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Future Directions in Therapy of Whole Body Radiation Injury

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DISCLAIMER

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INTRODUCTION:

At times, a brief introspective look at old research may help to understand how we got where we are today. Shielding and transplantation of bone marrow were initiated long ago. Chiari (1) (1912) demonstrated that bone marrow of the rabbit when transplanted into the spleen would grow only if the spleen was shielded and the rest of the animal were irradiated. Fabricius- Moller (2) (1922) clearly showed that shielding of portions of the skeleton prevented the fall in blood platelets and consequently radiation hemorrhage. Jacobson et al. (3) attained nearly 100% protection from lethal dose of radiation when the mouse spleen was shielded. Brecher and Cronkite (4) (1951) showed that shielding of one parabiotic rat protected the other rat from fatal irradiation. These studies, clearly demonstrated that protecting something in the spleen of the mouse or bone marrow of the guinea pig prevented the sequelae of marrow aplasia and that some protective substance or cells circulated from the non-irradiated parabiont to the irradiated parabiont. Lorenz et al. (5) (1952) proved that the protection was from cells located in the bone marrow or spleen since one could protect mice from lethal irradiation by transfusion of marrow cells or spleen cells in the mouse. Ford et al. (6) (1956) proved that transplantation of donor hemopoietic cells had occurred by using "marker chromosome".

Clinicians have long known that marked granulocytopenia predisposed patients to bacterial infections either from pathogens or commensal organisms with which an individual usually lives in harmony. Evidence that infection was of major importance derives from several observations: a) clinical observations of bacterial infection in human beings exposed to atomic bomb radiation in Hiroshima and Nagasaki, in reactor accidents, and in large animals dying from radiation exposure, b) correlative studies on mortality rate, time of death, and incidence of positive culture in animals, c) challenge of irradiated animals

with normally non-virulent organisms, d) studies of germ free mice and rats, e) studies of the effectiveness of antibiotics in reducing mortality rate. The above are covered in detail by Bond, Cronkite, Conard (7) (1969).

General knowledge and sound experimental data on animals and man clearly demonstrated that the sequelae of pancytopenia (bacterial infection, thrombopenic hemorrhage, and anemia) are the lethal factors. A lot of research was required to demonstrate that there were no mysterious radiations toxins, that hyperheparinemia was not a cause of radiation hemorrhage and that radiation hemorrhage could be prevented by fresh platelet transfusions (Cronkite, Bond and Conard 8, 1969).

THE CLASSICAL SYNDROMES PRODUCED BY UNIFORM WHOLE BODY RADIATION:

Radiation syndromes produced by exposure to ionizing radiation are dependent on the total dose, energy of radiation and the ensuing depth dose patterns. Three somewhat arbitrary and overlapping syndromes are:

Central nervous syndrome (CNS) occurs after large doses of several thousand rad. Death may occur during exposure in some laboratory animals. This is preceded by hyper-excitability, ataxia, respiratory distress, and intermittent stupor. Doses capable of producing this syndrome are uniformly fatal. It is highly unlikely that anyone will come up with methodology to reverse the necrotizing lesions of brain. Accordingly I would predict this is not a fertile area for investigation.

THE GASTROINTESTINAL SYNDROME (GIS):

The GIS is produced by a wide range in doses (200-2000 rad). Doses in excess of 1000 rad are fatal within 3 to 9 days in laboratory animals and probably this also applies to humans beings. It is characterized by marked

nausea, vomiting, diarrhea, and denudation of the small bowel mucosa. The severe and persistent syndrome was observed in Japan and described by Oughtersen and Warren (9) and in some accidents by Hubner et al. (10), Conard et al. (11) prolonged life of dogs exposed to 1200 rad by intensive administration of intravenous fluids and plasma. Treated dogs surviving doses up to 1200 rad regenerate the mucosa of the small intestine within 6 days (Brecher et al. 11). Survivors of this syndrome then experience the sequelae of marrow depression. The GIS and hemopoietic syndrome were observed in Japanese exposed in Hiroshima and Nagasaki (9). Since the gastrointestinal syndrome is due to failure of timely renewal of the gastrointestinal epithelium, a probable area of profitable research would be searching for unknown molecular regulators or applying known regulators that control steady state, self-renewal in the gastrointestinal tract and see if one can accelerate the repletion of the G.I. tract.

THE HEMOPOIETIC SYNDROME (HS):

The HS is not necessarily fatal. Its clinical picture is seen in the range of 150-800 rad in all mammals including man. The HS is usually preceded by a transient nausea, vomiting and diarrhea of a few hours or days in duration. Clinical hematologists have long been familiar with management of granulocytopenia, thrombopenia and anemia with bacterial infection and purpura. It present no mysteries to the practicing hematologist and oncologist. The only question is when should one transplant marrow?

RADIATION INJURY IN THE JAPANESE IN HIROSHIMA AND NAGASAKI:

The CNS was not observed by the Japanese in Hiroshima and Nagasaki nor would one have expected it to be observed since doses to produce the syndrome were well within the area of total destruction and no survival. The GIS, with

death in the first week was well documented clinically and pathologically (9). The sequence in depletion of blood counts is different in human being and animals. It takes longer for the hemopoietic syndrome to develop in man. For example, deaths from infections were most prevalent in the second and fourth weeks (maximum incidence during the third week) and from hemorrhagic phenomena during the third to six weeks (maximum incidence in the fourth week). Deaths from radiation hemorrhage and infection occurred in the Japanese as late as the seventh week. This is in contrast with other animals, where deaths are uncommon later than the 30th day. The neutrophil count after irradiation has been correlated with mortality in animals exposed to bomb-gamma radiation at the Pacific Proving Ground and also in the Japanese in Hiroshima and Nagasaki (12). The neutrophil count is probably the best clinical sign of severity of injury (15).

THE PROBABILITY OF SURVIVAL FOLLOWING EXPOSURE TO WHOLE BODY RADIATION:

After study of the report by the Joint Commission on the effects of the Atomic Bomb in Japan and the analysis by Oughtersen and Warren (9) I proposed in 1951 (13) that there are three types of survival groups based on signs and symptoms respectively - survival, improbable, possible, and probable.

Survival improbable: vomiting occurs promptly or within a few hours and continues. It is followed in rapid succession by prostration, diarrhea anorexia and fever. Death will probably occur in 100% of these individuals within the first week without extensive symptomatic therapy.

Survival possible: Vomiting may occur but will be of relatively short duration, followed by a period of well-being. In this period of well-being, marked changes are taking place in the hemopoietic tissues. Lymphocytes are profoundly depressed within hours and remain so for months. The neutrophil

count falls to low levels. The degree and time of maximum depression depends upon the degree of radiation injury and is described by Jacobs et al. (12). Signs of bacterial infection may develop when the neutrophil count falls below 500/μl. Probability of infection is increased by burns and open wounds. Platelet counts may reach very low levels within two weeks. Bleeding may occur within 2 to 4 weeks. This group represents the lethal dose range in the classical pharmacological sense. The latent period lasts from 1 to 3 weeks with little clinical evidence of injuries other than slight fatigue. At termination of the latent period, the patient may develop purpura, epilation, cutaneous ulcerations, infections of wounds or burns, diarrhea and or melena. With therapy of antibiotics and/or sulphonamides, platelet transfusions, the survival time and rate can be expected to be increased. In Japan, many soldiers had nausea and vomiting, recovered, felt well, returned to duty to later develop purpura, epilation, cutaneous lesions, and then died of infections. This is well documented by Oughtersen and Warren (9). The data of Kikuchi and Wakisaka (14) indicate that there was a more rapid decrease of granulocytes in individuals that could be assigned to the SURVIVAL IMPROBABLE AND SURVIVAL POSSIBLE as compared to the SURVIVAL PROBABLE GROUP. Fliedner et al. (15) has done an extensive analysis on existing human radiation injury cases, correlating survival with changes in the peripheral granulocytes and platelets counts and developed a computer model for predicting the probability of survival. An area for further research is continuing correlation of existing data of hematologic response with probability of survival.

The recent research of Storb et al. (17) on dogs suggests that matched bone marrow transplantation is probably indicated in this group because dogs exposed to varying doses of radiation will reject the marrow if it is not needed and accept it if required for life saving restoration of aplastic marrow. Graft

versus host disease will develop in a variable fraction of transplanted individuals. A clinical axiom states, "it is better to have a live ailing patient on your hands rather than a cadaver". This group may benefit very substantially from the judicious administration of the now available molecular hemopoietic growth factors. Extensive clinical and animal research is required to develop the best methods of using these agent to accelerate regeneration of hemopoiesis and/or the regeneration of transplanted bone marrow.

SURVIVAL PROBABLE:

This group consists of individuals who may or may not have had nausea, vomiting and diarrhea on the day of exposure. For example one quarter of the Marshallese had nausea and vomiting. Many Japanese had a significant depression of leukocytes and platelets but no clinical sequelae of bone marrow depression. If there has been no GI symptomatology the only way to detect individuals in this group is to perform serial studies on the blood with particular reference to granulocytes, lymphocytes and platelets. The lymphocytes may reach a low constant level early within 48 hours and show little evidence of recovery for many months after exposure.

Granulocytes may show some depression during the second and third week. Late fall in granulocytes during the sixth and seventh week after exposure may be observed. Platelets counts reach the lowest levels at approximately the 30th day at the time when maximum bleeding was observed in the Japanese who were exposed at Hiroshima and Nagasaki. Lowest platelets counts were also seen in the Marshallese exposed to fallout radiation around 30 days after exposure. Individuals with neutrophil counts below 1000/μl may be asymptomatic. Likewise, individuals with platelet counts of 75,000/μl or less may show no external signs of bleeding. Individuals in this group do not need treatment. Radiation doses,

for reasons to be discussed later, may be misleading and are not very helpful. It is known from the studies in Japan that after exposure to 200 rad, a sublethal dose of radiation, there was about a 10% incidence of leukemia. Theoretically one could argue that individuals exposed to doses of radiation that increase the incidence of leukemia, such as 50 or more rad, should not receive hemopoietic molecular regulators to accelerate regeneration because premature stimulation of initiated cells may fix a lesion in DNA conducive to the later development of leukemia and thus possibly increase the late incidence of leukemia or decrease the latency.

An area for further research is the determination in the appropriate animal models of whether the administration of hemopoietic molecular regulators such as G-CSF and GSF will force initiated cells into mitosis, fix a lesion in DNA and thus increase the incidence of leukemia or shorten the latency between exposure and ultimate development of leukemia.

WHAT IS THE LD_{50} SINGLE DOSE OF UNIFORM PENETRATING RADIATION?

The mortality response of man to whole body uniform radiation is not known with precision. Cronkite and Bond (18) approached the problem by looking at the Marshallese response to 175 rad total body radiation and the response of animals in general. It would appear that the near maximal sublethal dose of radiation is in the vicinity of 200 rad. By using the slope of many mammalian dose mortality curves one can estimate that about 225 rad would produce a mortality of 5 to 10% and 500 rad a mortality of about 90%. The LD_{50} would be approximately 360 rad in the absence of treatment. It is established that the LD_{50} would be increased by the use of antibiotics to control infections, by platelet transfusions to control bleeding and now clearly by the use hemopoietic molecular regulators to stimulate early recovery of hematopoiesis.

INADEQUACIES OF PHYSICAL DOSE ESTIMATES FOR PROGNOSTICATING PROBABILITY OF SURVIVAL AFTER EXPOSURE TO IONIZING RADIATION

The dose unit used is the Gy. This is a physical dose unit and is equal to 10^4ergs/gram in tissue. It is independent of quality of radiation (LET). The Gy is 100 rad, an older radiation dose unit. One cGy is a rad.

In laboratory studies on animals or therapeutic exposure of patients, radiation exposure is deliberately designed for maximum uniformity of deposited energy in all tissues. In this situation the dose in tissue is meaningful and useful. The exposure geometry is designed to minimize effects of inverse square, attenuation and scatter of impinging photons. The photons hit electrons and these are accelerated in tissue at energies from near that of the impinging photon to near zero energies. With doses exceeding several cGy, the number of Compton electrons hitting the reference nuclear volume of 270 x 10^{-12} cm is large and uniform. As doses fall below 1 cGy, the number of electrons absorbed in a reference nucleus approaches one and with lower doses the number (fraction of cells hit) decreases. The average absorbed dose per hit cell becomes a constant with number of cells hit progressively decreasing as the dose continues to decrease. This is of major importance in considering the risk of carcinogenesis from small doses of radiation. The cells at risk receive a constant dose with a fewer number involved. Thus there is a point at which the average calculated tissue dose from internal or external radiation becomes totally meaningless with low level exposure.

Next, the distribution of dose in tissue equivalent phantoms for different "point sources" is illustrated in Figure 1. The sources are 250 kVp x ray, ^{60}Co, 2000 kVp x ray, and initial bomb gamma radiation. The widely different patterns of energy deposition are evident. Focus on 250 kVp x ray. There is a large buildup of energy deposition in the first 2-3 cm followed by a decrease as the

result of inverse square and attenuation. Hemopoietic stem cells (HSC) located in the first 2-3 cm receive a much higher dose than the HSC in the exit 2-3 cm. For such a situation there is no single dose that can be used for prognostication. In fact, one is not interested in a single dose, but the distribution of dose to HSC and the effect that these doses have upon the clonal survival of HSC, the time that these cells must rest, "lick their wounds" before they can respond to molecular factors that control their self-renewal and differentiation.

In Figure 2, depth dose curves in a tissue equivalent phantom are shown for initial bomb gamma radiation and mixed wide spectrum beta-gamma radiation. An air dose or surface dose with fall-out radiation may be over 1,000 cGy, but the meaningful tissue dose would be only about 100 cGy and definitely sublethal. An air dose of 100 cGy from initial bomb gamma radiation would represent dose to the first 3-4 cm of tissue on the proximal side whereas the tissue dose to the distal 2-3 cm would be 50-60% of the dose to the proximal side. There is a radiation dose in air in which HSC near the proximal surface will be killed and HSC near the distal surface will in part survive and rescue the casualty.

The effect of exposure geometry and energy on mortality is clearly shown in Figure 3 from studies of Tullis et al. (20) on irradiation of swine by unilateral, bilateral, and atomic bomb gamma radiation. The LD_{50} for unilateral 200 kVp x ray is 500 rad in air. For bilateral radiation the LD_{50} is 400 rad and for atomic bomb gamma radiation the LD_{50} is 230 rad.

In the case of radiation accidents, the inhomogeneity of absorbed dose in tissue is even more marked. Hands and feet may receive thousands of cGy with ultimate destruction of tissue necessitating amputation. More distant bone marrow may receive only a few hundred cGy or less with a lifesaving number of HSC surviving. These HSC given time will self-renew and differentiate into the

different hemopoietic lineages restoring hemopoiesis. If a radiation dosimeter was close to feet or hands, one would conclude that the individual had been fatally irradiated. If the dosimeter was further away on the side away from radiation, one would underestimate the damage to hands or feet and correctly prognosticate a reasonable probability of survival. Thus, single personnel dosimeters will rarely be helpful in accidents. Painstaking reconstruction of the accident involving movement of exposed personnel and estimation of dose is required to provide an approximation of the variation of absorbed dose to critical organ systems such as intestine and the bone marrow. This requires a mock-up when possible to measure dose rate at various positions in air and the conversion to absorbed dose distribution in tissue, a time-consuming procedure. Clinical decisions are required and must be made on the basis of signs and symptoms, and not on the basis of an air dose.

It is understandable why physicians desire a radiation dose and its probable mortality. If estimated mortality is approaching 100%, the management will be more aggressive utilizing all available therapeutic armamentaria. If estimated mortality is low or sublethal, watchful waiting is justified. In the case of accidental poisoning, the agent is known, but the dose is usually very uncertain. The therapy is determined by the properties of the agent and the clinical signs and symptoms and such is the case with radiation accidents.

The "doses" of radiation used by Gale are not physically measured or calculated doses based on source strength. The "doses" are derived from biological response - chromosomal aberrations, lymphocyte, granulocyte and platelet levels. Such "doses" are clearly not a measured physical entity. Markedly different doses in air will produce equivalent depression in total lymphocytes, platelet and granulocyte counts. The determinant of probability of survival is the number of HSC that survive and the time they require to undergo

self-renewal and differentiation into the life-saving hemopoietic lineages.

The importance of surviving HSC is demonstrated by several experimental studies. Swift et al. (23) delivered a fatal dose of radiation to half of the body of rats and as quickly as possible moved the lead shield to the irradiated half and delivered a fatal dose to the shielded half. In that short interval migratory HSC had migrated into the shielded area in sufficient numbers to provide protection. Brecher et al. (4) fatally irradiated one member of parabiotic rats while the other was shielded. HSC or other cells migrated from the shielded parabiont in sufficient number to protect it from fatal irradiation. Shielding of one leg of a mouse (about 6% of bone marrow) or spleen provides marked protection from otherwise fatal irradiation to the rest of the body.

It is emphasized that a physically derived or measured dose in cGy or a biologically derived dose except under rigidly controlled conditions in the laboratory are of limited, if any, value. Accident casualties have a markedly inhomogeneous deposition of radiation energy that may result in late necrosis of proximal tissue and survival of HSC in distal tissues.The methodology developed by Fliedner et al. (15) which predicts survival of HSC based on sequence of events involving changes in blood lymphocytes, granulocytes, and platelets appears to be the most clinically useful approach to predicting survival and guiding therapy.

COMBINED RADIATION, THERMAL BURNS AND TRAUMATIC INJURIES

The management of burns and trauma takes precedence over radiation injury. The mortality of radiation injury is clearly increased by concomitant trauma and thermal injuries. Surgery should be completed before the development of granulocytopenia and thrombopenia.

SUMMARY AND CONCLUSIONS

There are no mysteries about pathogenesis of the radiation syndromes. Common clinical sense directs its management. A few areas in which further research is desirable are:

1) Search for and application of molecular regulators, controlling growth of gastrointestinal epithelium and their application in control of the gastrointestinal syndrome.

2) Application of single and multiple hemopoietic molecular regulators in

a) accelerating host marrow regeneration and/or that of transplanted bone marrow,

b) determine if the use of the hemopoietic molecular regulators will increase the incidence of hemopoietic or solid neoplasms or shorten the latency between irradiation and appearance of tumors.

3) Analysis of existing hematological data on human beings to prognosticate the probability of survival and to provide a guide for appropriate supportive and replacement therapy.

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Figure 1: Depth dose curves for different unilateral sources of radiation. The 250 kVp, ^{60}Co and 2000 kVp x-ray are essentially point sources with substantial inverse square effect. Atomic bomb gamma radiation is a broad source and at a distance in which inverse square is negligible.

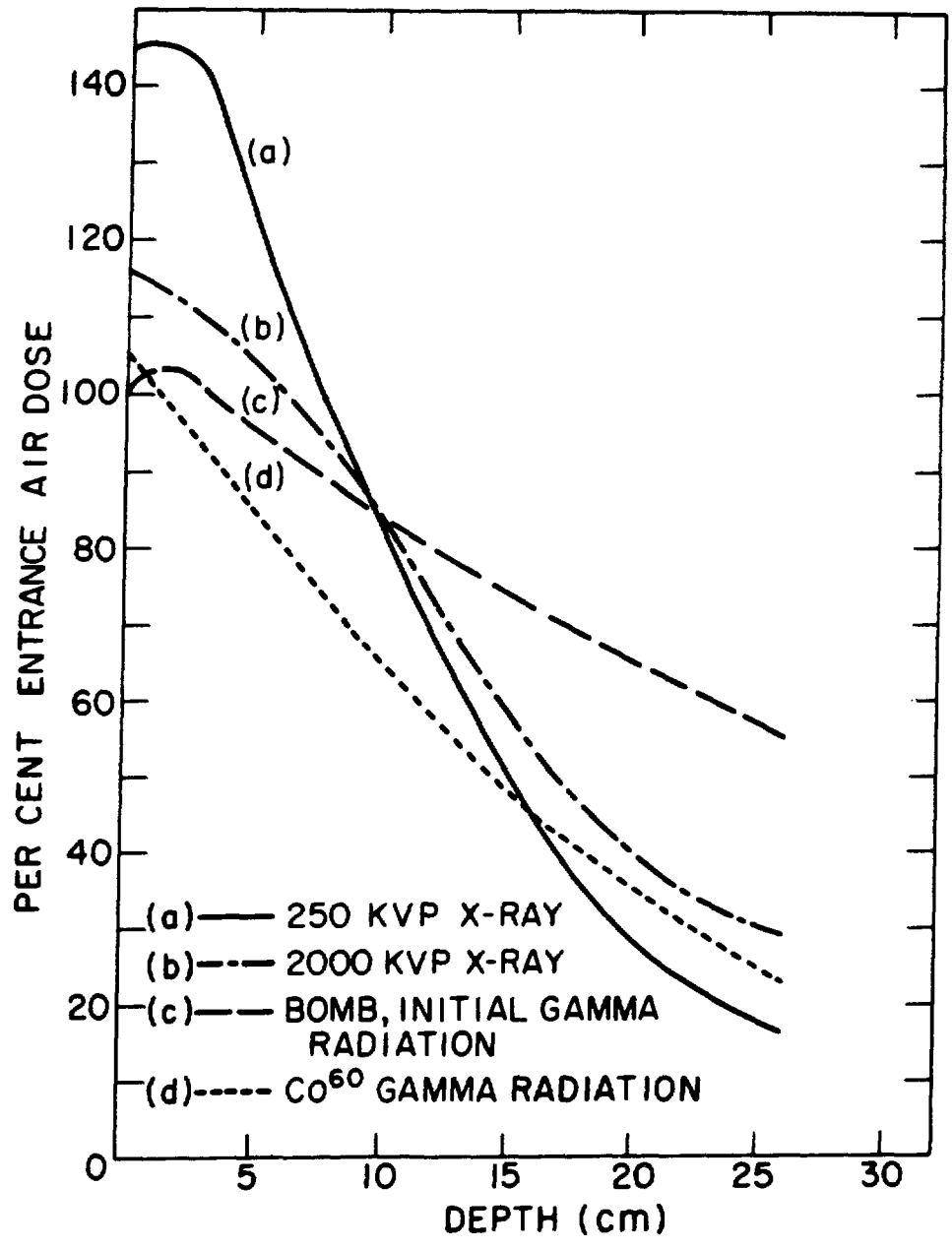
PER CENT ENTRANCE AIR DOSE
140
120
100
80
60
40
20
0
5
10
15
20
25
30
DEPTH (cm)
(a)
(b)
(c)
(d)
(a)—— 250 KVP X-RAY
(b)--- 2000 KVP X-RAY
(c)—— BOMB, INITIAL GAMMA RADIATION
(d)----- Co60 GAMMA RADIATION

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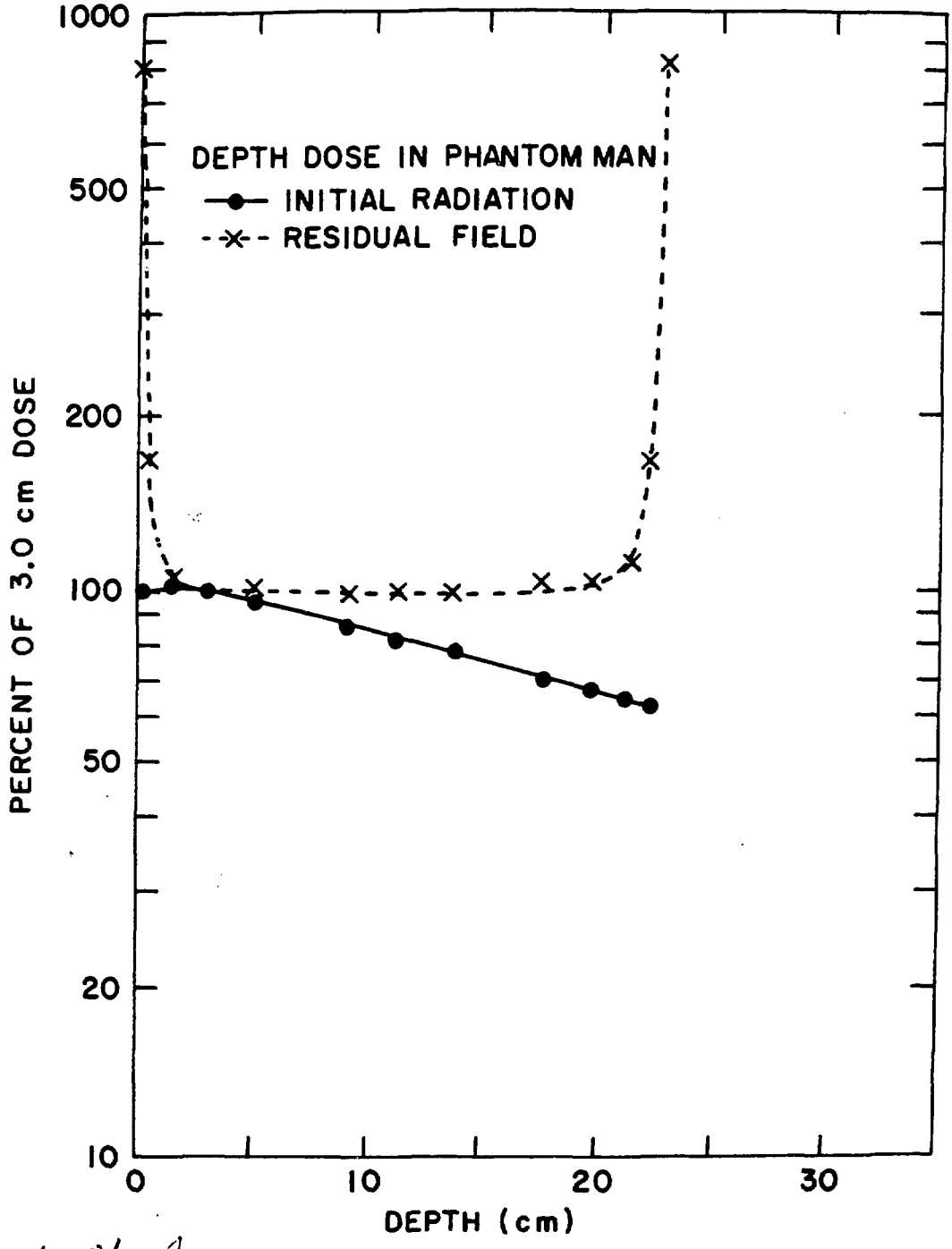
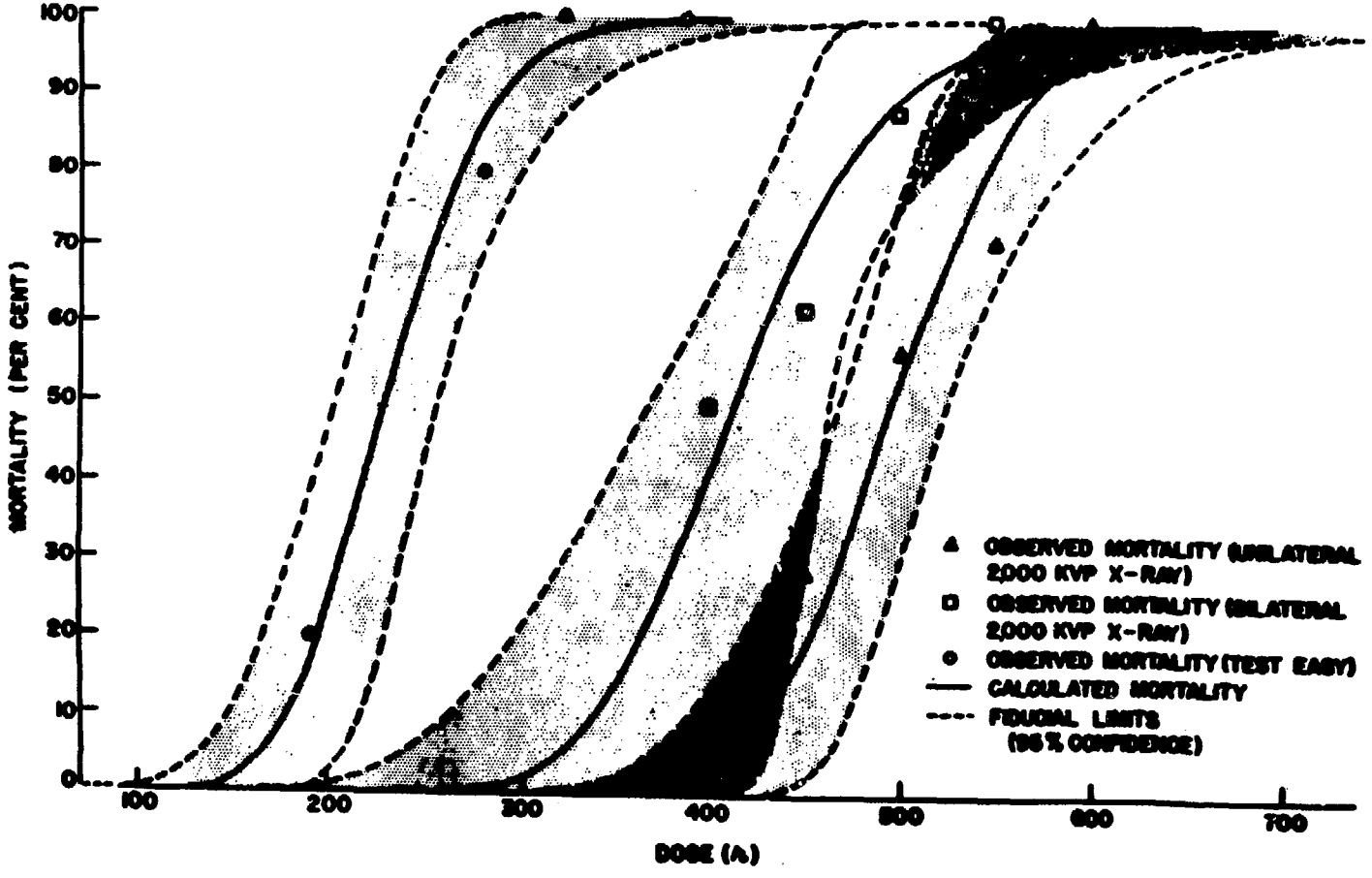
Fig 1

Figure 2: (8-61-81) Comparison of depth dose curves for deposition of energy in tissue-equivalent phantoms for initial gamma radiation from an atomic bomb and from a fallout field of fission products from an atomic bomb. The dose in tissue is expressed as % of the 3 cm dose in tissue since air and surface dose from the beta and very low gamma radiation is exceedingly high with very little penetrating power.


DEPTH DOSE IN PHANTOM MAN
INITIAL RADIATION
RESIDUAL FIELD
PERCENT OF 3.0 cm DOSE
1000
500
200
100
50
20
10
0
10
20
30
DEPTH (cm)

#8-61-81 Fig 2

Figure 3: Dose mortality curves for unilateral and bilateral 2000 kVp x-ray and for initial atomic bomb gamma radiation. In the case of 2000 kVP x-ray, there is a substantial inverse square effect and negligible inverse square effect because the bomb source is broad beam and at a large distance compared to size of the swine.



H9-294-58 Fig 3