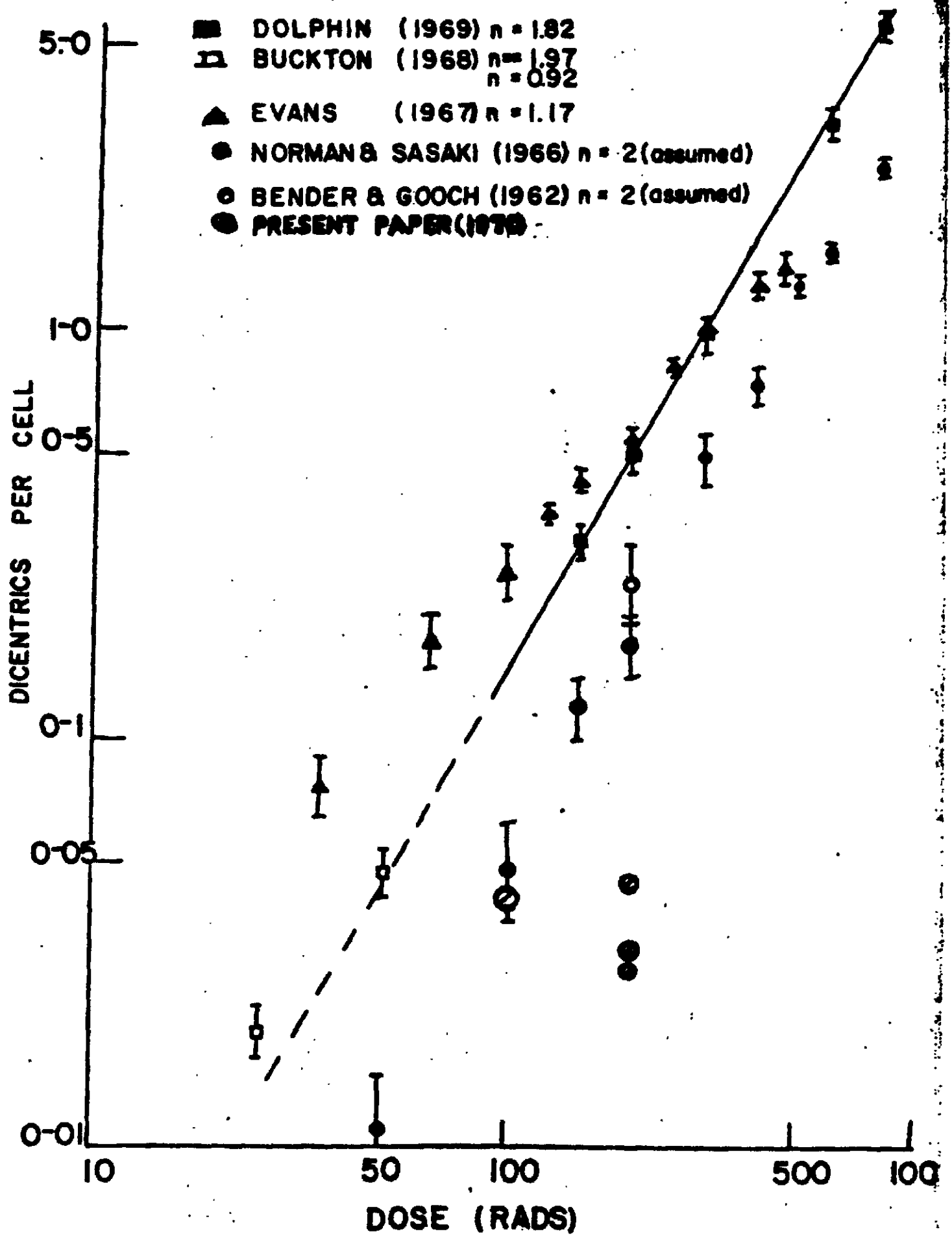

DOLPHIN (1969) n = 1.82
BUCKTON (1968) n = 1.97
n = 0.92
EVANS (1967) n = 1.17
NORMAN & SASAKI (1966) n = 2 (assumed)
BENDER & GOOCH (1962) n = 2 (assumed)
PRESENT PAPER
5·0
1·0
0·5
0·1
0·05
0·01
DICENTRICS PER CELL
10
50
100
500
DOSE (RADS)

Figure 4

frequent mild anemia. The radiation technique and chromosome culture technique appear in Appendices A and B. The patients are all ambulatory and some of them are disease free, receiving prophylactic irradiation). In vivo damaged lymphocytes may be rapidly removed from the circulation, and since our radiation time may extend over an hour, we might miss seeing many cells containing chromosome aberrations. However, our blood samples are obtained from the patient just before and immediately after irradiation. Our dose rate, 3 to 6 rads per minute of Cobalt-60 gamma irradiation is lower than that employed in the other in vivo data (7,35). Perhaps there may be greater resistance to radiation-induced chromosome breakage in vivo than in in vitro or more rapid repair of chromosome breaks in vivo. In vivo-in-vitro comparisons have been made largely from partial body or inhomogeneous irradiation which has been extrapolated to whole body equivalents (22,40, 47) with moderately good agreement.

9. Even if all the difficulties in calibration listed above can be overcome, we are still left with the problem of inhomogeneous exposure which is always difficult to quantitate exactly. A heterogeneous dose of radiation will obviously yield fewer aberrations than the same dose given over the whole body. The numbers of rings and dicentrics found will be related both to the volume of tissue irradiated and to the number of lymphocytes contained within that tissue. For example, there are far more lymphocytes in a 125 gram spleen than in a 1400 gram human brain. The mean residence time of the human lymphocyte in the blood has been calculated at 4.7 to 7.5 minutes by one estimate (45). If lymphocytes all circulate very rapidly back into the intravascular compartment, then blood from a person with partial body radiation delivered over some significant period of time might show the same incidence of chromosome aberrations as if it had been delivered over the whole body. This does not occur when 300 rads is delivered homogeneously over a two hour period to the lower half of the body (31).

10. Other agents, such as viruses and drugs, may cause chromosome aberrations. In addition to the non-specificity of the test system, there is always the possibility that the individual has received prior radiation of which there is no record.

The kinetics of dose-response are quite important in interpreting inhomogeneous exposure. For single break aberrations one might theorize that 1,000 rads distributed over 10% of the body might give the same chromosome aberration response (after time for complete mixing of irradiated and unirradiated cells) as 100 rads to the whole body, assuming of course that the distribution of lymphocytes to the body is everywhere the same. However, for rings and dicentrics this logic does not hold if one assumes dose-squared kinetics. For if one examines the effect of 1,000 rads over 10% of the body in terms of the dicentric and ring yield, one should find ten times as many rings and dicentrics as single break aberrations. This is because the ratio of $(1,000)^2$ to $(100)^2$ is 100 to 1 so that even after total mixing of radiated with unirradiated cells after an exposure of 1,000 rads to 10% of the body, there is dilution of the ratio of dicentric-ring to single break aberrations from 100 to 1 to 10 to one. This logic has been employed to confirm inhomogeneous distribution in a radiation accident (22). Dolphin (34) has used the Poisson distribution of dicentrics at a given radiation dose (24) to construct histograms to predict the fraction of the body irradiated, although our preliminary data with excellent dosimetry for partial body radiation do not confirm his theoretical discussion (31), as the aberration frequency appears to be much lower.

Clearly much more <u>in vivo</u> data are required with good dosimetry. We are pursuing this goal at whole body radiation doses up to 250 rads with even higher doses planned with the support of marrow autotransfusion and laminar flow "sterile" rooms. Large volume partial body irradiation is also being performed to learn more

about the efficacy of chromosome aberrations as a radiation dosimeter in the more frequent situation of inhomogeneous exposure. With a linear accelerator we hope to study the effects of various dose rates *in vivo* as well.

ETIOCHOLANOLONE STUDIES OF GRANULOCYTE RESERVES IN IRRADIATED PATIENTS.

The absolute lymphocyte count of the peripheral blood drops much more rapidly than do the counts of the cells produced in the erythroid, myeloid and megakaryocytic series. Similarly, as noted above, lymphocyte chromosomes may be analyzed immediately after radiation for radiation-induced aberrations. Chromosomes of the myeloid and erythroid series may be analyzed also. Here, however the situation is even more complex than with the lymphocyte series because bone marrow cells are in all stages of the cell cycle (G_1,S,G_2,M) while 99.9% of the lymphocyte are in G_1(12). Since radiation sensitivity varies during the cell cycle, interpretation of observed aberrations is even more fraught with error than in the lymphocyte system at present. How then can we evaluate failure of the myeloid series soon after irradiation? Our Laboratory has chosen to examine bone marrow granulocyte reserves for this purpose.

Etiocholanolone, a naturally occurring steroid metabolite of adrenal and gonadal origin is a potent stimulus to leukocytosis in man (49, 50). The increment is solely in cells of the granulocytic series, largely neutrophilic polymorphonuclear granulocytes (51). At a dose of 0.10 milligram per kilogram of body weight given intramuscularly the normal average maximum granulocyte increase within 24 hours is 5,850 $\pm$ 770 per cubic millimeter in men and 6,700 $\pm$ 1,400 per cubic millimeter in women. The lower limit of the normal granulocyte increment is 2,600 per cubic millimeter. In a series of 151 injections of etiocholanolone we recently analyzed, the maximum increment occurred at 16 hours in 46%, 20 hours in 32%, and at 24 hours in 22% of the injections. We give the etiocholanolone at 1600 hours and obtain blood counts

at 0800, 1200, and 1600 hours the following day.

The increment in the peripheral blood count after etiocholanolone is the result of mobilization of granulocytes from the bone marrow reserves (53), and is not merely the result of redistribution of extramedullary cells from marginal pools to the circulating granulocyte pool. Endotoxin has also been used to evaluate bone marrow reserves (53, 54, 55). Pyrexal, an endotoxin of Salmonella abortus, has been withdrawn from the American market, but a Pseudomonas product, Piromen, is available for this purpose (54). However, this material must be injected intravenously; endotoxemia may trigger intravascular coagulation, although this side effect has not yet been reported with Piromen. We also prefer etiocholanolone because its only side effects are local inflammation at the injection site and occasional fever never exceeding 2° Centigrade. Also, intramuscular rather than intravenous injection allows a technician to administer this steroid without resorting to venepuncture. As opposed to endotoxin, repeated doses of etiocholanolone can be given without causing reticuloendothelial blockade, and the latter is also nonantigenic (49).

Our patient population has been described above. When one is dealing with patients who are not entirely "normal", the question arises as to whether this patient population can be compared to normal controls studied by others. However, the fact that the average maximum granulocyte increment prior to radiation in our patients was 6,200 cubic millimeters (normal average maximum increment 5,850-6,700) indicates that the two groups are indeed comparable. This maximum increment does not diminish with age. These patients received 100 to 300 rads whole or partial body radiation doses (see Appendix B for technique).

Fifteen patients have been studied (Table 3). In only 1 did the maximum granulocyte increment become subnormal after the white blood cell count had fallen below 5000 (by 2 days). In 10 of the 15 the fall in maximum granulocyte increment to subnormal levels preceded any white blood cell count drop.

In 6 of these 10 whose white counts eventually did go under 5000 per cu. mm., the abnormality in etiocholanolone response preceded the leukopenia by an average of 12 days, suggesting that this biological dosimeter may be of significant assistance in giving warning of an impending leukopenia. In 4 of the 15 the maximum

Table 3

ETIOCHOLANOLONE AS A PREDICTOR OF LEUKOPENIA

Patient	Dose (Rads)	Day of first Etiocholanolone response under 2600 per cu. mm. (white blood count per cc. mm on that day in parenthesis)	Day of white blood count falling under 5000 (or by 1000 if control count 5000) (white blood count per cu. mm. in parenthesis)
099	250 WBR*	6 (3700)	6 (3700)
095	200 WBR	6 (4300)	6 (4300)
087	200 WBR	7 (5900)	9 (3400)
091	200 WBR	9 (9000)	24 (4900)
098	200 WBR	6 (4900)	6 (4900)
093	150 WBR	8 (4300)	6 (3500)
088	150 WBR	2 (9400)	7 (3300)
096	100 WBR	6 (6400)	34 (4900)
097	100 WBR	6 (4100)	6 (4100)
086	100 WBR	8 (10,200)	*****
102	200 M-P**	6 (11,000)	20 (2500)
092	150 M-P	9 (4700)	27 (2300)
089	200 UBR***	1 (9200)	*****
094	150 UBR	8 (7400)	12 (4300)
100	300 LBR****	9 (10,000)	*****

*WBR = Whole body radiation
**M-P = Manubrium to pubis
***UBR = Radiation of the half of the body above the xiphoid
****LBR = Radiation of the half of the body below the xiphoid
***** = White count always over 5000 per cu. mm.

granulocyte increment dropped under 2600 per cu. mm. on the same day that the white count fell under 5000. The subnormal etiocholanolone response generally occurred on days 6 to 9 after radiation. One hundred rads of whole body radiation was sufficient to cause the test to become abnormal as was 150 rads to approximately 40% of the marrow volume.

The etiocholanolone response was less helpful in predicting recovery, becoming normal before the white count had returned to normal levels in half the patients who had leukopenia. The etiocholanolone response returned to normal in all patients by 9 weeks at the latest (range 6-62 days).

The measurement of the maximum granulocyte increment post-radiation allows one to predict whether an irradiated individual will experience leukopenia. However, neither the timing, granulocyte count nor granulocyte increment in the initial drop in the etiocholanolone response indicates how severe the eventual leukopenia will be.

The lower limit of the sensitivity of this test of marrow granulocyte reserves has not yet been determined and this is under study now. It is significantly lower than that in a study employing endotoxin where it was found that at least 40% of the marrow must be irradiated to dosage levels over 1500 R before the endotoxin response became abnormal (54).

The timing of recovery of marrow reserves resembles that noted in patients with Hodgkin's disease given extensive fractionated radiotherapy (56).

Deoxycytidine

Following the report of a radiation-induced increase in urinary excretion of deoxycytidine (CdR) in the rat, our laboratory has examined deoxycytidinuria in man as a biological dosimeter (58, 59, 60, 81). Using a sensitive colorimatric technique (59) we found that the urinary and blood deoxycytidine levels of rats were elevated about six hours after X-irradiation, reaching a maximum in blood at 9 hours, urine at 12 hours.

Deoxycytidine excretion in the rat was proportional to the amount of radiation up to 200 R. Approximately, a six-fold increase from the average pre-irradiation value of 0.7 mg per 24 hour urine followed 200 R.

With tritiated CdR labelled on carbon-5 of cytosine, rats irradiated with 200 R excreted 21% of the total radioactivity while only 13% of radioactivity was excreted by unirradiated rats (61, Fig.5). Since specific radioactivity of CdR isolated from the urine of irradiated rats decreased 2 to 6 fold as compared with that of CdR in the urine of unirradiated rats, the free CdR pool size was increased in the irradiated rat (Table 4). This radiation-induced CdR excretion could be suppressed with serotonin and L-cysteine, the respective dose reduction factors being 1.7 and 1.5 for this variable.

Man, however, excretes a much smaller quantity of CdR in his urine than does the rat. An average pre-irradiation value of 0.007 mg of CdR per 24 hour urine was found in man (Table 5) as compared to 0.7 mg in the rat. The low CdR excretion in man may be caused by the activity of a CdR deaminase in human plasma (31) and liver (82). However, the range in our cancer patients was 3.9 to 26 micrograms for 24 hours (Table 6). Following whole or partial body radiation at dose of 150 rads or above CdR excretion rose 50 to 350% on day one post irradiation, returning to normal on day two (Table 6). However, this is not a dosimeter specific to radiation injury. A patient with lymphoepithelioma and several burned patients also showed abnormally high urinary CdR excretion in proportion to the severity and extent of the burn (Table 7). Thus, deoxycytidinuria appears to be related to general tissue catabolism from several causes, including radiation. Other problems in using urinary CdR include variations in excretion due to race (57) and age (92).

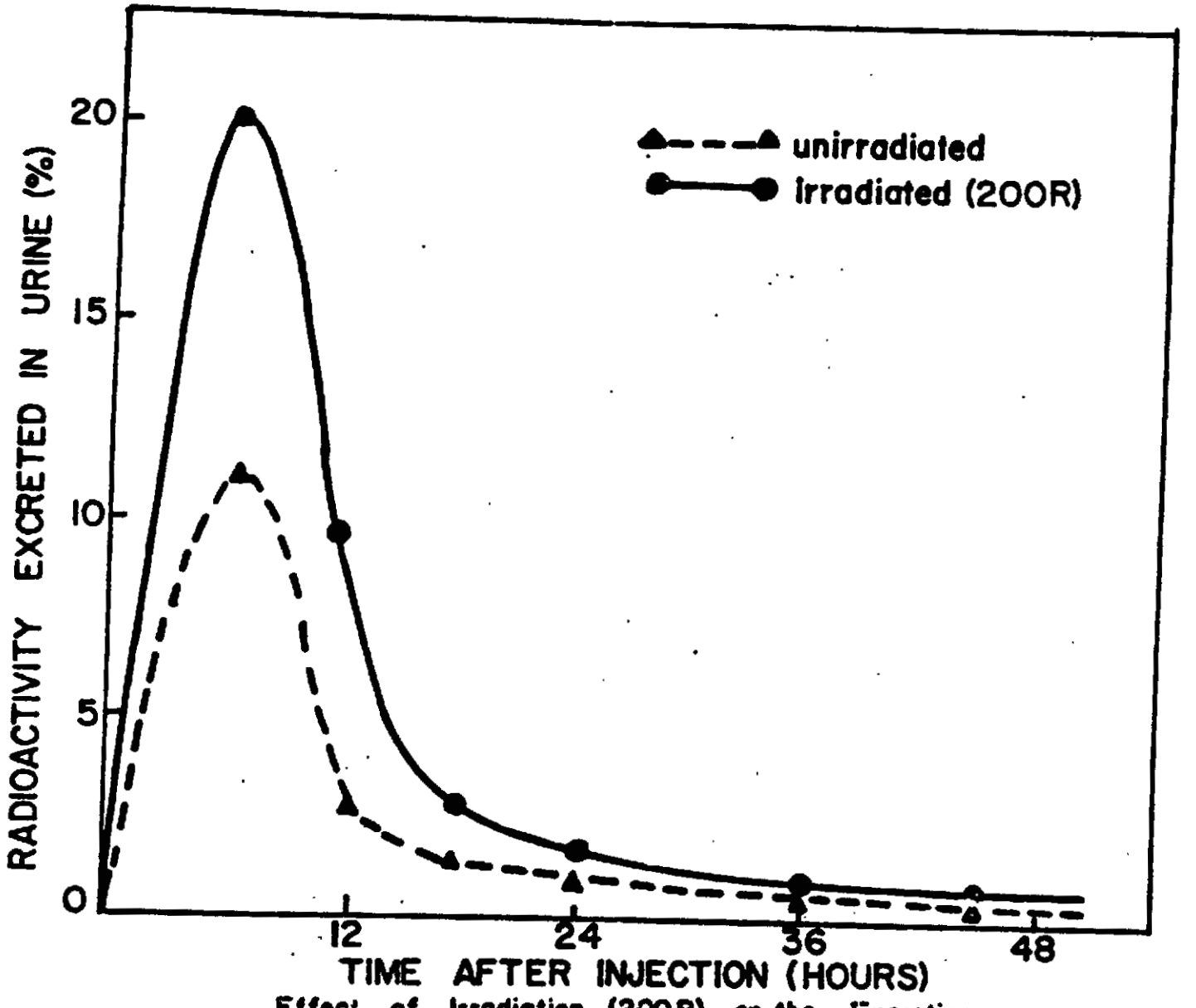
Creatine

Radiation-induced creatinuria in rats (61) follows a failure of muscle tissue to utilize creatine synthesized at a normal rate by liver and muscle (62). It is dose-dependent, reaching a peak over 4 days after a single whole body dose in the rat, at least up to 650 R. However, we have been unable to demonstrate increased amounts of creatine in the urine of our patients post-irradiation as measured by the increased creatine to creatinine ratio (83). These studies were done at doses of 100 rads or less of whole body radiation however, perhaps below the sensitivity of this dosimeter in man.

Beta-Aminoisobutyric Acid (BAIBA)

Another nucleic acid metabolite, beta-aminoisobutyric acid, a product of thymidine catabolism has been found in increased amounts in irradiated humans, with disagreement as to the proportional increase in BAIBA with absorbed radiation dose (63, 80). However, the increase has not been consistent in our patients (Figures 6,7).

Figure 5



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

Table 4

^{3}H-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

Table 5

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 (ug)
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 ± 0.24	6.68 ± 3.67

Table 6

CdR in the Urine of Irradiated Patients

PATIENTS			DOSE	CdR in 24 hour urine (ug)			
				Pre-irradiation	Post irradiation(days)		
Case No.	Sex/race/age	Diagnosis	(Rads)	average	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.

Table 7

CdR DEAMINASE ACTIVITY IN SERUM AND CdR CONTENT IN URINE FROM PATIENTS WITH VARIOUS DISEASES.

Patients				Serum CdR deaminase activity (Units / mg Protein)	CdR in 24 hour urine (µg)
	Sex	Age	Diagnosis		
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

Figure 6

URINARY EXCRETION OF β AMINO ISOBUTYRIC ACID BEFORE AND AFTER TOTAL BODY RADIATION

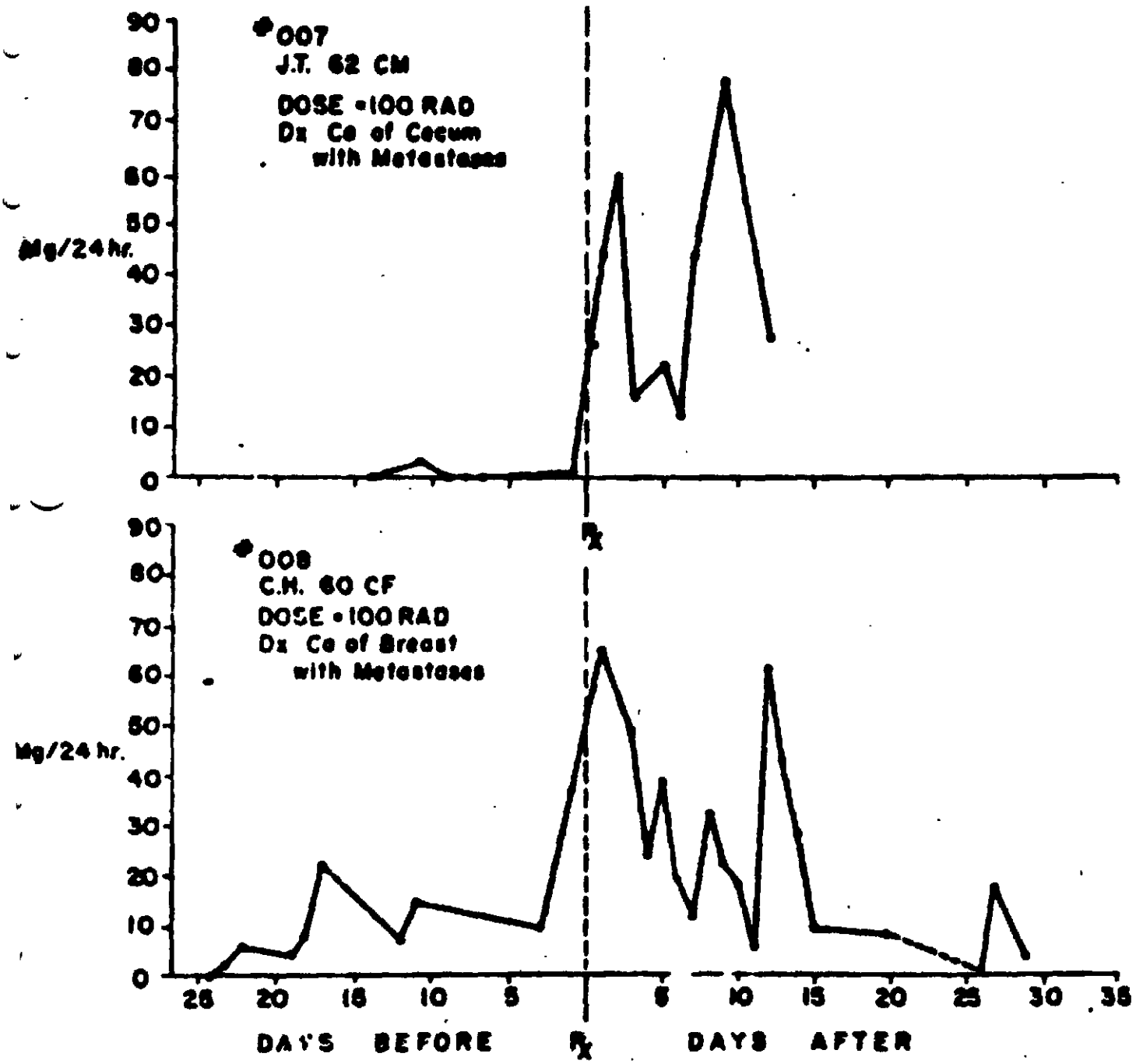
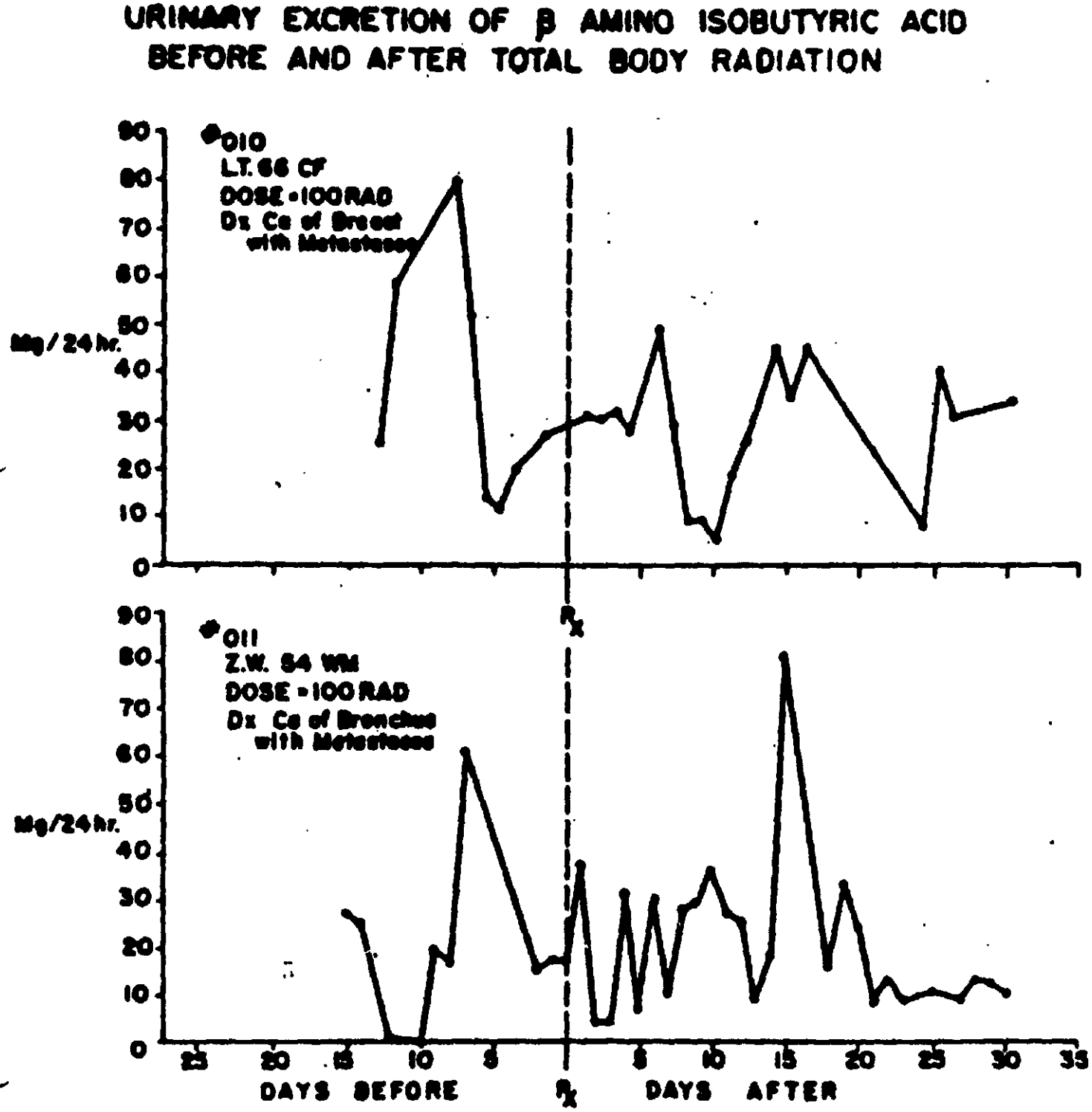


Figure 7


URINARY EXCRETION OF β AMINO ISOBUTYRIC ACID
BEFORE AND AFTER TOTAL BODY RADIATION
#010
L.T. 66 CF
DOSE = 100 RAD
Dx Ca of Breast
with Metastases
Mg/24 hr.
#011
Z.W. 54 WM
DOSE = 100 RAD
Dx Ca of Bronchus
with Metastases
Mg/24 hr.
Rx
DAYS BEFORE
Rx
DAYS AFTER

Another problem in interpreting urine BAIBA data is that there is an hereditary asymptomatic condition of high excretion (10% of people examined) (64). This compound, too, is a non-specific sign of tissue breakdown.

Taurine and Other Amino Acids

Another amino acid, taurine, is excreted by the rat and dog, but not the guinea pig, in excess amounts after whole body radiation (65, 66, 67, 68, 69). A second radiation exposure in about a week following the first does not elicit a similar excretion of taurine (67). Previous work has shown that an air dose greater than 450 R is required to raise urinary taurine after human whole body irradiation (65). There was no significant increase in the taurine excretion among our patients up to a dose of 200 rads. Nor was there any significant change in excretion of any of the urinary amino acids examined (Table 8). Urinary taurine levels have been found in children after surgery or infection and are therefore also a non-specific sign of tissue breakdown (84). Another variable difficult to control in evaluation of urinary amino acid levels in general, and taurine specifically, is that the levels of most amino acids in the urine are greatly influenced by dietary protein intake. In summary, our laboratory has been unable to confirm that there are any significant differences between the amounts of these urinary amino acids excreted by cancer patients before or after whole body irradiation at levels of 50 to 200 rads (81, 83).

Glycoproteins Including Transferrin; Serum Iron

Serum glycoprotein levels have been reported to have prognostic significance after radiation injury (70). Using pre-irradiation levels as controls the concentration of total protein-bound carbohydrates, particularly transferrin and haptoglobin (71) are found to rise to high levels in mice, rats and dogs who have died after radiation exposure, while survivors showed little change. However, another investigator reported no significant difference between the mean serum glycoprotein concentration in rats' blood 88 to 90 hours after 600 R of X-irradiation and their unirradiated controls (72) but this may well be due to the experimental design employed (69). The measurement of total iron binding capacity (transferrin) showed no significant rise after irradiation in our patients (Table 9). Since all our patients survived their treatment this is at least consistent with Evans' predictionn that lack of glycoprotein rise correlates with survival.

Table 8

The Urinary Amino Acids Analyzed with No Change after Radiation:

Glutamic acid	Valine	Phenylalanine
Serine	Taurine	Proline
Glycine	Beta-aminoisobutyric acid	Histidine
Threonine		Aspartic acid
Alanine	Lysine	Cystine
Glutamine	Tyrosine	Methyl histidine
Beta-alanine	Leucine	Ethanolamine

Table 9

CHANGES IN TOTAL IRON BINDING CAPACITY (TRANSFERRIN) FOLLOWING HUMAN IRRADIATION

	Dose (rads)	Change in total iron binding capacity (percent)	Day of maximum change post radiation
99	250 WBR*	+6%	0
095	200 WBR	-8%	1
087	200 WBR	-13%	9
091	200 WBR	-16%	9
098	200 WBR	-23%	0
093	150 WBR	-29%	9
088	150 WBR	+1%	3
096	100 WBR	+6%	6
102	200 M-P**	+4%	4
092	150 M-P	-8%	2
089	250 UBR***	-12%	9
094	150 UBR	-14%	6
100	300 LBR****	-7%	13

*WBR = Whole body radiation
**M-P = Manubrium to pubis
***UBR = Radiation of the half of the body above the xiphoid
****LBR = Radiation of the half of the body below the xiphoid
***** = White count always over 5000 per cu. mm.

Radiation-induced damage to the erythroblasts in bone marrow should lead to a rise in serum iron as erythropoiesis decreases. Serum iron levels rose over the first 9 days post irradiation in only 20% of our patients studied, and the average change overall was an insignificant drop of 17 micrograms per 100 ml. serum (Table 10). Thus, our material does not confirm some promising animal work (73, 74). The diurnal variation in serum iron and the variation in the levels when the serum is taken at the same time daily (as we did) is significant (75, 76) and diminishes the value of the serum iron as a dosimeter. The total iron binding capacity (transferrin) does not have such diurnal variation apparently (75).

Absolute Monocyte and Lymphocyte Counts

Changes in cell counts following radiation are the result of damage at the molecular level. The degree of post-radiation lymphopenia at 48 hours has been related to the severity of the radiation injury (77). Yet at 72 hours, 5 of 11 of our patients receiving 200 rads whole body radiation still have absolute lymphocyte counts greater than 1,000 per cubic millimeter. By Andrews' criteria (77) 4 of the 11 patients receiving 200 rads would have been classified as having sustained "very severe" injury, 3 "severe" injury at 48 hours (See Table 11), both of these carrying grave prognostic significance. Perhaps this concept needs revision.

The mouse monocyte is apparently quite radiosensitive. Four hundred rads of whole body x-ray reduces the mouse absolute monocyte count to one-tenth of the pre-irradiation level within 24 hours (78). Our data indicated no clear downward trend in human monocyte levels until about day 15 following 200 rads whole body radiation (see Table 12). Thus, the monocyte count has little value in the period following irradiation and the absolute lymphocyte count somewhat less than has previously been stated.

Urinary Gonadotrophins

A yet unexplored area of pituitary hormonal response to radiation has recently been spotlighted in a report that urinary gonadotrophins may rise as early as the 7th day after acute irradiation (79). The response did not seem dose related in the patients studied. We are currently examining this finding in our own patients.

Table 10
CHANGES IN SERUM IRON AFTER HUMAN IRRADIATION

ent	Dose (Rads)	Maximum change from pre-radiation levels of serum iron within nine days post radiation (percent)
	250 WBR*	-31%
[illegible]	200 WBR	-59%
087	200 WBR	+78%
091	200 WBR	-33%
098	200 WBR	+152%
093	150 WBR	-60%
088	150 WBR	-18%
096	100 WBR	-6%
102	200 M-P**	-35%
092	150 M-P	-56%
089	200 UBR***	-58%
094	150 UBR	+9%
100	300 LBR****	-75%

*WBR = Whole body radiation
***UBR = Radiation on the half of the body above the xiphoid
**M-P = Manubrium to pubis
****LBR = Radiation of the half of the body below the xiphoid

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	408
091	910	658	264	170
093	2001	2220	—	1140

Table 12

ABSOLUTE MONOCYTE COUNTS OF PATIENTS WITH 200RADS TOTAL BODY RADIATION

(Normal: Wintrobe, Hematology, Ed. 6, p. 260 – 95% confidence limits are 140 – 860/mm^3)

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	605	976	1050	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

(cells per cu. mm.)

Amylase

Elevated serum amylase levels (88) after parotid salivary gland radiation have been noted with doses as low as 100 R (tumor dose) (85). The amylase rose to a peak value at 24 to 36 hours after irradiation, then declined to normal over another one or two days. The response appears to be organ specific (31, 85, 86) and hyperamylasemia does not result when the patient receives doses to the pancreas (the usual source of serum amylase) comparable to those causing enzyme release from the salivary glands. The amylase released from the damaged glands is at least grossly related to the absorbed dose of radiation (85, 86).

Our data (Table 13, Figures 8,9) confirm these findings for whole and partial body radiation in the human. The graphs show serum and urine levels in patients receiving radiation to the salivary glands. The least striking of the three serum responses is in a patient whose parotid glands were not in the radiation field. Only the patient receiving the highest cumulative radiation dose shows elevated urine levels of the enzyme, however, suggesting that this is a less sensitive test than serum amylase. Both urinary and serum responses are prompt, however, and both diminish as the cumulative radiation dose destroys glandular function. Table 11 indicates that the sensitivity of this biochemical dosimeter is at least 100 rads. Radiation below the neck does not increase serum amylase in doses up to 300 rads over the pancreas (not on chart). Our laboratory is currently performing agar gel electrophoresis on the serum of irradiated patients to separate the isoenzymes of amylase.

Other Human Urine and Serum Protein Studies

A number of other human serum and urine proteins have been examined for their response to whole body radiation up to 250 rads and half body radiation up to 300 rads. These are listed in Table 14. These tests have been found to show absent or inconsistent changes following irradiation.

Table 13

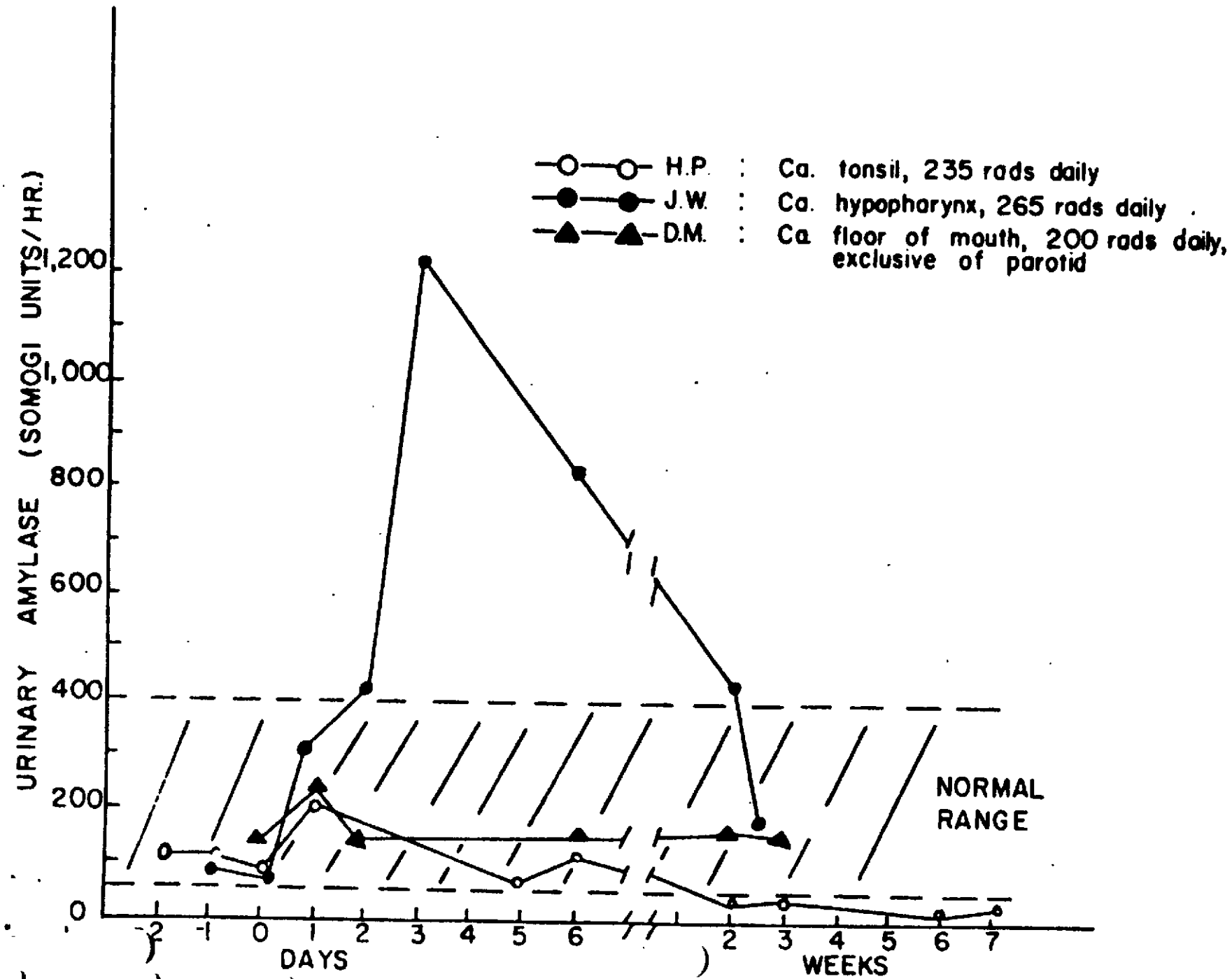
SERUM AMYLASE LEVELS IN IRRADIATED CANCER PATIENTS

Patients			Dose*	Amylase (Somogi units/100 ml)				
Case No.	Sex/Age	Diagnosis	(Rads)	Preirradiation Average	Post Irradiation (hours) 2	20	24	48
87	F/11	Ewing's Sarcoma	200	112	160	3,000	2,250	750
98	F/45	Ca. Colon	200	126 ± 15	139	900	1,200	600
95	F/66	Ca. Colon	200	150 ± 0	150	225	225	-
90	F/80	Ca. Bladder	150	112 ± 21	120	-	300	180
88	F/54	Ca. Lung	150	300	360	360	360	-
86	F/57	Bronchogenic	100	87 ± 11	106	600	600	150
96	M/42	Ca. Colon	100	160 ± 10	257	560	600	300
97	M/65	Lymphoma	100	168 ± 14	138	-	225	225
92	F/69	Ca. Breast	150 partial*	142 ± 6	178	145	133	178
94	F/69	Ca. Lung	150 partial*	180 ± 0	180	180	180	180

*unless otherwise indicated, the irradiation was to the entire body.

*Base of neck to pubis

Figure 2


H.P. : Ca. tonsil, 235 rads daily
J.W. : Ca. hypopharynx, 265 rads daily
D.M. : Ca. floor of mouth, 200 rads daily, exclusive of parotid
URINARY AMYLASE (SOMOGI UNITS/HR.)
1,200
1,000
800
600
400
200
0
NORMAL RANGE
-2 -1 0 1 2 3 4 5 6
DAYS
2 3 4 5 6 7
WEEKS

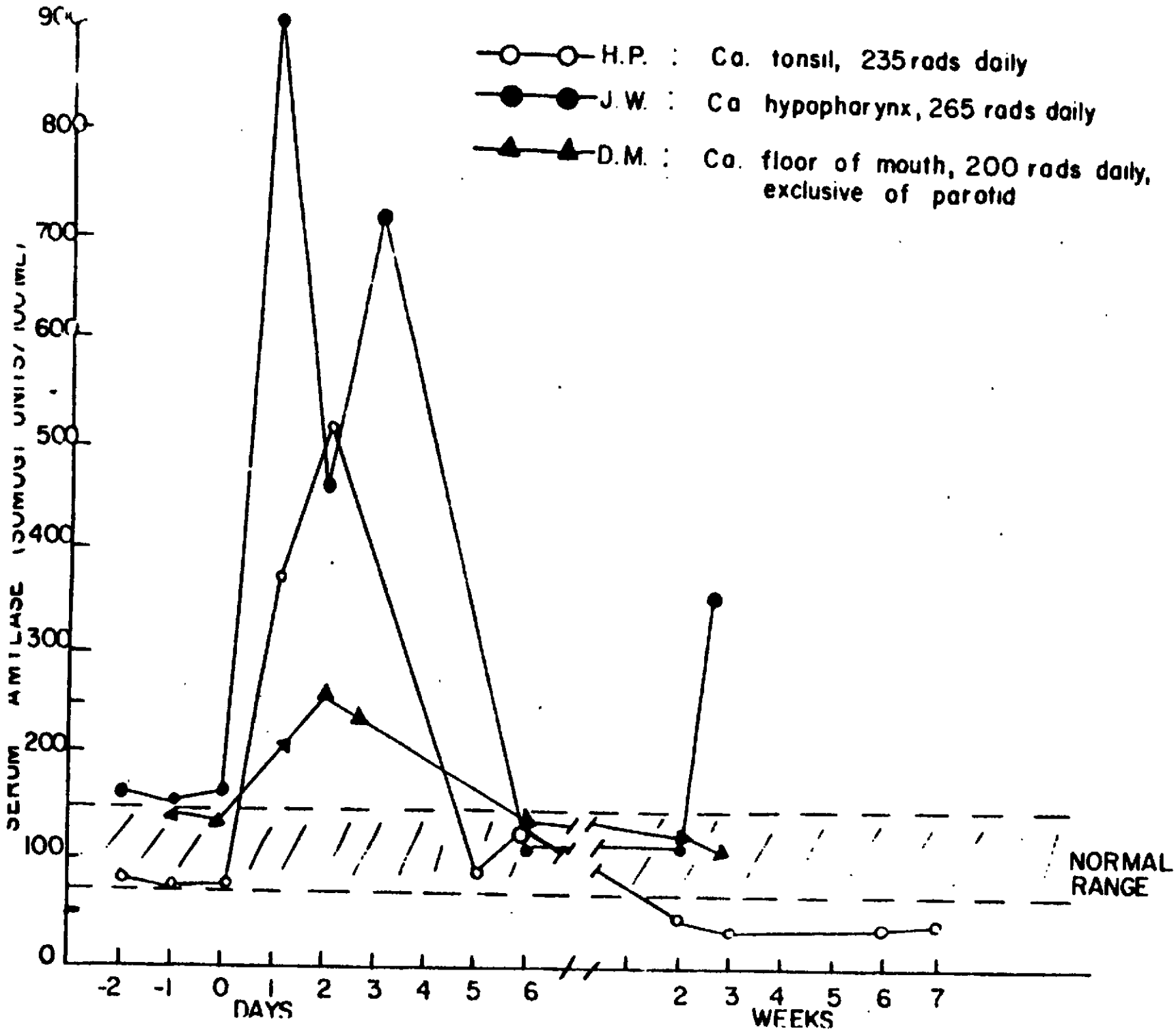

H.P. : Ca. tonsil, 235 rads daily
J.W. : Ca hypopharynx, 265 rads daily
D.M. : Ca. floor of mouth, 200 rads daily, exclusive of parotid
SERUM AMILASE (SOUMOGI UNITS/100 ML)
900
800
700
600
500
400
300
200
100
0
-2
-1
0
1
2
3
4
5
6
DAYS
2
3
4
5
6
7
WEEKS
NORMAL RANGE

Table 14

HUMAN SERUM PROTEINS UNAFFECTED BY RADIATION IN DOSES UP TO 300 RADS

Deoxycytidine deaminase	(31)
Muramidase	(88)
Acid phosphatase	(89)
Alkaline phosphatase	(89)
Beta-glucuronidase	(90)
Beta galactosidase	(91)
Lactic dehydrogenase	
Glutamic oxaloacetic transaminase	
Immunoglobulins G, A, M	
Serum protein paper electrophoresis	
Serum immunoelectrophoresis	

APPENDIX A

PROTOCOL FOR CHROMOSOME CULTURE

1. A 10 ml. syringe is moistened with 0.1 ml. heparin (1 ml. = 5,000 U.S.P. units containing 1% benzyl alcohol) and 10 ml. venous blood is aspirated under sterile conditions.

2. Blood is then transferred to a sterile screw cap tube. It is mixed gently and the red cells are allowed to sediment while under refrigeration for one hour.

3. 0.5-1.0 ml. leukocyte rich plasma is added to 4 sterile, disposable flasks containing 4-5 ml. of the following media: 80% Minimum Essential Media,* 15% Fetal Bovine Serum, 2.4% phytohemagglutinin, 1.2% l-glutamine, and 1% penicillin and streptomycin.

4. Incubate the culture at 37°C for 46-50 hours at ambient pO_2. No CO_2 is added to the system.

5. Then 0.1 ml. 0.0004% colchicine in Hank's** balanced salt solution is added to each culture which is returned to incubator for 1-2 hours.

6. The flasks are agitated and contents emptied into a serologic tube which is centrifuged for 2 minutes in an Adams Sero-Fuge.

7. One then aspirates the supernatant and discards it. The cells are washed with 37° C 0.7% sodium citrate and placed in a 37°C water bath for 4-7 minutes, then centrifuged as in Step 6.

8. One next aspirates the supernatant and discards it. Without disturbing the cell button, one adds 1-2 ml. Carnoy's fixative (3 parts Methanol: 1 part Glacial Acetic Acid) and allows the button to stand 30 minutes.

9. Then one resuspends the cells and centrifuges as before.

10. Steps 8 and 9 may be repeated as needed, usually twice.

11. Next we add sufficient Carnoy's fixative to obtain an opalescent appearance, about 0.5 ml.

12. Slides are prepared by dropping 3-5 drops of cell suspension on clean slides which has been wet in cold distilled water, igniting them momentarily in an alcohol burner.

13. They are stained with 1:10 Giemsa stain for 14 minutes.

14. Next we rinse with acetone twice, acetone: xylol (1:1) once and then place the slides in 100% xylol until all are ready to mount.

15. We mount by adding 1 drop*** Permount and a coverslip.

*Gibco, Grand Island Biological Co., Grand Island, New York.

**Difco Pharmaceuticals, Detroit, Michigan.

***Fisher Scientific, Fairlawn, New Jersey.

APPENDIX B

DOSIMETRY:

1. Total Body Radiation

Cobalt - 60:

The radiation is delivered by a Cobalt 60 Teletherapy Unit under the following exposure conditions:

The radiation beam is directed horizontally at a wall 338 cm. away with the patient midline at 282 cm. from the source. The beam area for the 50 percent isodose curve at the patient midline distance is a square approximately 72 cm. by 72 cm. (Figure 10). The patient is placed in a sitting position with legs raised and head tilted slightly forward. The irradiation is given by delivering half the specified exposure laterally through one side of the patient. The patient is then turned and the other half exposure delivered laterally through the other side.

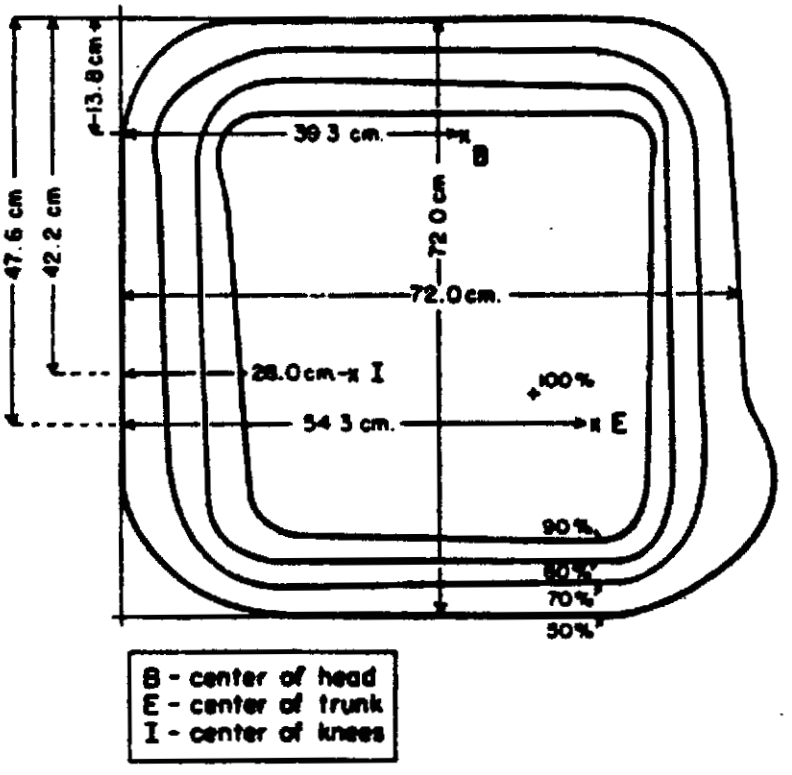
The variation of air exposure with distance from the source was determined with a Victoreen 25r chamber. The results indicated no departure from the inverse square law relationship for distances used in the study. Therefore, no correction was required for a possible dose contribution to the patient due to backscatter from the wall.

Preliminary measurements were made in a masonite phantom using dosimeters placed on lateral surfaces and at the midline of the head, trunk and knee portions of the phantom. If the midline doses to the trunk, head, and knees are compared, the maximum variation in these doses is about 16 percent.

The exposure to the patient was determined as follows. The percentage depth dose at different depths for a 400 cm^2 field area and a source-skin distance of 80 cm is given by H.E. Johns, "The Physics of Radiology," Charles C. Thomas, Springfield, Illinois. The depth dose at the greater source-skin distances used for the patients was found by multiplying the depth doses at 80 cm. by the "F" factor postulated by Mayneord and Lamerton (Brit. J. Radiol. 14:255, 1941).

Figure 10

Isodose Curves for Radiation Technique Employed
With Patient Midline at 282 cm. From Source



$$F = \frac{(D_d)_{f_2}}{(D_d)_{f_1}} = \left(\frac{f_2}{f_1} \times \frac{f_1 + d}{f_2 + d} \right)^2$$

where f_1 and f_2 are source-skin distances and d is the depth.

By using the corrected depth dose at the patient midline (one-half lateral dimension of the trunk) and a conversion factor of 0.97 rads per roentgen for Cobalt gamma radiation, the surface dose and midline air exposure required to give a desired midline absorbed dose in rads was calculated.

A direct comparison of the calculated and measured (phantom) doses was made for one patient who had the same lateral trunk dimensions as the phantom. The relative depth dose for each lateral exposure to this patient is given in Figure 11. The doses indicated by crosses are measurements made in the phantom and compare quite well with the calculated doses. The combined dose of the two radiation fields is also given in this figure and shows a good homogeneous dose distribution through this patient. The maximum variation in lateral dose distribution was + 13 percent for one patient having a lateral trunk dimension of 36 cm.

Partial Body radiation:

In the individuals receiving partial body radiation, the teletherapy collimator is used to restrict the beam. The isodose curves for this latter case is shown in Figure 12. The relative dose for upper body radiation is shown in the Figure. These phantom measurements were determined with thermoluminescent dosimeters. For partial body radiation, the xiphoid was used at the boundary. This technique is similar to that described by Hanse, Michaelson, and Howland (The Biological Effects of Upper Body X-irradiation of Beagles, UR 580, University of Rochester Atomic Energy Project, 1960).

Figure 11

Relative Depth Dose for Each Lateral Radiation Exposure

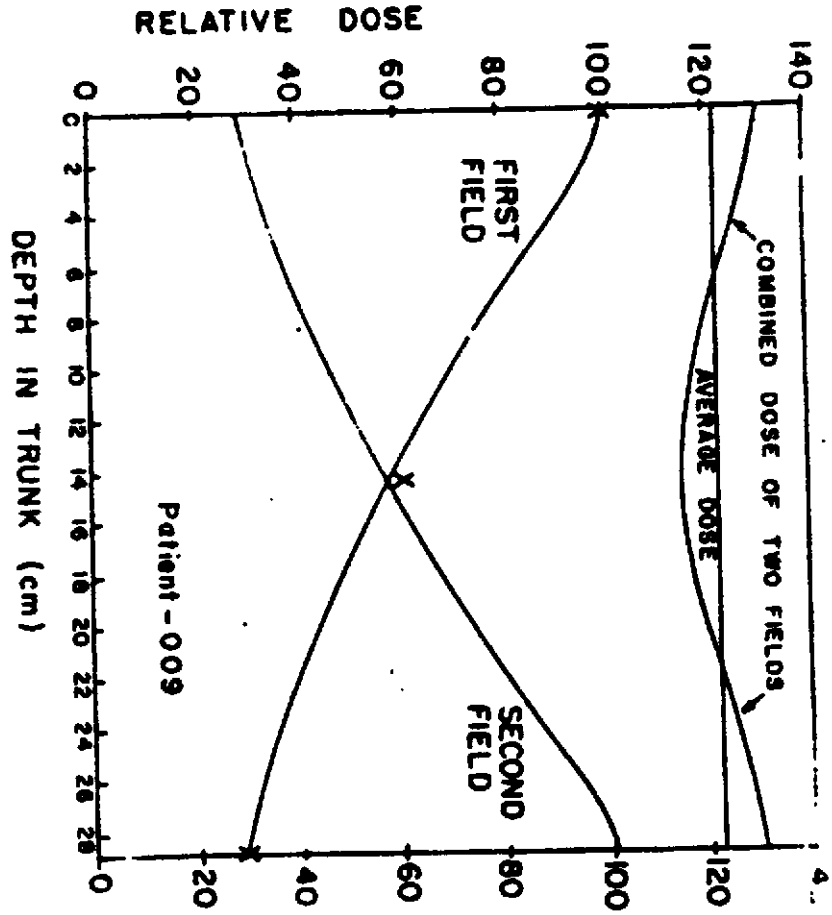
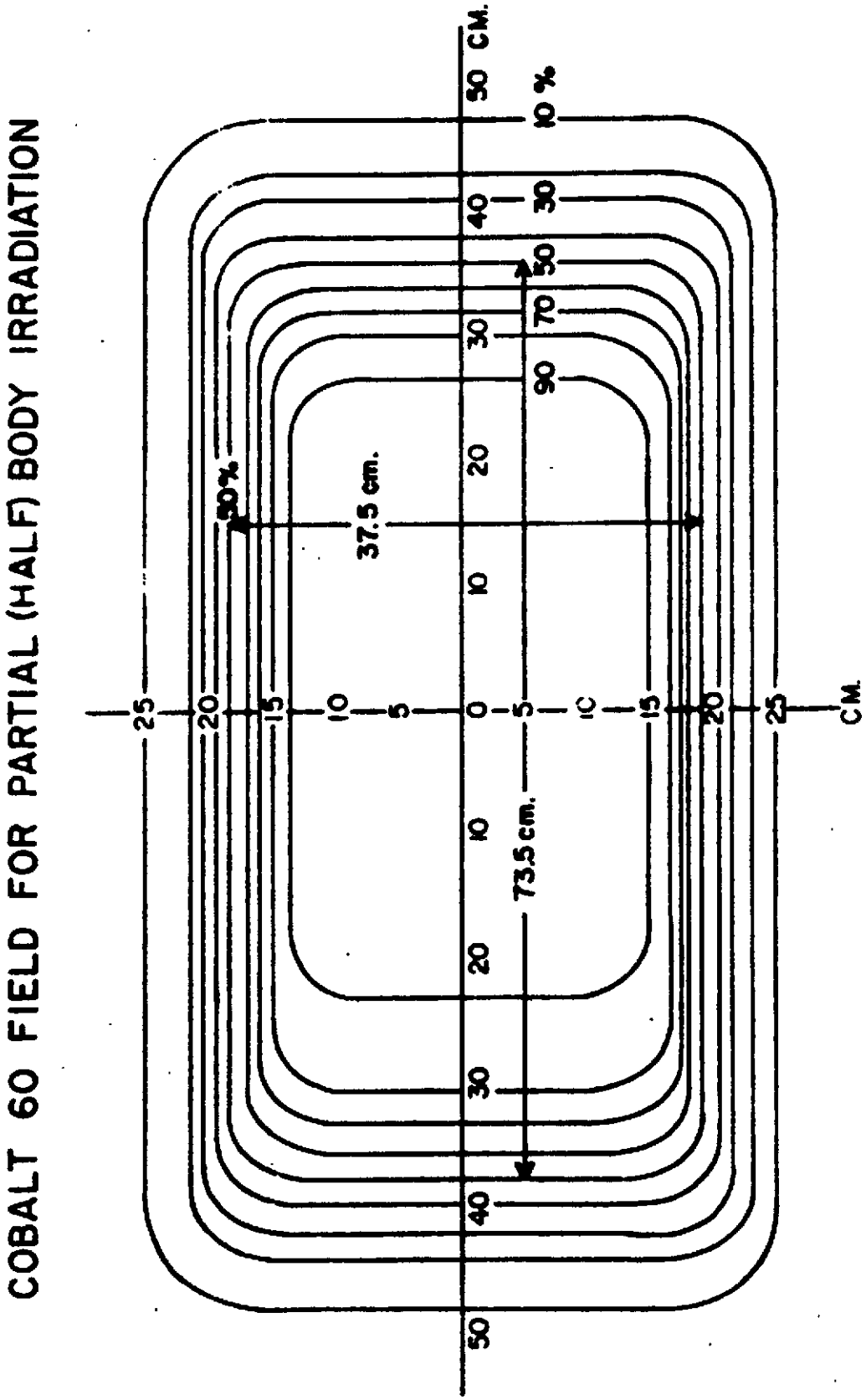


Figure 12


COBALT 60 FIELD FOR PARTIAL (HALF) BODY IRRADIATION
CM.
50
40
30
20
10
0
10
20
30
40
50
10 %
30
50
70
90
50%
37.5 cm.
73.5 cm.
25
20
15
10
5
0
5
10
15
20
25
CM.

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