PATHOLOGIC EFFECTS OF CHRONIC ^{90}Sr INGESTION IN MINIATURE SWINE*

by

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Over 700 female miniature swine, extending through three generations, have been exposed to daily feedings of from 1 to 3100 μCi ^{90}Sr. In addition, there were 200 untreated, female, littermate controls. Body burdens of ^{90}Sr reached approximately 7.5 and 10 times the daily intake in the original and F_1-F_2 generations, respectively, with the soft tissue radiation doses ∿ 1/1000 that for bone.

Although radiation osteitis was a common finding, only 7 pigs had evidence of 11 individual bone tumors, with >80% occurring in the skull. These tumors were classified morphologically as osteosarcomas (73%) or giant cell tumors (27%).

The most consistent disorders associated with chronic ^{90}Sr feeding were effects on the hematopoietic system. At levels >25 μCi/day (5000-20,000 rads accumulated skeletal doses), there occurred a progressive decrease in circulating leukocytes and platelets, and a precipitous, terminal fall in erythrocytes, with many of these animals dying of hemorrhagic diatheses. A second syndrome, observed particularly in animals at the 125 and 625 μCi/day levels, was a broad spectrum of myeloproliferation ranging from myeloid metaplasia to frank blast cell leukemia.

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DISCLAIMER

INTRODUCTION

In attempting to define the potential hazards of ^{90}Sr to man, there have been many animal studies performed over the past 30 years, utilizing numerous animal models to evaluate the biologic damage. Interest in ^{90}Sr arose because of its relative abundance as a long-lived (28 year radioactive half-life) radionuclide present in nuclear fallout. ^{90}Sr, by emission of an 0.54 MeV beta particle, decays to ^{90}Y, which in turn emits a 2.27 MeV beta particle with a 64 hour radioactive half-life. Since strontium is metabolized in a manner similar to calcium, it is deposited primarily in, and excreted slowly from, the skeleton, thereby producing relatively high radiation dose rates to osseous tissue and bone marrow.

The majority of animal studies have utilized single or multiple injections of radioactive strontium in rodents or dogs. This mode of administration, as opposed to ingestion, results in uneven skeletal distribution, producing areas of high strontium concentrations and severe focal bone damage. Because of their small bone mass, rodents lose approximately 70% of the ^{90}Sr radiation energy from bone.[1] This energy loss in man and miniature swine was found to be 12%[1] and 13%[2], respectively.

To simulate the most probably route of ^{90}Sr entry and its distribution in man, our laboratory initiated a study in 1958 using miniature swine exposed to ^{90}Sr by daily ingestion. This species was selected

because it is an omnivore with a mature weight and bone mass similar to man, and an estimated life span in excess of 12 years.[3] This study, coupled with a similar experiment at the University of California at Davis using beagle dogs, was designed to supplement the rodent studies and provide the data necessary for extrapolation of the biohazards of ^{90}Sr to man.

MATERIALS AND METHODS

The experimental design for this study has been previously reported in detail.[4] Briefly, the original generation female Pitman-Moore miniature swine were started on a daily ^{90}Sr feeding regimen at 9 months of age and subsequently bred to a control boar to produce the F1 ggeneration, which in turn produced the F2 generation. Thus, the F1 and F2 offspring were exposed to ^{90}Sr in utero, from their dam's milk, and then by daily feeding. Weaning was accomplished at 6 weeks of age, at which time the animals were started on daily ^{90}Sr feeding at 1/4 their dams level. This was increased by 25% of the destined ^{90}Sr dose every six weeks, so that by 6 months of age they were at full level. This regimen permitted the dietary calcium-strontium ratio to remain constant during the rapid growth of adolescence.

Over 700 miniature swine representing 3 generations have been exposed to ^{90}Sr at 1, 5, 25, 125, 625, and 3100 μCi/day over the past 13 years. In addition, there have been approximately 200 female controls.

A second major group, comprising 47 miniature swine, have been exposed to ^{90}Sr at 5 different periods: 1) in utero only, 2) nursing only, 3) in utero and during the nursing period only, 4) from conception throughout adult life, and 5) from the nursing period and throughout adult life (Table 1). The dams, and those offspring continuing on ^{90}Sr, received 125 μCi/day. The offspring are being held for lifetime observation.

The animals were kept in groups of 3 to 6 swine per pen within controlled temperature buildings. Individual feeding stalls were utilized within each pen so that strict dietary control could be maintained. The ^{90}Sr chloride solution fed these pigs was absorbed into a large feed pellet which was fed with the morning ration.

Blood samples were obtained at intervals from the anterior vena cava using commercially available evacuated tubes*. Routine hematologic and serum biochemistry parameters were determined using the Coulter Model B, and more recently the Coulter Model S, and the Technicon Auto-analyzer. Methods of analysis have been previously reported.[5] Bone marrow samples were aspirated, (without the use of anticoagulants), from the sternum using a Rosenthal needle.

About 250 animals have been killed at various ages for the express purpose of determining the tissue distribution of the deposited

*Becton-Dickinson Vacutainer

^{90}Sr, and to evaluate the early effects of the radionuclide ingestion. The remainder have been maintained for lifetime observation and killed as their clinical condition dictated. At death, complete gross and histologic examinations were performed on all tissues, and autoradiograms made on selected cases.

Cytogenetic studies were performed by standard methods on peripheral leukocytes and aspirated bone marrow.[6]

RESULTS

Radiation Dose

The methods of dosimetry and assays for skeletal ^{90}Sr accumulation in miniature swine ingesting 1 thru 625 μCi ^{90}Sr per day from birth to approximately 8 years of age have been reported by Palmer et al.[2] Original sows started on daily ^{90}Sr at 9 months of age accumulated a ^{90}Sr body burden approximately 7.5 times the daily intake, whereas the F1 and F2 generations reached about 10 times their daily intake. Less than 1% of the absorbed ^{90}Sr was located in soft tissue, so that the radiation dose to extraosseous tissue was approximately 1/1000 that received by bone. The radiation received by the ovaries was essentially the same as other soft tissues.

Thermoluminescent dosimeters were used to determine the radiation dose to fetuses at various periods during gestation. At approximately

midway in gestation (55 days), the dose rate to the fetuses of dams ingesting 125 μCi/day was approximately 28 mrad/day, whereas at term a mean dose rate of approximately 50 mrad/day was obtained. The osseous tissue dose rate at 55 days was approximately 50 times that received by soft tissue, and 500 times greater at term. There was no significant maternal contribution to the radiation dose received by the fetal thymic area. The accumulated radiation to a term fetus would be about 50 rads from a 125 μCi/day dam, and approximately 400 mrads from a 1 μCi/day dam.

Farrowing Performance

An extensive statistical analysis of the farrowing performance of the animals ingesting ^{90}Sr has been previously published.[7] Except for weaning weights of offspring from the original 625 μCi/day dams, there were no differences in litter size, percentage of stillborn, birth weights, or weaning weights between control and animals ingesting up through 625 μCi/day. The lower weights of 625 μCi/day offspring were probably due to the severe radiation effects produced in the dams resulting in reduced lactation during the nursing periods, and to the accumulative radiation effects on the neonates.

Farrowing parameters in the F1 generation dams, ingesting 0 thru 125 μCi/day, were indistinguishable, with the exception of larger litters in the 25 μCi/day group. The reason for this difference is not apparent.

Original sows of the 3100 μCi level failed to survive the gestation period, and 625 μCi/day offspring died before sexual maturity, so that there are no F1 nor F2 generations, respectively, in these groups.

It is important to note that the lowest level fed these swine (1 μCi/day) results in a body burden approximately 5 times higher than the International Commission for Radiation Protection body burden limits for occupational exposure in man[8], and is 2000 times greater than the highest ^{90}Sr level ever reported in American diets.[9] Even at levels 125 times these values, there were no adverse affects noted on farrowing performance.

Life Span Effects

Currently there are 78 swine still alive that were assigned to the original study. These include thirty-two controls, twenty-eight 1 μCi offspring, eleven 5 μCi offspring, and two 25 μCi original sows and five of their offspring. The results of cumulative mortality data, though incomplete at this time, indicate increased deaths in original pigs of the 625 and 125 μCi/day groups after 1 and 5 years, respectively, and possibly after 10 years in the 25 μCi/day group.[10] Cumulative mortality in the offspring of the 1, 5 and 25 μCi/day groups was not significantly greater than control values through 9 years of age. The high mortality rates in the 125 and 625 μCi/day groups were due to the extreme stresses placed on the hematopoietic system by ^{90}Sr. The

vast majority of deaths, or cases requiring euthanasia, in all groups over 5 years of age were due to uterine tumors or faulty dentition.

The mortality rates in the uterine milk exposure study are extremely interesting. The animals that have received ^{90}Sr exclusive of the gestation period, that is only during the nursing period and then by feeding, had a 70% mortality by 36 months of age, whereas those exposed to ^{90}Sr in utero, nursing, and by subsequent feeding experienced only a 22% death loss over the same time period. The one death in the group exposed in utero only, was a non-radiation related acute necrotizing pancreatitis.

Osseous Lesions

Radiographically, there were no definitive lesions at ingestion levels less than 125 μCi/day. At 125 μCi/day, radiolytic areas became apparent in the mandible after approximately 4 years of ^{90}Sr ingestion. The same was true of 625 μCi offspring taken off ^{90}Sr feeding and allowed to survive 2 to 3 years. In these higher dose levels, there occured rather severe periodontal osteonecrosis resulting in early loss of teeth and/or suppuration. These observations were not surprising since greater than 30% of the ^{90}Sr body burden was located in the skull,[11] partially due to a greater ^{90}Sr deposition per gram of bone in this area.[12]

Histologically, the ^{90}Sr induced bone lesions consisted of irregular calcification and an increase in resorption cavities, reactive bone, and fibrosis, progressing to severe osteonecrosis at ^{90}Sr levels of 625 μCi/day and above. A detailed analysis of histologic changes by dose levels has not been made at this time due to diminished bone effects at the lower dose levels. As the 1, 5, and 25 μCi/day groups accumulate a greater radiation dose, a difference may be detectable if the survival time is sufficiently long.

Although a high incidence of bone tumors was predicted as an end result of ^{90}Sr feeding, this has not proved to be true. Only seven animals in the chronic toxicity study have developed detectable bone tumors. Five of the animals were 125 μCi/day offspring, and two of these had multicentric tumors. They had received ^{90}Sr throughout their life and died at 744-1210 days of age. The remaining two animals with bone neoplasia were 625 μCi/day offspring that received 156 μCi ^{90}Sr/day for approximately 6 weeks after weaning and then were removed from further radionuclide ingestion for 1093 and 1561 days before death. Accumulated skeletal radiation doses ranged from 9000-15000 rads in both the 125 and 625 μCi offspring. Nine of the eleven bone tumors were located in the head region, and one each in a rib and ulna.

Histologically, 73% of these tumors were classified as osteosarcomas, 27% as giant cell tumors or osteoclastomas, and in most cases appeared to arise from the periosteal surface. A detailed description of these tumors has been previously reported.[12]

Chromosomal Effects

Karyograms from both peripheral blood leukocytes and bone marrow cells have failed to show any consistent, or an increased number of chromosomal aberrations in animals ingesting 1 thru 625 μCi ^{90}Sr/day. The abnormalities observed in animals developing hematopoietic neoplasia have not been constant nor different than those in control animals.

Hematopoietic Effects

Peripheral Blood

The effects of chronic ^{90}Sr ingestion on the peripheral blood values are best demonstrated at the highest feeding level, i.e., 3100 μCi/day (Figure 1). Four weeks after 9-month-old animals were started on ^{90}Sr ingestion, the platelet, segmented neutrophil, and lymphocyte values were reduced to approximately 50% of the pre-exposure levels. These continued a steady decline until death occurred approximately 3 months later. There was a lag in erythrocyte response, compared with other cellular elements, and the effect was less pronounced until near the time of death. Erythrocyte depression was, however, similar in magnitude to that observed in leukocytes and platelets. These animals failed to survive the gestation period so there was no F1 generation for study.

A similar sequence of events was observed with 625, 250 and 125 μCi ^{90}Sr/day, although the magnitude of change and time of death shifted

to a longer interval as the daily ^{90}Sr feeding level was reduced. Original animals started on 625 μCi/day survived 9-12 months, so were able to produce an F1 generation, which if maintained on ^{90}Sr after weaning, survived only about three months.

The F1 generation, 250 μCi ^{90}Sr/day, animals experienced pronounced depression in platelets and leukocytes, and 6 of 20 died of a hemorrhagic syndrome by 7 months of age. With the exception of two animals, ^{90}Sr feeding was discontinued at 200 days of age. This resulted in partial recovery of peripheral blood leukocytes and platelets. One of the animals removed from further ^{90}Sr feeding developed a neoplasia characterized by an abnormal serum protein and plasmacytoid cells in the blood and marrow, which has been tentatively diagnosed as multiple myeloma.

At 125 μCi/day, original animals lived 4-6 years with moderate development of thrombocytopenia, neutropenia and lymphopenia. Their offspring manifested much more severe hematopoietic depression, so that by one year of age their leukocyte and platelet values were approximately 50% that of control animals, and deaths occurred at about three years of age. Many animals in this group developed hematopoietic neoplasia which will be detailed below.

In the 1, 5 and 25 μCi/day levels there have been no definitive changes observed to date in the circulating cellular elements of either

original or offspring pigs. There was a suggestion of a slight depression in neutrophil values in the 25 μCi/day group, but this observation awaits confirmation by statistical analysis. As the animals in these groups age beyond 5 years, evaluation of hematologic data becomes complex because of complications from uterine tumors, oral infections, and other causes of leukemoid reactions.

In the uterine-milk exposure study, the peripheral blood values of animals kept on 125 μCi/day have been consistent with those previously observed at that level. Cellular elements of those exposed in utero only, milk only, or in utero and milk only, have not been different than those of the controls (Figure 2). Examination of aspirated sternal bone marrow when these animals were 33 months of age revealed a shift to the left in the maturation curves of both the erythroid and myeloid series in those animals that continue to ingest ^{90}Sr (Figure 3 and 4).

Hematoproliferative Disorders

The spectrum of proliferative disorders observed in animals at the various dose levels is shown in Table 2. The histopathology of these dyscrasias has been previously described.[18] At the 3100 μCi/day level two of three animals developed areas of myeloid metaplasia that were most evident in the liver, spleen, lymph nodes and kidneys, but with scattered foci in the myocardium and adrenals.

The 625 μCi/day offspring experienced an incidence of myeloid metaplasia of approximately 50%. In addition, there was one case each of myeloid and lymphoid neoplasia. Most animals in this group died of an acute hemorrhagic syndrome associated with profound thrombocytopenia, leukopenia and anemia.

At the 125 μCi/day level, only 5 of 42 animals considered at risk developed myeloid metaplasia. However, the incidence of hematopoietic neoplasia in the parents was approximately 40% and in the offspring 70%, with the mean age at death being about 6 and 3 years, respectively. Of these, 41% were considered myeloid, 19% lymphoid and 7% stem cell proliferations.

With lower accumulated radiation doses (1, 5, and 25 μCi/day), the incidence of metaplasia, and particularly neoplasia, was reduced and there was a greater tendency for production of lymphoid neoplasms.

The hematopoietic neoplasms generally developed relatively late in the particular lifespan for each dose level, and after accumulated radiation doses of 6000 to 20,000 rads, the majority occurring at approximately 15,000 rads. Clinically, these neoplasms were characterized by being very acute in nature with only a few weeks between the presence of blast forms in the peripheral blood and death of the animal. About one-half of the myelogenous leukemia cases had leukemic peripheral blood

values. The majority of the myelogenous leukemias were classified as granulocytic, with one each of eosinophilic, basophilic, DiGuglielmo's disease, and two myelomonocytic forms.

There were two cases of myelogenous leukemia observed in 62 control animals at risk. Curiously, both of these animals developed eosinophilic forms. There have been no cases of lymphoma observed in our control population.

DISCUSSION

Although significant postnatal radiation effects of ^{90}Sr have been manifested at several high dose levels, there was no evidence of increased fetal or neonatal mortality even at accumulated fetal radiation doses of greater than 150 rads. Since the fetus receives little radiation from maternal tissues, and ^{90}Sr is a bone-seeking radionuclide, the sensitive fetal tissue would be well differentiated prior to the time a significant ^{90}Sr concentration would begin accumulating. This does not, however, presume that bremstrahlung radiation from maternal tissues during the early period of the embryo could not result in an embryonal rest of neoplastic propensity which might become manifest under proper stimulation later in life. Vaughan[13], in a review of the literature, concluded that even at the relatively low dose rates of diagnostic procedures the incidence of leukemia in exposed fetuses is increased.

Comparison of radiation-induced deaths in the uterine - milk exposure study are particularly interesting. The greater than 3-fold increase in mortality in those exposed to ^{90}Sr during nursing and then to radioisotope feeding seems too much to be coincidental. It is interesting to postulate the development of a relatively ^{90}Sr resistant cell population during embryogenesis, or simply a homeostatic increase in the hematopoietic stem cell compartment which would require a greater accumulated radiation dose for depletion.

The low incidence of bone tumors in swine chronically ingesting ^{90}Sr is in direct contrast to the high bone neoplasia observed in rats and dogs injected with ^{90}Sr.[14,15] The latter method of administration results in uneven skeletal distribution and areas of high irradiation intensity or "hot spots", which result in severe necrosis and tumor development in these areas. Generally, the bone tumors that developed in our swine were also in sites of most severe osteonecrosis, where extensive destruction and active remodeling processes were occurring.

Of particular interest is the observation that in those cases where it was possible to determine the site of origin, the swine bone tumors appeared to arise from the periosteal surface. Following injection of ^{90}Sr in several other species, the bone tumors originated from the endosteal surface,[16] and in a study utilizing a single intravenous ^{90}Sr injection in miniature swine it was established that greater damage occurred

to the endosteum and trabeculae than to the periosteal surface.[17] The more even skeletal distribution of the isotope following chronic ingestion results in a relatively greater dose rate to the periosteum than following injection, but evidently not great enough to kill the cells that have the potential of becoming neoplastic.

The pathogenesis of the ^{90}Sr effects on hematopoiesis must be very complex with this long-lived, bone-seeking radionuclide, since the delicate homeostatic balance between stimulatory and repressor feed-back mechanisms would be under constant perturbation from the continuous marrow damage. In addition to this direct radiation damage, the cells responsible for maintaining the microcirculation are probably injured and contribute to the hematopoietic cell changes. It has, in fact, been shown by Crosby and co-workers[19] that, in X-irradiated animals, delayed bone marrow aplasia from the deterioration of the microcirculation results in the hematopoietic cells not being maintained. It is reasonable to presume that a similar situation could ultimately occur at higher ^{90}Sr dose levels, and could be primarily responsible for the terminal fall in peripheral blood elements, and contribute to the subsequent development of myeloid metaplasia.

It is apparent that continuous ingestion of ^{90}Sr, exclusive of the 125 μCi/day group, results in either a rather severe hematodepression and a terminal hemorrhagic crisis (3100, 650, or 250 μCi/day), or has no

readily detectable effect on the formed blood elements (< 125 μCi/day). The leukemogenicity, especially at the 125 μCi/day level, is particularly interesting and is in contrast to earlier studies in which ^{90}Sr by injection indicated that bone tumor production would be the most prevalent neoplasm encountered. This observation confirms the results of retrospective studies in the human by Vaughan[13], in that she found the latent period for leukemia induction was considerably shorter than that for osteosarcoma development.

The sequence of events terminating in acute hematopoietic neoplasms in these pigs is unknown. There are, of course, several possible mechanisms which may act independently or in concert. The effects of chronic leukopenia would undoubtedly influence the humoral feed-back control mechanisms, presumably by elevating "leukopoietin" levels. An elevated "poietin" level probably would also be related to a reduced chalone effect if early cell death occurred. There is some evidence from the bone marrow examinations of the uterine-milk study pigs that this may be occurring at the higher ^{90}Sr levels. The increase in blast and pro forms could be either a quantitative increase in the cell types or a relative increase if more distal cells have died. Also, Cooper et al.[20] demonstrated a prolonged granulocyte generation time in six pigs ingesting 625 μCi ^{90}Sr/day. Beirman[21] reports similar findings in human acute leukemia patients, along with defective maturation and altered release of cells to the peripheral blood. These effects would

certainly upset the feed-back control mechanisms.

An impaired immunological competence, with either a viral or neoplastic clonal etiology, must also be considered in the development of these hematopoietic neoplasms and is under investigation at this time. Viruses with certain characteristics common to known leukemia viruses have been isolated from some of these leukemic pigs, but their role in the etiology is unknown.

A scheme depicting the possible pathogenesis of ^{90}Sr induced hematopoietic neoplasms is shown in Figure 5. Bone marrow irradiation may produce some subtle somatic mutation, resulting in an enzymatic change and a maturation defect. This clone of cells could then become the dominate cell line, by either progressive radiation effects on the normal cell line, or by a failing immune system which had previously held the neoplastic cells in check. Probably both mechanisms would be active. In addition, this clone of immature cells might be especially susceptible to the cellular and humoral regulators that would be elevated from the constant marrow damage. It has been suggested that the spectrum of hematopoietic neoplasms in these pigs indicates that a pluripotent marrow stem cell is probably affected.[13,18] This, however, does not seem reasonable since most neoplasms have been of a single cell type, which would indicate the affected cell is probably a committed stem cell. It should be noted from Figure 5 that myeloid metaplasia is not a

part of the progression to neoplasia, but is probably a physiologic response to the pathologic process occurring in the bone marrow.

The "gross" effects of ^{90}Sr have been well documented in several species. However, there needs to be additional studies of in-utero and neonatal exposure of the hematopoietic system, correlated with the subsequent development of hematopoietic neoplasia. These more definitive studies would include determination of stem cell kinetics, the influence of poietins and chalones, and alterations in leukocyte kinetics. These questions need answers not only for clarification of cellular radiation effects, but also because non-radiation bone marrow insults may have a similar pathogenesis in the development of neoplasia. The miniature pig is particularly well suited for these studies because of life span and the ease of obtaining serial blood and bone marrow samples.

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LEGENDS

Table 1. Experimental Design of Uterine-Milk Exposure Study

Figure 1. Hematologic Response of a Miniature Pig Ingesting 3100 μCi ^{90}Sr/day

Figure 2. Peripheral Leukocyte and Platelet Values of Miniature Swine in the Uterine-Milk Exposure Study

Figure 3. Pertinent Erythroid Marrow Maturation in Uterine-Milk Exposure Study (Mean ± S.E.)

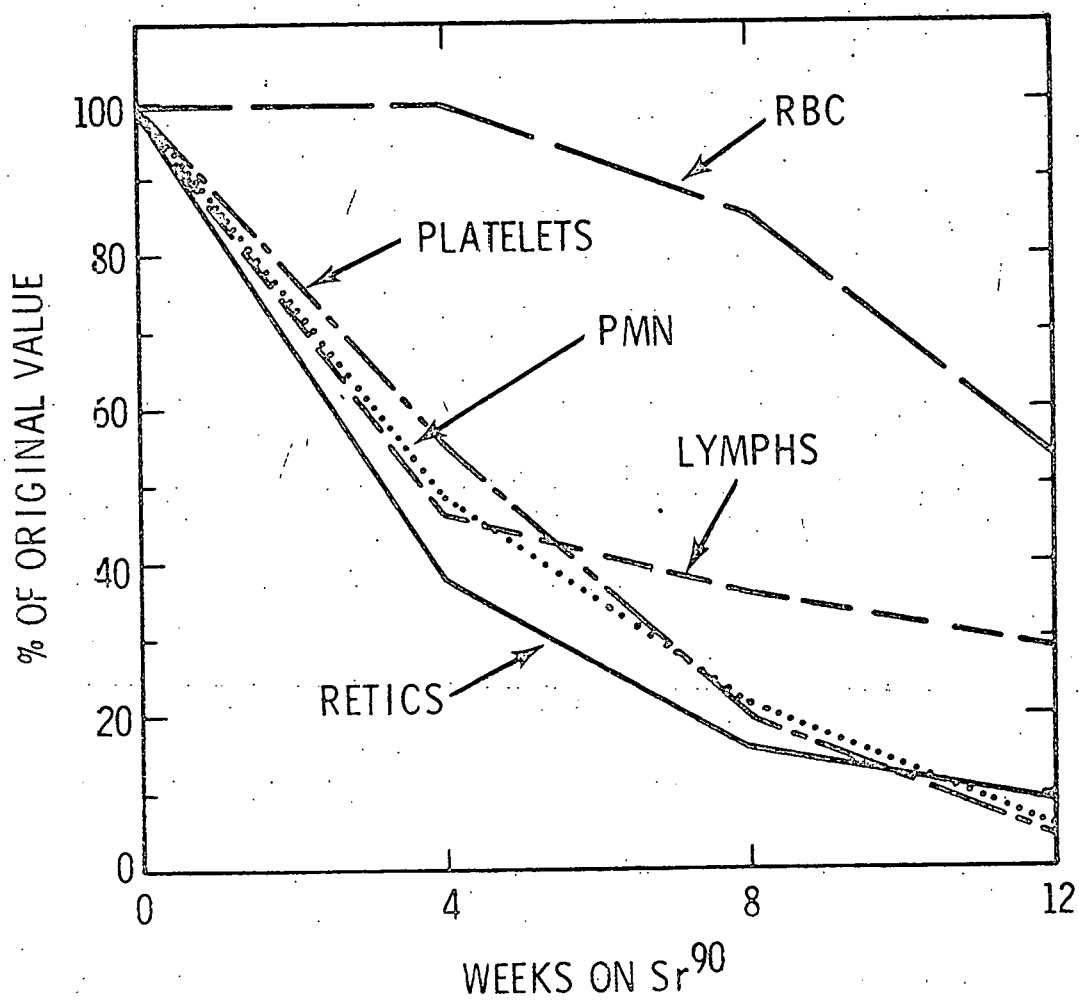
Figure 4. Pertinent Myeloid Marrow Maturation in Uterine-Milk Exposure Study (Mean ± S.E.)

Table 2. Hematoproliferative Dyscrasias in Swine Ingesting ^{90}Sr

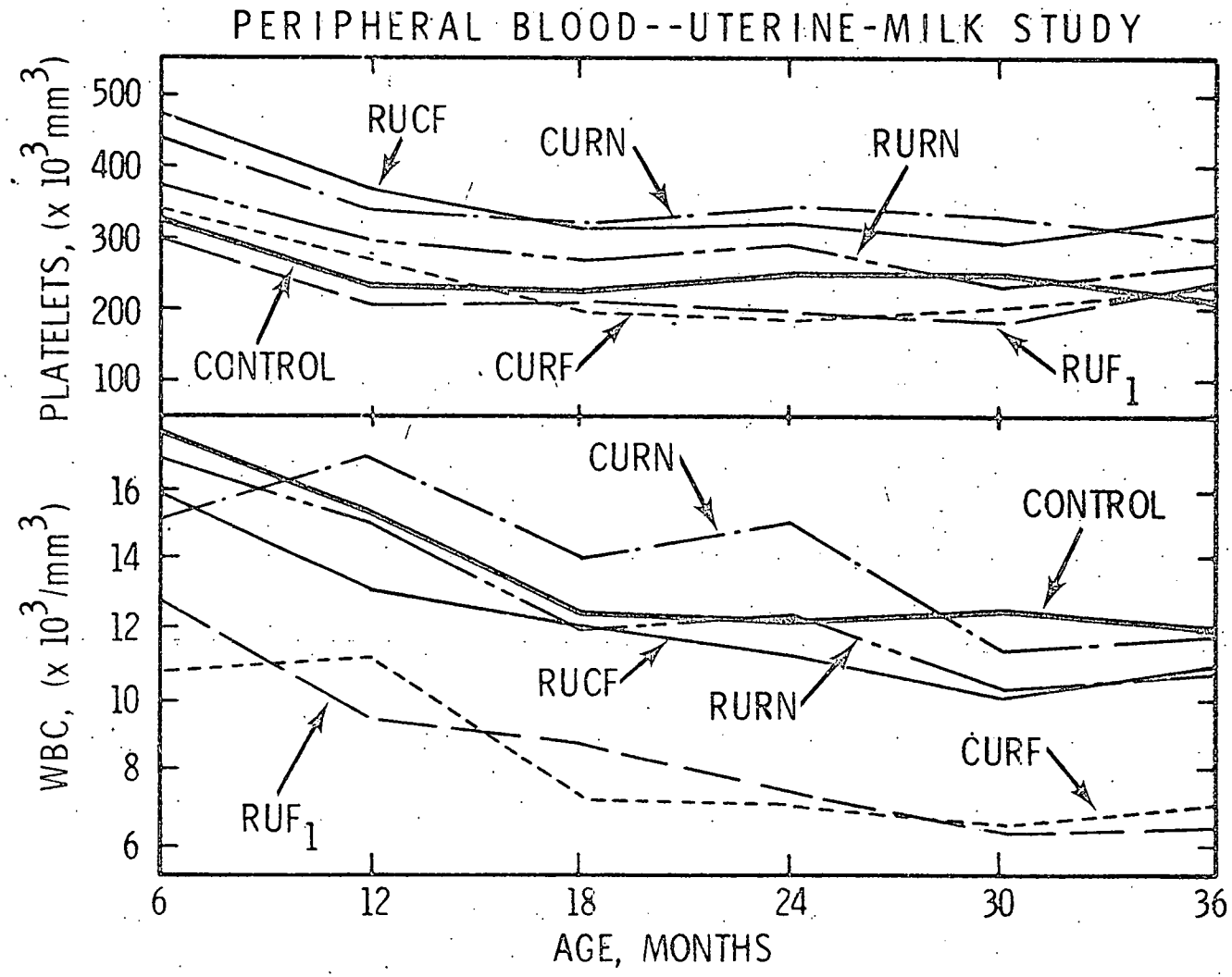
Figure 5. Proposed Scheme of ^{90}Sr Induced Myeloid Metaplasia and Neoplasia

EXPERIMENTAL DESIGN
UTERINE-MILK EXPOSURE STUDY

GROUP	DAM	Sr^{90} EXPOSURE	NO.
RUCF	125 uCi	IN UTERO ONLY	10
CURN	CONTROL	NURSING ONLY	10
RURN	125 uCi	IN UTERO & NURSING	8
CURF	CONTROL	NURSING & FEED	10
RUF_1	125 uCi	IN UTERO, NURSING & FEED	9



HEMATOLOGIC EFFECTS OF 3100 uCi Sr^{90}/DAY


PERIPHERAL BLOOD--UTERINE-MILK STUDY
PLATELETS, (x 10³mm³)
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400
300
200
100
RUCF
CURN
RURN
CONTROL
CURF
RUF1
WBC, (x 10³/mm³)
16
14
12
10
8
6
CURN
CONTROL
RUCF
RURN
CURF
RUF1
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12
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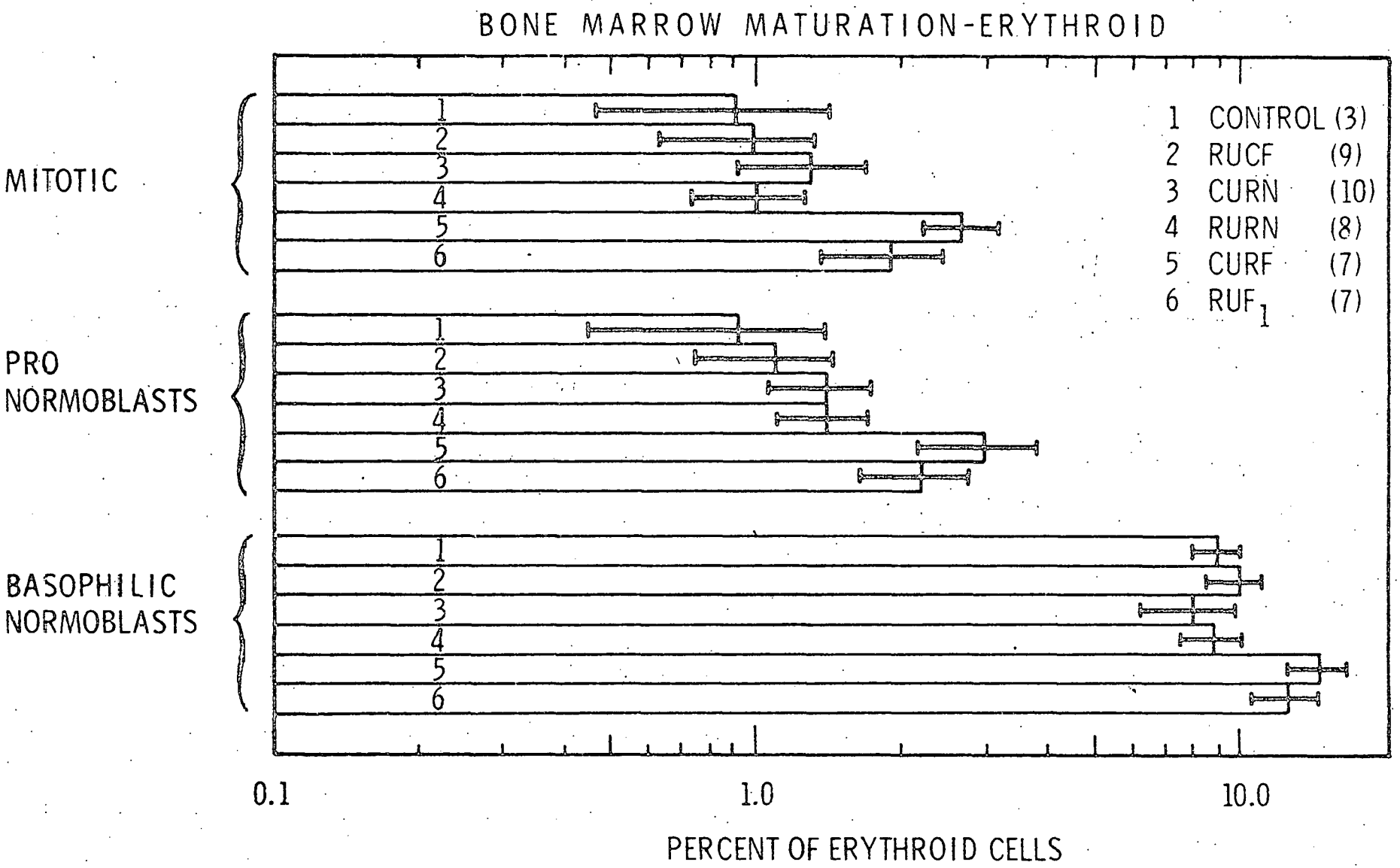
AGE, MONTHS


BONE MARROW MATURATION-ERYTHROID
MITOTIC
PRO NORMOBLASTS
BASOPHILIC NORMOBLASTS
1
2
3
4
5
6
1 CONTROL (3)
2 RUCF (9)
3 CURN (10)
4 RURN (8)
5 CURF (7)
6 RUF1 (7)
0.1
1.0
10.0
PERCENT OF ERYTHROID CELLS

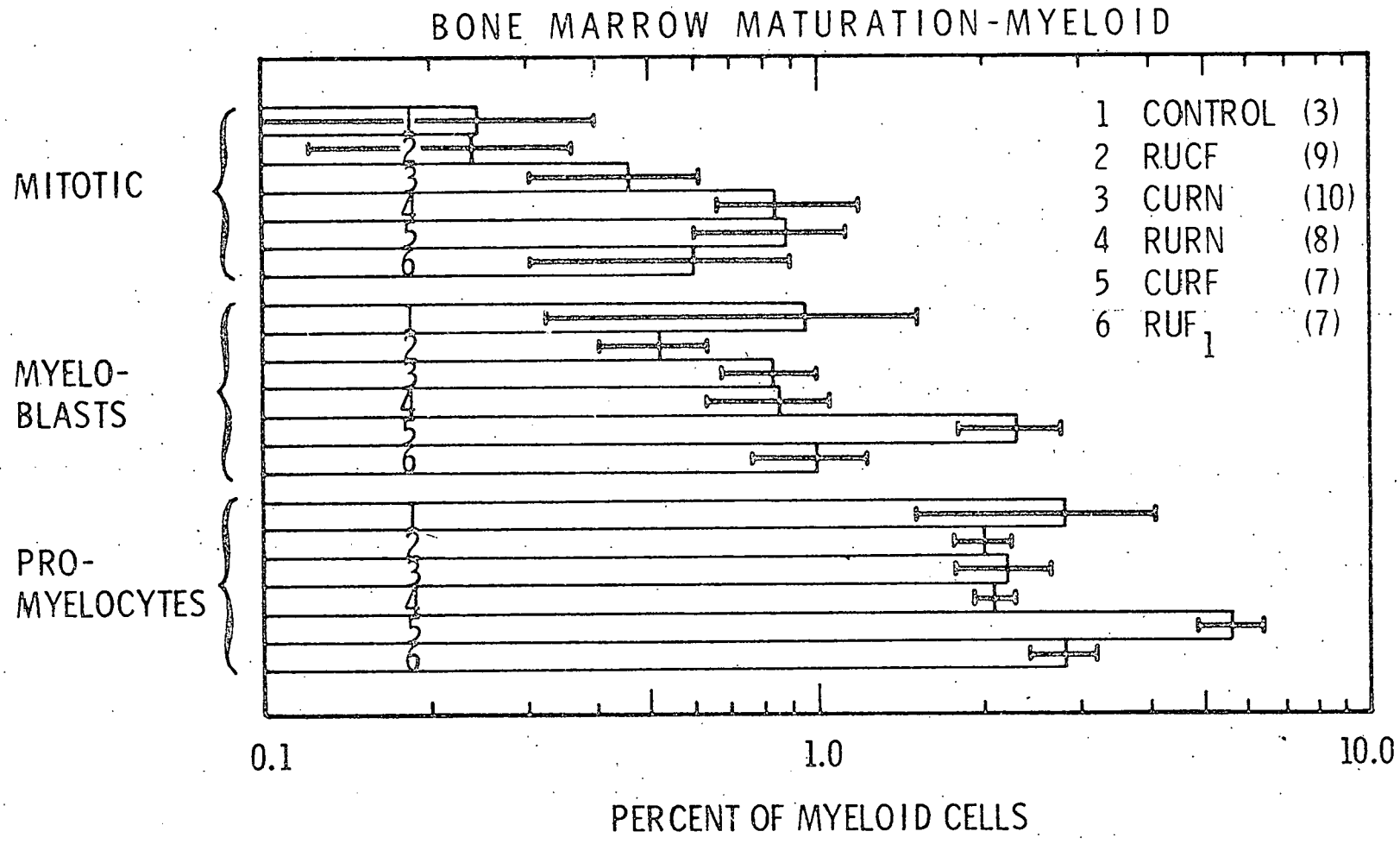

BONE MARROW MATURATION-MYELOID
MITOTIC
MYELO-
BLASTS
PRO-
MYELOCYTES
1 CONTROL (3)
2 RUCF (9)
3 CURN (10)
4 RURN (8)
5 CURF (7)
6 RUF1 (7)
0.1
1.0
10.0
PERCENT OF MYELOID CELLS

Table 2. Hematoproliferative Dyscrasias in Swine Ingesting ^{90}Sr

^{90}Sr Level (μCi/day)	Generation	Number of animals at risk	Age at death (months)*	Average rad dose (x 10^3) to skeleton*	Lymphoid neoplasms	Myeloid neoplams	Stem cell neoplasms	Myeloid metaplasia
3100	Parent	3	12-13	7-10	--	--	--	2
625	Parent	5	17-19	6-9	--	--	--	2
	F_1†	28	3-34	2-10	1	1	--	15
125	Parent	10	66-88	13-17	1	3	--	3
	F_1, F_2	32	24-57	10-20	7	14	3	2
25	Parent	12	54-123	2-6	--	2	--	--
	F_1, F_2	32	50-93	3-6	2	1	--	5
5	Parent	0	--	--	--	--	--	--
	F_1, F_2	24	82	1.0	1	--	--	--
1	Parent	17	92-96	<0.04	1	--	--	1
	F_1, F_2	59	52-81	<0.2	4	--	--	1
0		62	103-105	--	--	2	--	1

* For those animals with hemcproliferative disorders.
† Removed from ^{90}Sr feeding at 3 months of age.

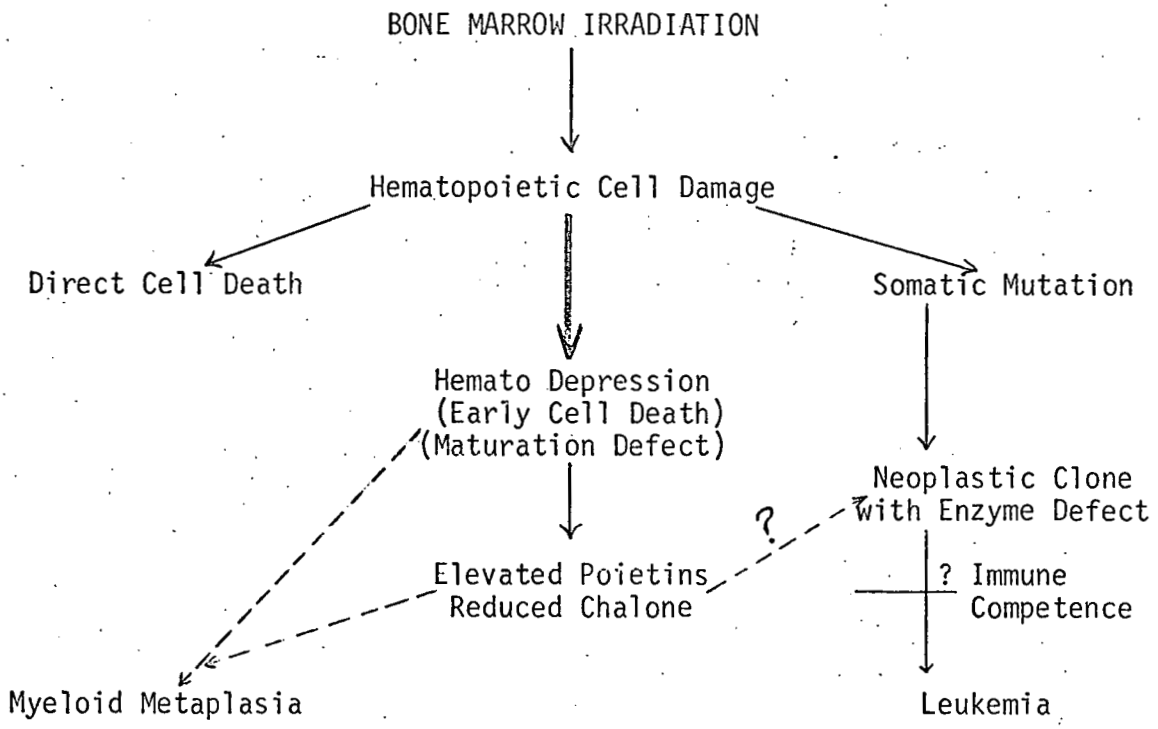


Figure 5

Proposed Schcmc of ^{90}Sr Induced
Myeloid Metaplasia and Neoplasia