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Hematologic Manifestations of Radiation Exposure in Man

NIEL WALD, GEORGE E. THOMA, JR. and GORONWY BROUN, JR.

I. INTRODUCTION

A. *Purpose and Scope*

IT IS THE PURPOSE of this review to present the hematologic manifestations of human radiation exposure, including both promptly appearing and more delayed effects resulting from doses delivered in both short and long time periods. The more recently developed methods used in such studies will be considered as well as the resultant data. The implications of the findings in relation to the diagnosis and management of clinical cases, and to the formulation of decisions affecting the health of occupationally exposed workers and the general public will be emphasized. Information obtained from pertinent animal experimentation will be introduced only where it is needed to illustrate concepts for which adequate supporting human data are not yet available.

In reviewing a subject which has attracted so much interest and study in recent years, it is clearly impossible to incorporate all related published work. In general, various aspects have been selected for detailed treatment on the basis of their particular interest and value to the reader who has not specialized in this scientific area. The most complete and recent reviews of each aspect have been cited, and references made to relevant material published subsequent to the reviews. The selections are not all-inclusive but, rather, reflect the limitations of space and the interests and capabilities of the reviewers.

B. *Definitions*

The terminology used in this review is essentially that used by the majority of workers in this field. However, to reduce the ambiguity of certain terms such as "acute" and "chronic," which have been used interchangeably to describe both radiation exposure and its effects, we have adhered to certain definitions set up by the Subcommittee on Hematologic Effects of the Committee on Pathologic Effects of Atomic Radiation, National Academy of Sciences-National Research Council.[1]

Acute and *chronic* are only used in the usual medical sense. *Short-term exposure* includes (1) total body exposure to radiation over a short period of time, e.g., in nuclear warfare and nuclear reactor or accelerator accidents, and (2) exposure to limited but substantial body areas when the radiation is delivered either as a single dose or fractionated over a few days or weeks; e.g., in therapeutic radiation, diagnostic radiology, tracer or therapeutic use of radioactive isotopes. In

From the Department of Occupational Health, Graduate School of Public Health, and the Department of Medicine, School of Medicine, University of Pittsburgh; and the Department of Internal Medicine, St. Louis University School of Medicine.

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considering short-term exposure, a dose of 50 rads or more is defined arbitrarily as a *high dose*, less than 50 rads as a *low dose*. *Long-term exposure* refers to continued or repeated exposure to radiation over long periods of time—months or years; e.g., routine occupational exposure, body burdens of radioactive isotopes with relatively long effective half lives, x-ray examinations repeated frequently over a long time, exposures to cosmic radiation, naturally occurring radioactive isotopes, and fallout.

The *immediate effects* of radiation are those events occurring in tissue during exposure as a result of the interactions of the radiation with matter. These interactions may lead to *hematologic* manifestations or observable alterations in the blood or bone marrow that occur promptly or may appear months or years after irradiation. The development of these hematologic clinical findings will depend not only on radiation but will also be influenced by secondary factors such as hormones. A distinction should also be made between those effects that produce a cytologic abnormality and those that produce a serious disease. An example of the former is the occurrence of binucleate lymphocytes; leukemia is an illustration of the latter.

It is not possible to draw a sharp distinction between early and delayed effects since some that occur soon after irradiation may persist. Nevertheless it is convenient to consider as *early effects* those which are observable within 60 days after the beginning of exposure. *Late effects* are those appearing more than 60 days after the beginning of exposure.

C. *Fundamental Radiobiological Concepts*

The details of the pathogenesis of radiation injury are uncertain, but there is agreement about the general nature of events. These are summarized to provide a basis for a clearer understanding of the effects on the hemopoietic tissue. Detailed considerations of the fundamental concepts of radiobiology may be found in several excellent publications.[2-4]

When living organisms are exposed to ionizing radiation, intracellular molecular ionization occurs at random and initiates a series of chemical and physicochemical reactions which ultimately lead to observable effects. These effects are qualitatively similar in all mammals, but vary quantitatively among species, tissues, and cells due to differences in radiosensitivity. The radiosensitivity of an individual cell of a particular type is related to its state of maturity, mature cells being less radiosensitive than young dividing cells.

Cronkite and Bond[5] have recently revised the listing of mammalian tissue in an order of increasing magnitude of resistance to radiation damage as follows:

1. Spermatogonia
2. Lymphocytes
3. Erythroblasts
4. The rest of the classical hemopoietic tissues
5. Lining of the small intestinal tract
6. Stomach
7. Colon
8. Skin

9. Central nervous system
10. Muscle
11. Bone
12. Collagen

The probability of damage to an individual cell is directly influenced by the amount of radiation incident upon its immediate environment. The severity of the direct injury sustained by a cell is independent of the severity of injury to the whole tissue or organism. The latter is a function of the proportion of its component cells sustaining injury.

In multicellular systems there is unquestionably a direct quantitative dose-response relationship which is a function not only of the amount of energy transferred to the tissue, but also of the dose rate. If the time-intensity relationship of the exposure is of such an order that it permits recovery to take place during the period of irradiation, the biologic effect will be cumulative, but not additive. The exact nature of the dose-response relationship, or the shape of the line of its graphic portrayal, remains to be elucidated.

In any case, in mammals dose dependency is primarily a function of the sensitivity of the tissues irradiated. The manifestations of damage to the entire organism, in turn, are a reflection of the roles played by the various affected tissues in maintaining homeostasis. This is aptly demonstrated in the acute radiation syndrome in man.

II. Early Hematologic Manifestations

A. *Short-Term Radiation Exposure*

1. *General Description of the Acute Radiation Syndrome*

a) *External exposure.* The exposure of man to a single whole-body dose of rapidly delivered ionizing radiation on the order of 100 rad or more results in the development of a complex of clinical symptoms, signs, and laboratory findings which are collectively termed the Acute Radiation Syndrome. The nature, frequency, time of onset, and severity of the elements of this syndrome are a function of the exposure and of the radiosensitivity factors which affect the response of living organisms to radiation. The sequence of clinical manifestations includes a prodromal stage, latent stage, and a stage of manifest illness, followed by death or recovery.

The classic prodromal symptoms are anorexia, nausea, and vomiting. Extreme sweating, fatigue, and prostration may also be observed. Within a few days after exposure, remission of these symptoms occurs. This latent period of clinical well-being persists for about 2 to 3 weeks, after which evidences of injury again become manifest. These include fever, infections, epilation, purpura and hemorrhage, diarrhea, ileus, cardiovascular collapse, severe lethargy, and sensorial changes. By the end of the sixth postexposure week, recovery of survivors begins. There is rapid clinical resolution and a return of the deranged laboratory findings to normal values.

The clinical and laboratory findings of the acute radiation syndrome in man have been reported and reviewed in detail by Oughterson and Warren (Japanese

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atomic bomb survivors)[6] Hempelmann, Lisco, and Hoffman (laboratory accident victims)[7], Miller, Fletcher and Gerstner (cancer patients receiving radiotherapy)[8] and others.[9-11]

Recently, Thoma and Wald[12, 13] reported an analysis of the clinical signs and symptoms and laboratory findings in the victims of nuclear criticality accidents. The data from these irradiated previously healthy individuals indicate that there are five well-defined clinical injury patterns into which patients can be grouped. The pertinent characteristics of each of these injury groups are summarized as follows:

Group I: Most of these patients are asymptomatic; a few may have minimal prodromal symptoms such as nausea and anorexia. Little therapy is required.

Group II: These patients develop the acute radiation syndrome in a mild form. After transient prodromal nausea and vomiting, laboratory and mild clinical evidence of hematopoietic derangement dominates the picture. Careful clinical observation but conservative therapy of symptoms is indicated.

Group III: Severe manifestations occur in these patients. Complications of hematologic malfunction, including hemorrhage and infection, are pronounced and, in the sicker members of the group, some evidence of gastrointestinal damage may also be present. Survival of these patients may depend on wise clinical management.

Group IV: An accelerated version of the acute radiation syndrome. Complications of gastrointestinal injury, such as diarrhea and ileus, dominate the clinical picture. The severity of hematopoietic disturbances is related to the length of survival time following exposure. Recovery is not likely.

Group V: A fulminating course with marked central nervous system impairment including paresthesias, excitement, and coma. A fatal outcome may be expected.

In the acute radiation syndrome, the very radiosensitive hemopoietic system is the most prone to manifest evidence of injury. It is only when injury is very severe that gastrointestinal symptoms dominate the picture as seen in Group IV. The relatively radioresistant central nervous system does not manifest clinical evidence of damage unless the injury is extreme. The predominance of gastrointestinal symptomatology in Group IV cases and central nervous systems signs in Group V cases does not indicate that at these levels severe hemopoietic damage has not taken place. These patients do not survive long enough to display the full manifestation of their hemopoietic injury.

The pathology of the acute radiation syndrome has been described by Warren,[14, 15] Liebow, Warren and Decoursey,[16] and Lacassagne and Gricouroff.[17] A number of review articles consider the histologic evidences of derangement of the hemopoietic system.[9, 18-20] A bibliography of articles on this subject from 1900 to 1956 has also been published.[21]

The basic pathologic lesion of the hemopoietic tissue is a progressive atrophy of lymph nodes, spleen and bone marrow. This is a result of inhibition of cell division which leads to depletion of these tissues as mature cells pass into the peripheral blood and are not replaced. There is also prompt destruction and disappearance of erythroblasts and small lymphocytes from the hemopoietic tissue and the latter from the peripheral blood as well. In the acute radiation

syndrome in man following a total-body exposure dose in the midlethal range, (Injury Group III), the early appearance of the bone marrow is one of hypocellularity, particularly of the granulocytic series. Reticulum and plasma cells remain, as do a variable number of erythroid precursors. Megakaryocytes disappear from the marrow by the end of the first postexposure week. This atrophy of hemopoietic tissue is reflected in the peripheral blood as pancytopenia.

Areas of bone marrow regeneration can be seen beginning early in the post exposure period. Proliferation of stem cells precedes regeneration of specific cell types. This occurs in a definite temporal sequence starting with erythropoiesis. Myelopoiesis follows and, finally, there is a return of young megakaryocytes.

A similar sequence of events takes place in lymphoid tissues, with both destruction and regeneration occurring at a somewhat more accelerated tempo. However, the return of peripheral blood lymphocyte levels to normal may be very protracted after major irradiation injury.

b) *Internal exposure*. The effects of internally administered radioisotopes on a particular tissue are a function of the radiation dose to that tissue and not of the isotope dose per se. If the radiation dose to the hemopoietic tissue is sufficient to produce detectable injury, the qualitative and quantitative manifestations in the peripheral blood will be identical with those seen in the acute radiation syndrome. Peripheral blood alterations have been reported following the therapeutic use of Au^{198},[22-25] P^{32},[26-27] Ga^{72},[28] Y^{90},[21, 29] and I^{131}.

The hematologic effects of large therapeutic doses of I^{131} in thyroid carcinoma have been described in detail by Rall et al.,[30] Seidlin, Yalow and Siegel,[31] Hahn[22] and Sheline and Miller.[32] From such reports and personal observations, it is concluded that: 1) Following single doses of I^{131} up to 200 mc, some patients may develop a temporary slight leukopenia lasting up to one month; others may show no evidence of injury to the hemopoietic tissue. 2) The lymphocyte count is the most sensitive and reliable early indication of sublethal damage to the hemopoietic tissue. 3) The fall in lymphocyte count after large doses of I^{131} is not well correlated with the number of millicuries of isotope administered, but is more a function of the integrated blood concentration of isotope plus an empirical factor derived from the integrated amount of isotope remaining in the body.

In a more recent publication, Rall and co-workers[33] reported marked leukopenia in several patients with metastatic thyroid carcinoma who were treated with 107 to 355 mc of I^{131}, and a severe thrombocytopenia (0-20,000) that persisted for 3–6 months in some cases. Wolins and Bond[28] reported similar platelet count findings in patients after Ga^{72} therapy. Most of these patients had received previous x-ray therapy. The authors postulated that the depth and the duration of platelet count depression represent the best indices of the degree of marrow damage after radiation and may be indicative also of the total damage sustained by the marrow from previous exposure.

Significant changes in the blood counts of hyperthyroid patients after treatment with 3 to 20 mc of I^{131} have not been found. The only evidence to the contrary is that of Kafafova,[34] who reported a fall in the white cell count in the first 2–3 weeks after treatment in all of 53 hyperthyroid patients treated with 2.5 to 11 mc of I^{131}. The count characteristically returned to its original value after 2

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months. During the period of leukopenia, there was usually a neutropenia with an absolute lymphocytosis, monocytosis, and, in some cases, eosinophilia. It is noteworthy that lymphopenia was not observed in any patient in Kafafova's series despite evidence of injury to less radiosensitive hemopoietic elements. In 31 of these 53 patients there was a leukopenia, primarily due to a neutropenia, before radioiodine was administered. Additional corroborative work is needed before reaching a conclusion that the doses of I^{131} used in the therapy of hyperthyroidism produce significant peripheral blood count alterations.

2. *Hematologic Findings*

There has been increasing emphasis on investigations which attempt to go beyond the enumeration of changes in the number and morphology of cells of the traditional types in the period after short-term radiation exposure. In these newer areas of investigation, attempts have been made to quantitate the effects of radiation on the dynamic stages of proliferation of the blood forming tissue by measuring reproductive capability in various ways. Also, studies have been made to identify, by histochemical and cytogenetic methods, the specific points of disturbance in blood cell proliferation which result from radiation exposure.

a) *Cytokinetic observations.* It is evident that a deeper knowledge of the cycle of events by which a proliferating cell renews itself would provide an improved basis for understanding the changes in the cycle produced by radiation exposure. This is of much interest since the cellular effects are reflected by changes in the organ in which such cells are found as well as by resultant changes in the entire organism. The development of new techniques employing tracers such as P^{32}, Fe^{59} and H^3 have helped to make this possible.[35, 36] Resultant investigations have made it quite clear that a proliferating cell, following division, undergoes a postmitotic rest period, a period of synthesis of deoxyribose nucleic acid (DNA), a premitotic rest period, and then a period of mitosis.

On the hypothesis that changes such as radiation-induced bone marrow aplasia would be reflected first in the mitotic index (a ratio of dividing to non-dividing cells), Fliedner et al.[37] investigated the mitotic index of human bone marrow in healthy individuals and a group of accidentally irradiated patients. A dose-dependent fall was noted on the fourth postirradiation day. The index returned to normal after four weeks but was found to be significantly elevated $4\frac{1}{2}$ months after exposure. It was of interest that although the total population of DNA synthesizing cells was diminished, the ability of individual remaining cells to synthesize the material was apparently unimpaired. However, the control mechanism that ordinarily would suppress DNA synthesis after doubling the amount prior to mitosis seemed to be inoperative, and giant cells were produced. Furthermore, it appeared that the mechanisms that ordinarily initiate cell division were also disturbed after radiation exposure. Ribose nucleic acid (RNA) synthesis seemed unimpaired. Studies in this area have been summarized in recent reviews.[5, 35, 36, 38, 39]

In another test of proliferative function of the radiation-exposed bone marrow, the techniques of leukopheresis and thrombopheresis[40, 41] were used. By these methods, in which white blood cells and platelets respectively are drawn off continually from the circulating blood of dogs, it was possible to demonstrate the impaired ability of the irradiated marrow to mobilize leukocytes and platelets in response to this type of stimulus.

b) *Fluorescence microscopy observations.* In 1939, Hercik[42] reported a study using fluorescence microscopy to analyze the effect of alpha radiation on plant cells. The following year the modern fluorochrome acridine orange was introduced for the vital staining of protoplasm. Krebs[43], in 1944, proposed the use of this fluorochrome as a method to study damage to cells by radiation. By 1953, using this technic, his group[44] was able to demonstrate early effects of radiation on plant cells. They noted a color change of involved cell nuclei from green to orange-red.

The following year Meisel and Sondak[45] carried out similar fluorescence microscopic studies on the peripheral blood of x-irradiated animals. In 1956, the same workers[46] modified the method by adding congo red to the fluorochrome as a quenching agent to dim the fluorescence of undamaged cells and thus render the damaged cells more visible. Within a half hour or less after total body irradiation, small necrotic foci of damaged cells were observed in the bone marrow preparations of white rats and mice. Their number increased with increased radiation doses and also reached a maximum with increased time after exposure. There was a subsequent decrease due to absorption and destruction by macrophages. In a further extension of the study it was noted that shielding of a limb prevented the appearance of the micronecroses. Breivis[47] confirmed the finding of these cellular agglomerations and of individual cells with increased fluorescence after x-ray. He also observed them following administration of chloroethylamines and considered them to be the result of early changes in nucleoprotein metabolism.

Although the changes in nuclear fluorescence after irradiation have usually been attributed to nucleic acid depolymerization, Brodskii and Suetina[48] performed ultraviolet absorption microscopy and histochemical analyses of bone marrow cells that appeared morphologically intact, and concluded that the radiation depolymerization of the nucleic acids was not very great but that there was a marked fall in the nucleotides, i.e., nucleic acid metabolites and precursors which they thought could account for the change in staining reaction. Joshi and Korgaonkar[49] confimed the color change in irradiated cell nuclei and felt that DNA depolymerization was not present in significant amount but that an intramolecular disorientation involving internucleotide bonds might expose additional sites for stain binding and thus, the color shift.

More recently Khodas,[50] while confirming the work of Meisel and Sondak,[45] has questioned the results of other studies because nonuniform, nonstandardized technics of fluorescence microscopy of the blood were used. He tested the effect of a number of variables and proposed an optimal standardized procedure on the basis of his studies.

In general, it would appear that the sharp color change of the blood cell nuclei from the usual green fluorochrome staining to an increased frequency of orange and red staining occurs as a prompt result of radiation exposure of peripheral blood and bone marrow cells. The exact significance of this "pathological" fluorescence is not clear but it appears to be an early indicator of disturbance in DNA metabolism.

c) *Cytogenetic observations.* A rapid series of technical developments in the field of mammalian cytogenetics within the last decade has made it possible to study the individual chromosomes of the dividing somatic cell in many species

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including man. Among the fruits of this advance has been the determination that the human diploid chromosome number is 46, not 48 as had previously been believed. Subsequently, deviations from the normal chromosome number and morphology have been described in studies of peripheral blood cells, bone marrow and other tissues of patients with certain clinical abnormalities. These include anomalies in sexual differentiation (Klinefelter's syndrome, Turner's syndrome, hermaphroditism), congenital malformations of the nervous and other systems (mongolism, polydysspondylism), and blood dyscrasias (acute and chronic leukemia). Several review articles and editorials summarize present progress in this area.[51-55]

In view of the well known facts that radiation produces abnormalities of chromosomes that are best seen during cell mitosis, and that abnormal mitoses themselves are a result of radiation, it was inevitable that the development of an appropriate methodology for examining blood cell chromosomes would result in experimental cellular radiation studies. Many of the experiments have been carried out in vitro, utilizing tissue culture cell populations.[56, 57] Although some of these colonies were originally produced from blood or bone marrow cells, they have generally reverted to a fibroblast-like cell after a period of time in culture. A more refined cell system was developed by Puck et al.[58] using a quantitative plating method whereby every cell produces an isolated colony or "clone."

On the basis of radiation studies carried out on fibroblast clones, Puck[59, 60] determined that the mean lethal dose for cell reproduction is about 50 r of x-ray. His work appears to confirm the chromosomal nature of the primary damage in such cells. When they are fixed a short time after exposure, chromatid and chromosome breaks and deletions are observed. If more time is allowed to pass, there is recombination of broken ends and only recognizably aberrant recombinations remain as the visible evidence of radiation injury. Under the optimal conditions, about 25 r is the mean dose required to produce one chromosome break per cell. On an average, therefore, it may be inferred that two such breaks can produce reproductive death of the cell. However, this result may pertain only to the particular in vitro cell system used, since recent work by Bender,[61] Chu,[62] and Fraccaro[63] suggests that different cell lines grown in vitro have different spontaneous and induced aberration frequencies, and that such aberrations may be much less frequent in vivo.

These studies form a basis for understanding the mechanism of the alterations in the mitotic index of bone marrow following irradiation, such as were observed by Fliedner et al.[37] in the victims of a radiation critically accident, discussed above. In addition to mitotic depression, they noted chromosomal stickiness, fragmentation, clumping and bridging in the early specimens.

More recently Tough et al.,[64] employing a short-term culture technique, examined peripheral blood cell specimens taken at serial intervals from two patients who were receiving x-ray therapy to the vertebral spine for ankylosing spondylitis. The first patient received a total skin dose of 1500 rad, given in ten equal fractions over ten days. There were significant changes in the distribution of chromosome counts and also a considerable increase in the number of cells carrying chromosomes with structural abnormalities. The second patient received one dose of 250 rad to the skin over the spinal column and was studied

for a period of ten days thereafter. Within twenty-four hours, the percentage of cells with the modal number of 46 chromosomes had fallen from 93 to 72, and the percentage of cells with structural abnormalities in the chromosomes had risen from 1 to 22.

It is worth noting in this connection that the authors counted any chromosomal fragment as an additional chromosome, and that the change in mode was due to a marked increase in the number of cells with 47 chromosomes. By the fifth day, the percentage of modal cells had returned to within the normal limits. The number of structural abnormalities also declined, but remained higher than normal even during the last two days of the observation period. In both patients, an unusual number of polyploid cells were seen.

Preliminary communications concerning similar cytogenetic findings in the peripheral blood cells of criticality accident victims over two years after exposure,[65] as well as in patients receiving radioiodine[66] and diagnostic x-ray examinations[67] have also appeared. More definitive information concerning the hematologic effects of radiation on the chromosomal level may be anticipated as more investigations utilizing this type of methodology are completed.

d) *Erythrocytic cells.* Significant changes in hemoglobin and hematocrit values and in erythrocyte count do not occur early as a result of radiation exposure in the lethal range. Splenectomized dogs given high doses of radiation (1000 r) die in 3–4 days. A slight decrease in red cell volume occurs during this period but, during the 10 hours prior to death, fluid loss causes a marked decrease in plasma volume. The result is an increase in hematocrit.[68, 69] A similar result, associated with vomiting and diarrhea, has been observed in man.[13] With lower doses, fluid loss of this magnitude does not occur and the change seen during the first week is a slight decline in the hemoglobin and hematocrit values.

Damage to the mature irradiated erythrocyte is thought to be one factor in the development of anemia after radiation, but the nature of this damage is not known. No morphologic changes can be seen by usual methods, but Lindemann,[70] using electron microscopy, found changes in erythrocytes exposed to P^{32}. These consisted of areas of "coagulation" which he thought were due to the radiation.

Osmotic fragility is not appreciably increased after radiation.[3] Lartigue and Duplan[71] reported that thermal fragility of erythrocytes is increased one week after total body irradiation of rats and guinea pigs. Whatever damage does occur is apparently slight and results in only a minor decrease in erythrocyte survival time. Stohlman and co-workers[72] suggested that such changes can be detected only if some other insult is applied to the red cell. They found post-irradiation alterations in the elution of Cr^{51} from dog erythrocytes, which was accentuated by exposure of the erythrocytes to an "extravascular circulation" as a result of bleeding into lymphatic channels. In addition, the procedure of Cr^{51} tagging per se appeared to decrease the ability of the cells to maintain their integrity after extravascular circulation. Chanutin and Word[73] found that the effects of phenylhydrazine and radiation apparently were additive, producing a more severe anemia in rats than would be expected from radiation or phenylhydrazine alone. Onset of the anemia was also earlier than that produced by irradiation alone.

A possible mechanism for such effects is suggested by the work of Trincher[74] who detected effects of 10,000 to 320,000 r delivered to rat blood in vitro by [illegible]ng

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the latent period of hemolysis in an alkaline solution as the subsequent test system. An inverse relationship to dose, in the form of an exponential function, was found. Using target theory, the sensitive volume and molecular weight of the structural unit of the red cell surface layer were determined. The weight was about that of lipoprotein, as found in human serum, that is assumed to constitute the surface layer.

Temporary radiation damage to some of the enzyme systems in the red cell might also play a role in the production of these effects. Rappoport and Sewell[75] have demonstrated inhibition of enzyme systems related to nucleoside metabolism in rat erythrocytes exposed to 500-4000 r.

While intrinsic damage to the mature erythrocyte may occur, damage to the erythropoietic cells of the bone marrow and hemorrhage are more important causes of post-irradiation anemia. Following irradiation there is a rapid decline in reticulocytes in circulation in mature animals and humans, although newborn and young mice, rats and rabbits show an abortive reticulocytosis.[76] Simultaneously, there is disappearance of nucleated red cells from the marrow[77] and decrease in uptake of radio-iron by the marrow[78, 79] accompanied by increased iron deposition in the liver.[80] The amount of iron appearing in circulating erythrocytes is reduced.[81, 82] There is a slight lag in these effects, apparently resulting from continued incorporation of iron by cells at the late normoblast stage. Suit et al.[83, 84] showed that in vitro these cells apparently can continue hemoglobin synthesis and maturation even after fairly large doses of radiation, although Schulman et al.[85] have presented some evidence of interference with hemin synthesis in vitro. In any event, maturation and division of more immature cells soon stop and as the normoblasts mature, no new cells take their place.

Severe anemia that develops suddenly following radiation and occurs at the time thrombocytopenia becomes severe is primarily due to hemorrhage. Its severity is increased by the inability of the damaged marrow to respond.

Various manipulations just before or immediately after irradiation, such as bleeding,[84] administration of para-aminopropriophenone which produces transient methemoglobinemia, administration of phenylhydrazine[73] or exposure to hypoxia in some way allow the erythropoietic tissue to recover more rapidly. In animals so treated, the initial anemia may be as severe as that seen in untreated irradiated animals and, in fact, may occur earlier. However, a reticulocyte response is seen earlier, incorporation of radio-iron into red cells which reach the circulation increases more rapidly, and final recovery is more rapid.

Sukiasian et al.[86] observed that recovery from anemia occured more rapidly when the irradiated animal was given polyvinyl pyrrolidone (PVP) after exposure. They considered this to be the result of renal excretion of toxic materials with the PVP. However, anemia occurred much earlier in the treated animals than in the irradiated controls, and it would appear that the mechanism might be similar to those of other treatments just mentioned. In contrast, polycythemia induced by cobalt or hypoxia was associated with decreased survival following radiation.[87]

The role of erythropoietin in the anemia produced by irradiation is not known. Linman and Bethell[88] found that erythropoietin levels are not decreased following irradiation. Stohlman and Brecher[89] also noted more rapid recovery of the

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capability for Fe^{59} incorporation by the erythroid cells of animals infused with plasma from anemic donors. They attribute this response to an erythropoietic factor in the anemic plasma.

Another kind of early effect of irradiation on the erythroid series, described by Atwood and co-workers[90, 91] is a change in the type-specific agglutination of red blood cells. This alteration occurred within two weeks after a 4 mc therapeutic dose of P^{32} in two patients with polycythemia vera. Scheinberg and Reckel,[92] using irradiated pigeons and polycythemic patients, found that the increased inagglutinability lasted for at least four months. The mechanism may be a radiation induced somatic mutation which alters the antigenic structure of the erythrocytes.

e) *Myelocytic cells.* The initial response of the myelocytic cell series to midlethal doses of radiation is the development of a neutrophilic leukocytosis very shortly after exposure. The initial granulocytosis represents mobilization either of cells from the large bone marrow reserve of mature granulocytes[93] or of noncirculating granulocytes from various capillary beds[94] or both. Craddock and associates[10] showed that dogs subjected to leukopheresis after radiation retained the capability to mobilize leukocytes in fairly large numbers. However, the response to this procedure was delayed and of lesser magnitude in irradiated dogs than in nonirradiated animals. After repeated leukopheresis for three days, the irradiated animal lost this ability to mobilize leukocytes. After the initial leukocytosis, the peripheral granulocyte count gradually declined. In human survivors of the acute radiation syndrome, the minimum granulocyte level is generally reached 14-28 days postirradiation. In fatal cases the count continues to fall until death. In most experimental animals the minimum level is reached somewhat earlier.

An abortive increase in myeloid precursors and mature neutrophils lasting about six days has been observed prior to complete recovery. This is followed by a second depression of both immature and mature forms in the marrow and peripheral blood. This abortive rise is seen in most experimental animals,[95] but its mechanisms are unknown. It is postulated that it represents an attempt of injured cells at regeneration. The cells involved in this abortive rise are often morphologically abnormal. About one week after the second fall, a new wave of proliferation and maturation initiates recovery.

The response of the granulocytic series indicates primary damage to the proliferation pool of myeloblasts and their daughter cells in the bone marrow. Morphologic changes can be seen in the immature granulocytes twenty-four hours after radiation.[96] It is possible that subtle damage to mature cells also occurs since hypersegmentation of the nuclei of some of the mature granulocytes has been observed, but this does not lead to removal of these cells from circulation in the immediate postirradiation period. Other morphologic alterations in mature neutrophils detectable by fluorescence microscopy[15, 50] or supravital staining[97] have been reported.

Eldred[98] reported that the changes in eosinophils in the peripheral blood parallel those of the granulocytes, except that in the recovery phase the eosinophil count is often above the pre-exposure level. This elevation may persist for a period of months.

The severe depression of granulocytes is a major factor in the development of infection of the irradiated animal.[99] Other factors such as interference with antibody production and tissue damage from hemorrhage may also play a role. This phase of radiation injury has been reviewed by Cronkite and Bond,[5] Bond,[100] Talmage[101] and Donaldson and Marcus.[102]

f) *Lymphocytic cells.* The response of the lymphoid tissue to total-body irradiation consists of rapid disappearance of lymphocytes, both from the circulating blood and from the lymph nodes, thymus, spleen, and other tissues. The loss of weight of these organs is due to loss of the lymphoid elements and is not accompanied by a decrease in the amount of connective tissue.[103] This change in weight can be detected after relatively small doses of radiation, indicating the extreme radiosensitivity of lymphocytes.

The pattern of response of lymphocytes is similar in all mammalian species studied. First, morphologic changes are seen, including pyknosis, intranuclear vacuolization and lobulation of the nucleus.[104] Other evidence of damage, such as the appearance of neutral red staining bodies in the cytoplasm in supravitally stained preparations, can also be noted. Phagocytosis of the damaged or dead lymphocytes follows. After several days, the lymph node will contain only a few young large lymphocytes and the remaining stromal elements.

The time of occurrence of maximum depression, reappearance and complete recovery of lymphocytes varies with species sensitivity and radiation dose. In rabbits given large doses (200 r), recovery may not be complete three months after irradiation.[105] In a human population, slightly reduced mean lymphocyte levels have been observed two and three years after exposure to 175 rad.[106]

In the lymphoid tissue the radiosensitivity of the cells is not a function of cell maturity as it is in other tissues. The earliest changes after radiation are seen in the small, mature lymphocytes. Resegotti[107] concluded that old and new lymphocytes have the same radiosensitivity, based on comparative measurements of the specific activity of Fe^{59} incorporated in the hemin of lymphocytes of irradiated and nonirradiated rabbits.

Hulse[108] has pointed out that the disappearance of lymphocytes from the peripheral blood and bone marrow of the rat after sublethal irradiation is bimodal. Initially there is rapid disappearance of a majority of the lymphocytes followed by a slower decline of the remaining population. The initial fall is thought to represent the destruction of small, mature lymphocytes, and the second phase to represent the combined effect of attrition of the remaining cells and lack of production. The few cells which remain at this time are almost all large immature lymphocytes.

The sensitivity of this cell type to radiation is also indicated by the finding of binucleate lymphocytes in persons exposed to small doses which do not produce quantitative peripheral blood changes.[109, 110]

g) *Megakaryocytes and platelets.* Simpson[111] has pointed out that the platelet producing system is different from the other hematopoietic tissues in that in the development from the primitive stem cell stage until platelets are produced, there are not complete cellular divisions. The processes of endomitosis (nuclear division) and platelet formation that occur during maturation do not seem to be radiosensitive. Thus, changes in the number of megakaryocytes[112] and platelets[11]

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after irradiation are a reflection of stem cell radiosensitivity and of the block in cell division preceding the megakaryoblast stage. After exposure to doses up to 150 r, a minimum megakaryocyte count in the rat marrow was found at seven days, suggesting that this is the cell's life span. These forms reappear at the same time that myeloid cell regeneration begins.

Although fluorescent microscopy[113] showed nuclear fragmentation and cytoplasmic lysis of megakaryocytes 20 minutes after 500 r of x-ray, moderate doses of radiation apparently do not affect the ability of the mature megakaryocyte to produce platelets. Nevertheless, the platelets so produced may be morphologically, and perhaps functionally, abnormal.[114] However, in rabbits there is apparently no decrease in life span of platelets in circulation at the time of irradiation.[115]

Upton[116] reviewed the pathogenesis of the hemorrhagic state in radiation sickness and concluded that it probably results from a combination of thrombocytopenia, capillary fragility, and coagulation defects. The most important of these apparently is thrombocytopenia because not until its onset does the bleeding tendency become severe. In addition, transfusion of fresh platelets, less than four hours old, can help control the bleeding.[117] Hjort, Perman and Cronkite[118] suggested that abnormalities of coagulation may also be related, at least in part, to the deficiency of platelets, because transfusion of disintegrated platelets restored prothrombin consumption to normal, but did not control the bleeding in irradiated experimental animals.

Suggestive evidence that vascular fragility may allow bleeding in the absence of a fall in platelet level comes from the finding of early postirradiation hemorrhage in two unrelated studies. Brown[119] reported iridocyclitis, or free-floating red blood cells in the anterior chamber of the eyes of rhesus monkeys given 250 rep or more of fast neutrons to the head. Bond et al.[120] observed bone marrow sinusoidal dilatation and hemorrhage in rib biopsies of dogs exposed to 275 r or more of x-radiation. In both instances the bleeding developed in a matter of hours, and the speed of onset and magnitude of the phenomenon were related to dose.

3. *Clinical Implications of Early Hematologic Findings*

An important application of the previously described data obtained from studies of the early hematologic manifestations of short-term radiation exposure has been their use in recognizing and predicting the clinical course of radiation overexposure in man. This is a particular necessity because of the relative infrequency with which a physician is likely to come into contact with patients displaying the clinical phenomena of acute or delayed radiation injury. It is therefore necessary to substitute some objective diagnostic and prognostic criteria for the body of personal experience which enables the physician to deal readily with more familiar illnesses. The hematologic manifestations of radiation injury can serve this purpose.

a) *Relationship to diagnosis and prognosis of acute radiation syndrome.* A number of recent reports, including those of Cronkite et al.,[5, 9, 121, 122] Gerstner,[10] Bond et al.,[11] Thoma and Wald[12] and Wald and Thoma,[13] explore the relationship of various hematologic findings to the clinical problems of the acute radiation syndrome. Although most of these reports are based on similar observations,

a number of apparent, but probably not real inconsistencies are present. These stem from differences in the objectives for which the data are being employed, from lack of clarity concerning the particular time period in which a given end point is felt to be useful, and the absence of a uniform quantitation of magnitude of exposure or severity of injury.

There are two main approaches to the application of the hematologic data. Many workers have attempted to utilize the hematologic information as a type of "biological dosimeter" with which to extrapolate the delivered or absorbed radiation dose. The diagnostic or prognostic information is then developed on the basis of what that postulated physical dose can be expected to produce in the form of clinical radiation injury. The use of this approach implies that there is available to the user precise information concerning the relationship between physical dose and biological response over a wide spectrum of radiation energies of different types, and a means to deal with the great variability of a complex integration of response mechanisms. Rough approximations of such relationships can be made in order to generalize about probable results of exposures of large populations. Therefore, some generalizations resulting from this approach are summarized as follows:

Lymphocyte Count

The absence of any decrease has been equated with an exposure dose of less than 50 r[10] and less than 25 r[5]; mild decrease[10] and minor lymphopenia[121] with less than a 100 r dose; a fall of greater than 50 per cent[10] and 90 per cent[121] with a dose of greater than 100 r. A pronounced fall has been taken to indicate a dose in the "dangerous range" from 300 to 1,000 rad.[123] A lymphocyte count above 1500/mm.^{3} has been considered to mean less than 200 r; above 1,000/mm.^{3} to mean 200 to 400 or 500 r; less than 500/mm.^{3} to mean 400 or 500 to 900 r; and "virtually zero" to mean greater than 900 r.[11]

Neutrophile Count

A depression in count in the fourth and fifth week has been equated with a dose of less than 200 r; severe depression in 3 to 5 weeks with a dose of 200 to 400 or 500 r; and severe depression on days 10 to 20 with a dose of 400 or 500 to 900 r.[11]

Platelet Count

A moderate depression of the platelet count during the fourth and fifth week has been associated with less than 200 r; severe depression in 3 to 5 weeks with 200 to 400 or 500 r; and severe depression on days 10 to 20 with 400 or 500 to 900 r.[11]

Reticulocyte Count

An "unequivocal fall" in the reticulocyte count in five days has been equated with a dose of greater than 300 rad.[123]

Mitotic Index

A progressive decrease has been equated with a dose in the 50 to 200 rad range. The absence of mitoses by the fourth day has been equated with a dose of 200 rad or more.[37]

A more direct application of the early hematologic findings has been in the prognostication of the clinical course of acute radiation injury. This is particularly helpful in the individual case where delays or errors in physical dose measurement and variations in individual biological response patterns greatly reduce the clinical value of a physical dose estimate, even when it is available.

Various studies have indicated the usefulness of one or another of the components of the peripheral blood count as an indicator of clinical radiation injury. However, it has become evident that the analysis of changes in any single blood cell line is not sufficient to supply prognostic information at all times in the

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clinical course of all levels of radiation injury. The total leukocyte count comes closest to serving this purpose. However, the combined use of the lymphocyte, neutrophil and platelet levels has been a more productive approach. With the addition of information concerning the development of the classical prodromal symptoms of radiation exposure and subsequent signs of clinical injury, an even more reliable guide to prognosis and management is possible.

Based on results of an analysis[12, 13] of the data obtained from the study of patients overexposed in criticality accidents, a scheme has been devised for the early diagnostic classification of such cases (fig. 1). The clinical injury groups referred to in the flow sheet have already been described in Section II, A, 1,a. The lymphocyte level is the best early means of differentiating individuals whose radiation injury will not be clinically significant from those in whom a greater degree of medical effort will be required. However, because of the great radio-

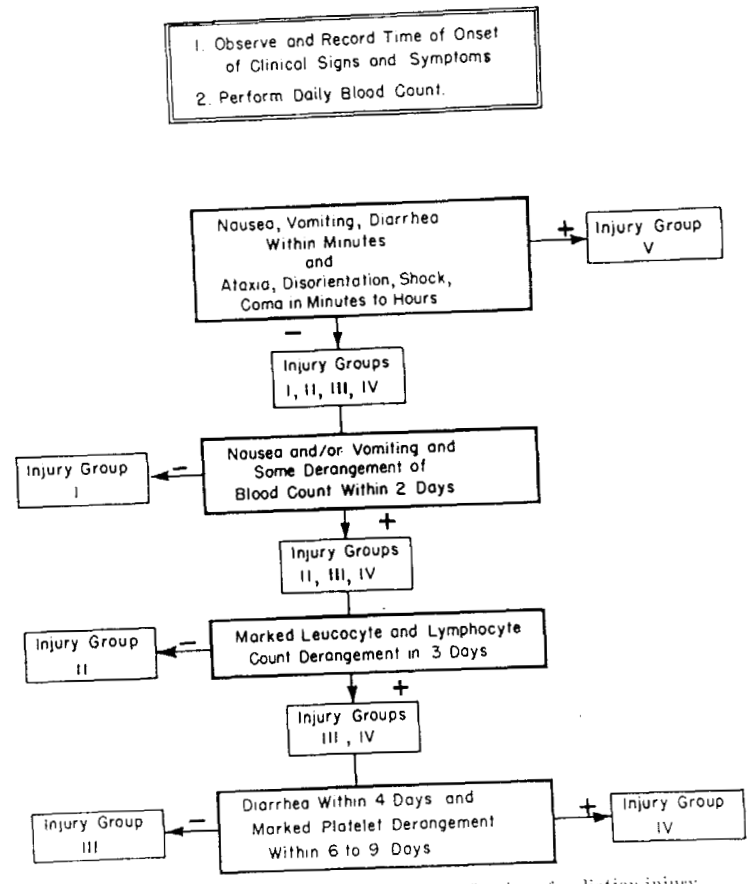

FIG. 1.—Flow sheet for early diagnostic classification of radiation injury.

sensitivity of this cell line, it is not useful in quantitating the severity of significant clinical injury. After an unstable period of one or two days, the neutrophil level begins to serve as a means of differentiating various degrees of severity of injury. Within a few more days the platelet count gives additional information.

Postirradiation leukocyte levels have been used as an indicator of a specific endpoint, i.e., death, by Jacobs et al.[124] They reviewed the results of blood counts performed by Japanese and American workers in the nine-week period following the atomic bombing of Hiroshima and Nagasaki. A correlation was found between the leukocyte counts and the ultimate survival or death of these patients. Although the circumstances of the data collection led to many kinds of error and bias, the results seem to justify the general conclusion that there is good correlation between depression of the leukocyte count during the third to fifth week after exposure and subsequent mortality. The correlation is best for counts during the third week. Under the conditions that existed in Japan at that time, the likelihood of spontaneous survival was very remote for individuals in whom the leukocyte count was below 1000 in the third or fourth week.

The peripheral blood counts have also been used in the course of radiation injury as a guide to clinical management. In general, it has been considered that the depth and duration of the depression of the various blood counts are related to the occurrence of significant clinical complications. For example, it has been suggested[11] that if the neutrophil and platelet counts approach zero in the second week and any evidence of infection or hemorrhage is present, functional replacement therapy should be started at once. If neutrophils and platelets are absent for more than twenty-four hours, it is recommended that such therapy be started even in the absence of any clinical manifestations of injury. On the other hand, the later in the course that such severe depressions of the blood elements occur, the less is the likelihood of complications. Under these circumstances more conservative management is indicated. In this connection it is pertinent to note that a rise of a previously normal sedimentation rate may be the only indication of occult infection at the time when the leukocyte system is unable to respond.[13]

Peripheral blood findings may also indicate a favorable outcome. It has been suggested that an early reticulocytosis heralds recovery, and that the magnitude of the response may be directly related to the level of previous injury.[123] Granulocyte depression which does not fall below 1500 cells per cubic millimeter has also been cited as a favorable prognostic sign. Another indication of recovery is the return of lymphocytes and platelets.

Serial examinations of the bone marrow after radiation exposure are not very sensitive indicators of the course or outcome to be expected in a given case. Hypocellularity is to be expected earlier in the bone marrow than in the peripheral blood because of the greater sensitivity of the precursor cells which disappear quite rapidly while their mature descendants continue to circulate in the peripheral blood. The duration of marked hypocellularity is perhaps a better guide to the prognosis, but this, too, can be misleading because of the nonhomogeneity of the bone marrow.

The likelihood that a single sample can be taken as representative of the state of affairs throughout all of the blood forming bone marrow is much less than is the case with a single sample of peripheral blood. Also, it has been observed[6]

that evidence of regeneration in the bone marrow does not necessarily correlate with recovery from the hematopoietic form of radiation injury. Return of erythroid and myeloid precursors has been observed in the face of falling peripheral counts and a subsequent fatal outcome.

b) *Relationship to occurrence of delayed manifestations.* A recent study by Jacobs et al.[125] was undertaken to see if a correlation exists between the incidence of neoplastic disease in survivors of the atomic bombing of Hiroshima and the degree of leukocyte depression that was recorded in the first fourteen weeks following the initial radiation exposure. Considerable bias may have been produced by the circumstances surrounding hematologic data collection in the initial post exposure period, and the factors influencing the likelihood of subsequent medical examinations that would detect the presence or absence of neoplastic disease. The conclusions of this small study cannot, therefore, be extended beyond the study population itself. However, internal comparisons within the study population of 405 cases indicate a good correlation between the degree of initial white count depression and the occurrence of leukemia and other forms of cancer. This result, while not necessarily surprising, does provide the first available human validation of animal experiments concerning this point. Whether the correlation with leukopenia simply demonstrates a relationship to exposure dose, or is an indication of a relationship between radiation sensitivity and subsequent carcinogenesis, must await completion of dose estimates[160] for the 405 individuals.

An interesting potential source of predictive information concerning the ultimate development of leukemia in cases of acute radiation injury is suggested by the cytogenetic methods already mentioned. Utilizing this approach, it may be possible to elucidate the relationship between the aberrations observed in blood cell chromosomes at various intervals after radiation exposure[64-67] and the ones occurring in chronic granulocytic leukemia.[126] Along the same line, there may be a relationship between the occurrence of possible somatic blood cell mutations in irradiated patients and several atypical blood cell changes reported in leukemia. The former is exemplified by the development of inagglutinable erythrocytes in patients with polycythemia vera treated[90-92] with P^{32} while the latter include an ABO blood group alteration in a patient with acute leukemia,[127] "acquired" Pelger-Huet anomaly of the granulocytes in 19 cases of leukemia and myeloproliferative disease[128] and possibly even the presence of fetal hemoglobin in a patient with actue myeloid leukemia.[129]

B. *Long-Term Radiation Exposure*

1. *General Description of Exposure Situations*

The recognition of early hematologic manifestations of long-term low-level radiation exposure has not been clear-cut. Reported studies have been limited to the early x-ray and radium workers, radiologists, and more recently, nuclear energy industry employees. A major shortcoming in these studies is the absence of any reliable information concerning the magnitude and duration of radiation exposure. Recently surveys have been proposed of population groups whose cosmic or environmental radiation exposure is above that of the general average, but no resultant data are available. It is, therefore, considered worthwhile to review the findings of the existing studies.

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2. *Hematologic Findings*

a) *Older observations.* An analysis of studies of this type by Ingram[130] indicates that the early radiologists and radiation workers developed alterations in the peripheral blood picture which characteristically took the form of moderate lymphocytosis and leukopenia. These changes were not only evident on a statistical basis but, in some instances, could be identified in an individual case. Macrocytosis, reticulocytosis and erythrocytosis were also described.[121] The general interpretation of these findings was that the initial injury depressed hematopoiesis and that subsequent attempts at recovery resulted in compensatory lymphocytosis and erythrocytosis.

b) *Recent observations.* In recent years, abnormalities of the peripheral blood pattern of workers exposed to radiation within or near the "permissible" occupational limits have consisted of mild leukopenia and lymphocytopenia. In addition, various morphological changes have been described such as an increased incidence of refractile neutral red granules in lymphocytes,[7] an increased incidence of binucleate lymphocytes[109] and changes in the ratio of large to small mononuclear cells.[131] Attempts to use the morphological findings, which are probably the most sensitive indicators of radiation injury, have been limited by their non-specificity, and by the demanding nature of the technical procedures. The latter objection may, in the case of the binucleate lymphocytes, be overcome by present attempts to utilize an electronic counter for this purpose.

c) *Combined Abnormalities.* It appears unlikely that any single peripheral blood change will prove to be a specific indicator of long-term radiation exposure. However, the use of a group of non-specific hematologic changes, each of which is very likely to occur as a result of low-level radiation exposure and unlikely to be present in the unexposed population, may have greater value than any one procedure by itself. Helde and Wahlberg[132] have used this approach in a series of studies of the blood changes occurring in occupationally exposed individuals. The index of change was based upon leukocytopenia, shift to the left, relative lymphocytosis, and presence of pathologic lymphocytes or hypersegmented neutrophils. When these were plotted against exposure dose in milliroentgens per week, little correlation was found. However, when the expression of the time in which the dose was received was reduced to a very low unit (less than a second) the correlation improved. A supporting animal study was also reported.[133]

Shiels[131] has used as indices of blood change the ratio of large to small lymphocytes, the ratio of monocytes plus large lymphocytes to small lymphocytes, the percentage of lymphocytes which show granules in the cytoplasm, and the percentage of monocytes which are of a particular morphology. These were applied to occupationally exposed workers and to radiation therapy patients. Unfortunately, the actual dosage of radiation received by the subjects was not known and the criteria of exposure was therefore the condition of being "well" or "not well." The latter condition was characterized by lassitude, weakness, and fatigue. Shiels' data analysis indicated highly significant differences between the two groups in relation to the indices described, while the usual peripheral blood tests showed little or no correlation. Confirmation and interpretation of the work of these two groups require further investigation.

It has recently been emphasized[1] that the physical methods of dosimetry are still the best indices of exposure of occupational populations to long-term low-level radiation. Routine annual hematologic studies of such persons are useful only to establish base lines for individual study in the event of significant accidental overexposure, and are inadequate for the detection of low-level radiation effects.

3. *Clinical Implications of Early Hematologic Findings*

a) *Relationship to immediate clinical course.* Since low-level long-term radiation exposure of the kind described in this section is not productive of any early clinical manifestations, the cytologic changes cannot be considered prognostic of any early clinical phenomena.

b) *Relationship to occurrence of delayed manifestations.* Older reports describe blood count abnormalities in irradiated individuals who "subsequently" developed leukemia. It is considered, however, that these were actually early hematologic findings of leukemia in a preclinical state, as described by Moloney and Lange,[134] rather than hematologic manifestations of radiation exposure which could be considered prognostic of later development of leukemia.

III. Late Hematologic Manifestations

The clinical phenomena which are considered as late manifestations of hematologic radiation injury do not differ qualitatively regardless of differences in the magnitude, type, and delivery rate of the evocative exposure dose. For this reason they are discussed as separate clinical entities, with supporting etiologic data presented from the various exposure circumstances that led to their development.

A. Leukemia

1. *Evidence for Causal Relationship*

The first cases of leukemia in individuals occupationally exposed to x-radiation were reported by Jagic and others about fifty years ago. Since then there has been a continuing series of case reports, some epidemiologic studies and many reviews suggesting a cause and effect relationship between chronic low-level radiation exposure and leukemia in man. More recently, the studies of the Atomic Bomb Casualty Commission of the survivors of the Hiroshima and Nagasaki bombings have supplied evidence for a similar relationship to a single high level exposure. More recently still, various patient populations exposed to therapeutic or diagnostic radiation in the course of their medical management have come under observation and analysis in epidemiologic studies of leukemia. Environmental exposure situations, both internal and external, have been examined as well. Also, over the past thirty years since the early work of Krebs and others, animal experiments under a variety of exposure conditions have shown the leukemogenic property of radiation exposure.

This general field has been of great interest to students of hematology, oncology, and radiobiology, and numerous reviews of the general subject matter have been published. Among the most recent and valuable of these are the reports of two subcommittees of the National Academy of Sciences-National Research Council Committee on Pathologic Effects of Atomic Radiation,[1, 135] the latter of which includes an extensive bibliography; Staff Report No. 1 of the Federal Radiation Council,[136] Storer and Grahn,[137] Cronkite et al.,[138] Hempelmann,[139] Loutit,[140] Court Brown,[141] Mole,[142] Bernard et al.,[143] Tubiana,[144] and

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Tullis.[145] To supplement the material in these reviews, an attempt is made to supply the latest information and pertinent references concerning each of the lines of investigation supporting conclusions in this research area.

a) *Occupational radiation exposure.* Beginning about a decade after the initial utilization of radium and x-ray as diagnostic and therapeutic medical technics, case reports of leukemia in radiologists and their associates began to appear in the literature. Twenty-five such cases have been collected by Cronkite et al.[138]

Another approach to the problem of radiation leukemogenesis among radiologists has been the retrospective epidemiologic study. A number of such investigations have been reported since 1944, and are summarized in table 1. These have involved the use of obituary notices and the like for case finding purposes and the acceptance of death certificate diagnoses. All of the United States studies indicate an incidence of leukemia in radiologists significantly increased above that in non-radiologists or in the general population. Also the incidence of leukemia in physicians is significantly above that in the general population. Although this is true for the United States studies, the one British study of this type reveals no excess of leukemia among radiologists,[151] possibly as a result of more stringent radiation protection measures taken earlier in that country. The results in general indicate that chronic repeated radiation exposure over a period of years is leukemogenic in man.

The major defect of these studies is the absence of any data pertaining to the radiation dose received by those who developed leukemia. Neither in the individual case reports nor in the retrospective analyses is there any possibility of providing more than a guess in this regard. One such guess by Braestrup,[155] a radiological physicist whose experience goes back to the early days of x-ray usage, is that as much as 100 r per year may have been received by the workers before 1930, whereas at the present time it averages considerably less than 5 r per year. His estimate of cumulative exposure in the 40-year practice lifetime of a radiologist who began in the early days of the profession is about 2,000 r. Lewis[156] assumed that the average exposure for all radiologists was 30 r per year or 1200 r in 40 years.

Another point in question in all of the studies is the validity of the diagnoses of leukemia. A further problem in the retrospective studies is the question of completeness of case finding and of professional sub-specialty identification. Nevertheless, the evidence seems good for the qualitative conclusion that long-term intermittent radiation exposure will increase the incidence of leukemia in man.

b) *Atomic bomb radiation exposure.* Evidence for the leukemogenic effect of a single dose of radiation delivered at a high dose rate stems from the results of continuing studies of the survivors of the atomic bombings of Hiroshima and Nagasaki, Japan in August 1945. Much of these data have been compiled by Japanese and American scientists connected with the Atomic Bomb Casualty Commission.* Intermittent reports and summaries of the findings have been

* A research agency of the United States National Academy of Sciences—National Research Council, administered in cooperation with the Japanese National Institute of Health of the Ministry of Health and Welfare, under a grant from the United States Atomic Energy Commission.

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TABLE 1.—*Incidence of Death from Leukemia in Physicians*

Occupation	Time	Place	Total Deaths*	Leukemia Deaths	Incidence	Ratio of Incidences—Radiologists: All Physicians	General Population Incidence	Reference
Radiologist	1929–43	USA	175	8	4.57%			March[146]
Non-radiologist	1929–43	USA	50,160	221	0.44%	10.3:1		
All Physicians	1933–42	USA	26,788	143	0.53%		0.39%	Henshaw and Hawkins[147]
Radiologist	1938–42	USA	95	5	5.3%	10.6:1		Dublin and Spiegelman[148]
All Specialists	1938–42	USA	2,029	19	0.94%			
All Physicians	1938–42	USA	12,419	62	0.50%			
Radiologist	1944–48	USA	124	6	4.84%			March[149]
Non-radiologist	1944–48	USA	15,637	113	0.72%	6.7:1		
All Physicians	1947–51	USA	11,481	133	1.2%		0.52%	Peller and Pick[150]
Radiologist	1949–58	USA	296	11	3.71%			Cronkite[138]
All Physicians	1949–58	USA	23,393	221	0.77%	4.8:1		
Radiologist	1897–56	G. Brit.	463	3	0.65%			Court-Brown[151]
		Eire						
Radiologist	1938–42	USA	205	8	3.9%			Ulrich[152]
Non-radiologist	1938–42	USA	34,626	158	0.44%			
Radiologist	1952–55	USA			3.57%	3.6:1		Melville in Schwartz and Upton[153]
Non-radiologist	1952–55	USA			1.00%			
Radiologist	1930–54	USA			3.65%			
Non-radiologist with X-ray	1930–54	USA			2.33%		0.39% (1950)	Warren[154]
Non-radiologist without X-ray	1930–54	USA			0.63%			

* With known diagnosis

TABLE 2.—*Average Incidence of Confirmed Leukemia in Residents of Hiroshima and Nagasaki 1947–1958 by City of Exposure and Distance from Hypocenter*
(from Brill, Tomonaga and Heyssel[159])

Distance from Hypocenter in Meters	Hiroshima			Nagasaki		
	Man-Years at Risk* 1947–58	Number of Leukemia Cases	Rate per 10^6	Man-Years at Risk* 1947–58	Number of Leukemia Cases	Rate per 10^6
0–999	14,638	20	1,366	5,330	3	563
1000–1499	126,446	39	308	37,758	20	530
1500–1999	214,629	9	42	44,197	3	68
2000–9999	747,827	21	28	925,653	34	37
Total	1,103,540	89	81	1,012,938	60	59

* Estimated number of person-years at risk, 1947–1958, for city residents.

published through the years, the most recent being those of Heyssel et al.[157] for Hiroshima and Tomonaga et al.[158] for Nagasaki. A later compilation has been completed by Brill et al.[159]

Of the surviving population of the two cities, some 60,000 people still living there in 1950 are presumed to have received some radiation exposure, and of these, some 7000 had experienced major symptoms of the acute radiation syndrome. In view of the tremendous value of a population of this size for studying the delayed effects of irradiation in man, a major effort has been made to establish to the limit of possibility, the specific radiation dose of each individual survivor. The current status of this effort, stemming from a joint program of the Health Physics Division of Oak Ridge National Laboratory and the Atomic Bomb Casualty Commission, has recently been reported by Arakawa.[160] A tentative dose assignment for each survivor has been made on the basis of theoretical and experimental information concerning the air-dose from the weapons, the location and shielding history of the individual, and the attenuation factors for the particular shielding. Since the major sources of error or uncertainty in this type of computation are the same in all cases, the relative exposure dose of one individual as compared to that of others is quite accurate but there is a large uncertainty about the absolute exposure dose in all cases. This uncertainty may be reduced by further theoretical and experimental work.

In Hiroshima from 1945 through 1958 there have been 127 cases of leukemia in which the diagnosis was confirmed by the Atomic Bomb Casualty Commission following review of hematologic material. In Nagasaki in the same period 82 cases of leukemia have thus been confirmed (table 2). In Hiroshima 89 of them were in persons resident in the city and in Nagasaki 60 occurred in city residents. Such cases can be subjected to statistical evaluation. This number of cases represents a highly significant increase in the incidence of leukemia, but it is numerically small for an epidemiologic investigation when analyzed by year of onset, sex, permanence of residency, exposure dose, type of leukemia, and various other essential parameters. Nevertheless, certain generalizations can be supported or suggested on the basis of these studies at this time.

It appears that the incidence of leukemia is directly related to the magnitude

of radiation dose for exposures of about 100 rad or more. Uncertainties make it difficult to generalize below that dose level. The increased incidence of leukemia commenced from two to three years after the exposure and has not yet subsided completely. However, the largest increase was in the period from four to eight years after exposure. There is tenuous evidence of a trend toward a shorter latent period among those leukemia patients who received the higher exposure doses. There seems to have been a somewhat greater susceptibility to leukemogenesis in the younger survivors and possibly in the male ones.

The total number of cases already observed in the significantly exposed populations represents a several fold increase over the total number to be expected throughout the entire life span of the group on the basis of the current Japanese leukemia incidence and life table statistics. This suggests that the increase represents more than a simple acceleration of the time of occurrence of leukemia among those susceptibles who would have developed it within a normal lifetime.

Of the various types of leukemia, there was an increase in the incidence of all except the chronic lymphocytic variety. The increased incidence of chronic granulocytic leukemia appeared to be greatest among those in the older age groups. The acute leukemias were also increased, and, where a distinction could be made as to type, there seemed to be a greater propensity for acute granulocytic leukemia to occur in the older age groups and the acute non-granulocytic varieties to be present in the younger ages.

Limitations in this study certainly do not detract from the clear-cut evidence that a single relatively large dose in radiation at a high dose-rate is leukemogenic in man. It is when more refined conclusions are sought that certain variables become troublesome.[161] The most obvious of these is the questionable validity of the reconstruction of the exposure dose in each case. Another major problem is the selection of appropriate control data. An example of this is the apparent greater susceptibility of males. This raises the question of the validity of comparing the male permanent residents present in the two cities under conditions of wartime conscription to the female residents who remained at home. It is certainly conceivable that the health status of the males was not at the same level as that of the females prior to the bombing.

Another question that has been raised concerns the validity of drawing conclusions from the findings in one ethnic group and expecting them to hold for all ethnic groups. The very low incidence of chronic lymphocytic leukemia in non-exposed Japanese is a related observation. However, the infrequency of this type of leukemia in any irradiated population[138] suggests that little distortion resulted from this difference. In addition, truncation errors may be present in these conclusions drawn from observations that were cut off arbitrarily at the time of reporting rather than at the end of the life span of the population under observation.[162] Many of these problems will be reduced or eliminated by the planned continuation of the biomedical and dosimetric studies of the Atomic Bomb Casualty Commission for an indefinite period.

e) *Medical external radiation exposure.* Since 1955, a gradually increasing body of information has been accumulating concerning the late effects of medically administered therapeutic and diagnostic external radiation. Groups receiving therapeutic radiation exposure have included patients treated for ankylosing

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spondylitis, gynecologic neoplasms and other malignant or benign conditions, and children treated for real or potential thymic enlargement. Groups receiving diagnostic radiation exposure have included adults and children. Some of the children received their exposure in utero or in early infancy.

Ankylosing spondylitis therapy. The case records of 13,352 patients presumed to have ankylosing spondylitis and given x-ray treatment for this condition at 81 British radiotherapy centers between 1935 and 1955 were analyzed in retrospect by Court-Brown and Doll.[163] Wide-field x-ray therapy had been administered to the full spine, and sometimes to the pelvis and extraspinal areas, in dosages ranging from 112 r to more than 3,000 r in from one to eight courses of therapy. In this population 33 proven and 5 probable cases of leukemia were found. The expected number of cases in this population was 2.9. The proportion of cases of the lymphocytic type was lower among those patients who had been irradiated than among those who were not, although one case of chronic lymphocytic leukemia was found among the irradiated patients. A number of other authors have reported cases of spondylitis treated by radiation with subsequent development of leukemia.[164] Cronkite et al.[138] have collected a total of 55 cases including the series mentioned here.

There are a number of difficulties in drawing general conclusions concerning radiation leukemogenesis from these sources. An initial difficulty is the lack of an adequate control population of ankylosing spondylitis patients not treated by x-ray and a paucity of information concerning the nature of the disease itself. Abbatt and Lea[165] collected a series of 679 cases of leukemia from the records of the United Kingdom Ministry of Pensions and National Insurance. They also used a control series of 813 cases of all diseases and injuries and another of 554 cases of neoplasms other than the reticuloses. In comparing the incidence in these series of various factors supposed to be leukemogenic they found an association between leukemia and irradiation and also an association between leukemia and the rheumatic diseases. O'Connell[166] recently reported a study of 70 families of 87 patients with ankylosing spondylitis. The results support the hypothesis that there is a strong hereditary factor in the production of ankylosing spondylitis as well as an association in the hereditary factor between ankylosing spondylitis and rheumatoid arthritis.

Another concern is the possibility that the other forms of therapy used for this disease may also be leukemogenic. Agents such as antipyrine, gold salts, and phenylbutazone are known to depress the bone marrow on occasion. Bean[167] reported the development of leukemia in six nonirradiated patients who had received phenylbutazone. Three of these patients had spondylitis.

A certain possibility of error exists in the assumption that the response to radiation of a patient who has an hereditary chronic inflammatory disease of bone and who has received potentially leukemogenic drugs for its treatment, will not differ from the response of the normal population. In spite of this, the spondylitis data do provide strong suggestive evidence of a qualitative relationship between localized bone marrow exposure to high doses of fractionated short-term x-radiation and the development of leukemia.

A major obstacle to quantitation in the ankylosing spondylitis series is its complicated physical dosimetry. Only ten of the British patients which subsequently developed leukemia had a single course of fractionated exposures. In other instances, up to eight courses separated by as many as eight years were administered. Cobb et al.[164] devised a method for dealing with the multiple course situation in analyzing this population for mean latent period before development of leukemia. The peak incidence was about four years after exposure and more than 90 per cent of the cases occurred within nine years after exposure.

Phantom studies were carried out in the British study and doses were expressed in terms of dose to the bone marrow in the spinal column and also in terms of whole body integral dose. The spinal dose was given as mean dose to the marrow and maximum dose to a point in the marrow. These complexities of dosimetry become of great importance in attempting to work out a dose-response relationship. Only 2 patients out of 17 who subsequently developed leukemia received spinal radiation alone, and only 3 patients out of the 32 receiving spinal and extra-spinal radiation had been given a dose below 500 rad for their spondylitis. Two cases of lymphocytic leukemia, one of them chronic, are included among them. Therefore, it would seem improper to make any generalizations for doses below 500 rad.

Therapy of thymic enlargement and other head and neck conditions. A number of prospective epidemiologic studies have been made of the occurrence of neoplasms, including leukemia, in individuals who received therapeutic x-irradiation during childhood for benign conditions. The findings of these studies are summarized in table 3. In 1955, Simpson and Hempelmann[168] initiated an investigation of children treated with local x-ray for thymic enlargement. Subsequent expansions of their study led to the collection of a composite group of 2393 cases in upstate New York, 87 per cent of which were traced.[139] Nine confirmed and one unconfirmed leukemia deaths were found instead of the one expected, and 15 cases of other malignant neoplasms were found instead of the 3.6 cases expected. No deviation from expectations was found among the 2722 untreated siblings of the children. Four of the cases of leukemia occurred in children with a cumulative exposure to less than 200 r. In contrast, all the cases of other malignant neoplasms occurred in children who received over 200 r. The latent period between exposure and leukemia death in this series ranged from 2 to 14 years. The mean latent period was 5.3 years.

Murray, Heckel and Hempelmann[169, 170] extended this investigation further by carrying out a prospective study of children in Monroe County, New York, who were treated with x-ray for a variety of benign conditions, including some not involving the thymus in order to avoid making any assumptions about the role of the thymus in this potential form of radiation leukemogenesis. They report the occurrence of six leukemic deaths in 2750 children treated for thymic enlargement, exceeding expectations by 4.5 times. It should be pointed out that a large number of these children were included in the earlier reports and that the six leukemia deaths reported by Murray occurred in those children who were included in the previous study. Thus from these combined studies the composite group of children locally irradiated for thymic enlargement is increased to 3744, but the number of leukemia deaths remains at nine (or ten?), since no leukemia deaths were found among the new patients added to the series.

Murray's study of children irradiated for conditions not involving the thymus

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TABLE 3.—*Comparison of Prospective Studies of Leukemia and Other Malignant Neoplasms in Therapeutically Irradiated Children*

Study	Irradiated Patients								Non-irradiated Patients		
	Region Treated	Number Treated	Dose range (r) Total Group	Dose range (r) Leukemia Patients	Deaths from Leukemia	Latent Period (Years)	Other Malignancies	Dose (r)	Number	Number Leukemias	Other Malignancies
Simpson and Hempelmann[168]	Thymus	3,714	75–600	<200	4	2–3	15 (16?)	>200	2,722	0	6
Hempelmann[169]				200–600	5 (6?)	5–14					
Murray and Hempelmann[169]				500?–750	2	?	1	?			
Murray, Heckel and Hempelmann[170]	Chest (pertussis)	49	?	?	1		3				
	Head and neck	1,073			1				2,923	3	0
	Skin	2,460	75–450		0		0	150–200,?			
	Thymus	1,564	50–600	200	1	5.5	4	100–1,700	3,777	3	6
Conti et al.[171]	Thymus	867	50–1,200+	?	1	4	17				
Latourette and Hodges[172]	Head, neck or chest	1,644			(thymus)			?			
Saenger et al.[173]	Thymus	125	?		0		2		185	0	0
Moloney[174,175]	Thymus	148	100–1,800		0		0				
Snegireff[174]											

revealed two leukemic deaths in 49 children treated for pertussis, exceeding expectation by 66.7 times. Another leukemic death occurred in 1073 cases treated for lymphoid hyperplasia, exceeding the expected number by four times. One leukemia death occurred in 2460 children who were given radiation therapy to the skin for hemangiomata, warts, and dermatitis. No leukemia occurred in 141 cases treated for bursitis and other inflammations. The dosimetry in this study was imprecise but, nevertheless, the doses for thymic enlargement, pertussis, and lymphoid hyperplasia were considered to exceed those used in the inflammatory and skin conditions.

Because of the difficulty of finding a population of children who were diagnosed as having thymic enlargement at birth and were not treated with x-rays, the converse situation was studied by Conti et al.[171] In 1948 they reported on a group of 1564 children examined by x-ray among whom 96 per cent were found to have normal sized thymus glands at birth. Eighty-eight per cent of them were then treated with 75 to 300 r, averaging 150 r in the region of the manubrium, while the remainder received 200 to 450 r. It was possible to study 90 per cent of these children 11 to 18 years after the therapy. Four cases of malignant disease including one of leukemia were expected in this group, but none were found. There was no significant difference between the expected and observed cases of malignancies in the control group of untreated siblings. The possible explanations of this result were that all the neoplastic diseases occurred in the untraced 10 per cent of the treated children or that the volume of tissue exposed through the smaller treatment port that was employed in this series was only one third of that in the previously mentioned studies. Another possibility is that this type of radiation exposure is not leukemogenic in children with normal-sized thymus glands.

Latourette and Hodges[172] found one leukemia death in a group of 867 children who received thymic irradiation in doses ranging from 50 to 600 r. The dose to the thymus in the leukemia case was 200 r.

Saenger[173] found one case of leukemia in 543 patients treated for thymic enlargement out of a total of 1644 traced from a group of 2230 which were irradiated over the head, neck, and chest in infancy and childhood for a variety of reasons.

In other studies of the sequelae of radiation therapy for thymic enlargement, Snegireff[174] reported that no malignancies including leukemia were found in 148 children traced out of 1131; and Moloney[175] observed seven cases of thyroid neoplasms including two malignant ones, but no leukemia, in 125 children followed out of 700.

In another approach to the problem, retrospective studies of leukemic children have disclosed five instances of therapeutic radiation, but none for thymic enlargement, among 677 children dying of leukemia[176]; five histories of thymic irradiation among 856 leukemic children[174]; a history of thymic irradiation in 4.3 per cent of 261 leukemic children compared with 0.8 per cent in a comparable group without malignant disease[177]; and a history of x-ray therapy in eight instances, including five for thymic enlargement, among 65 leukemic children; with only two instances in 175 living siblings, and none in 65 matched dead controls.[170] Unfortunately, these data are inadequate to determine whether any

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increased incidence of leukemia is related to the radiation therapy or to the thymic enlargement which served as the indication for that therapy.

It is evident that these studies suggest, but do not demonstrate beyond doubt, an association between radiation exposure and subsequent development of leukemia. There is a hint that the leukemia incidence rate is increased in those patients who received the largest doses of radiation. It does not seem possible to draw any more refined conclusions until additional prospective studies provide further clarification.

Therapeutic and diagnostic radiation in adults. A number of case reports have appeared concerning leukemia arising in patients treated for a variety of diseases by x-irradiation. Moloney[178] reviewed these and collected 18 instances in which adequate documentation of both the exposure and the subsequent leukemia was available. The diseases included cancer of the breast, seminoma, uterine fibroids, asthma, mycosis fungoides, psoriasis, arthritis and osteochrondritis. There were ten females and eight males in this group, almost all in the older age range, and all received high dosage of x-radiation, administered usually in more than one course and directed to various areas of the body.

A statistical study was recently performed by Simon et al.[179] to determine the incidence of leukemia among patients with carcinoma of the cervix treated with radium therapy. From large treatment centers all over the world, a total of 71,582 patients was collected, with a crude total of 22 cases of leukemia. Further refinement led to an incidence of between 62 and 116 cases per million. Comparing this to the British death rate of 58 per million for leukemia in 55 year old women and the rate of 90 per million for a similar group in the United States, they concluded that the incidence was not increased by radium treatment. Unfortunately, 25 per cent of the patients did not survive one year after therapy and 60 per cent of them did not survive five years. Therefore, the population at risk was largest at the early part of the latent period when the incidence of radiation-related leukemia would be expected to be relatively low. At the time when clinical manifestations of this leukemia might have been expected, the population was diminishing rapidly. Furthermore, the study ended well before the time when most of the cases would have become evident.

Using the cases of leukemia reported to the Danish Cancer Registry during the years 1950 to 1953, Faber[180] carried out a retrospective study of the incidence of diagnostic and therapeutic irradiation preceding the development of the disease. Beginning with 828 cases, he dropped the 258 cases below 41 years of age since previous irradiation appeared to be of no significance in them. The 278 cases of chronic lymphocytic leukemia were used initially as a control population because it was not likely that these cases were related to radiation exposure. A history of radiation therapy was found in 8 per cent of the cases of acute leukemia, 7.8 per cent of the cases of chronic granulocytic leukemia and 1.8 per cent of the cases of chronic lymphocytic leukemia. Among the patients with acute leukemia a history of diagnostic irradiation more than five years before illness occurred in 8.7 per cent, and within five years in 26 per cent; for the chronic granulocytic leukemia patients, 12.6 per cent and 24.4 per cent; and for the chronic lymphocytic leukemia patients, 8.4 per cent and 8.1 per cent respectively. Faber concluded that both the acute leukemias and the chronic granulocytic leukemias could have been induced by irradiation, and that while the former group had a mean latent period of five years or less, the latter group might have had a longer latency.

In a subsequent study of the incidence of x-ray exposure in patients with diseases other than leukemia, the findings did not differ significantly from that in patients with chronic lymphocytic leukemia.[181] More recently, this survey has been extended to cover the period from 1940 to 1954 including 442 cases of acute leukemia, 307 of chronic granulocytic leukemia, and 861 of chronic lymphocytic leukemia, as well as 395 non-leukemic controls.[182] Thirty-four and eight-tenths per cent of the acute leukemia patients had a history of diagnostic or therapeutic x-ray exposure; 32.6 per cent of the chronic granulocytic leukemics were similarly exposed, while 17.7 per cent of the chronic lymphocytic leukemia cases and 21.3 per cent of the controls had histories of medical radiation exposure. Faber found a latent period of from 10 to 60 months for the acute cases, and from 10 to 140 months for the chronic granulocytic cases with no notable peak in the distribution.

These data about adults exposed to medical irradiation suggest a causal relationship between exposure in the diagnostic dose range and subsequent development of leukemia. However, they suffer from the usual inability to characterize clearly the population from whence the leukemia cases came and therefore the resultant difficulty in defining an adequate control population with which to compare them. The absence of any sort of dosimetry in connection with the irradiation precludes any quantitation of these findings in terms of dose-effect relationship.

Prenatal diagnostic medical exposure. A large complex retrospective study of the relationship of prenatal diagnostic x-ray exposure to subsequent development of leukemia was completed by Stewart et al.[183] It involved an interview survey of the mothers of 1416 children among 1694 who had died of leukemia or cancer in England or Wales before their tenth birthday during the years 1953 to 1955. Six hundred and seventy-seven of the children had died of leukemia and 739 of other cancers. The mothers of an equal number of randomly selected live children matched only as to age, sex and locality were also interviewed. A most striking finding was that the mothers of children dying of cancer had almost twice as many abdominal x-ray examinations during the relevant pregnancy as the mothers of the control children (178 to 93 or 13.7 per cent to 7.2 per cent). In addition, of the 20 mothers who were certainly x-rayed in the first half of the pregnancy, 18 were mothers of children dying of cancer and only two were controls.

Among the leukemic children x-rayed postnatally for diagnostic or therapeutic reasons, the incidence of such exposure was almost twice as high as it was in the control population for the first three years of life. This effect was also present but not as marked among the children dying of cancer. Another point of interest was that the ratio of fetal irradiation in cancer cases as compared to controls was 1.73 for deaths up to the age of four years and 2.50 for deaths from five to nine years of age. The frequency of viral infections and threatened abortions was also significantly higher among the mothers of the dead children. Also excessive maternal age was related to an increased risk of leukemia as well as an increased

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incidence of mongolism. In addition to x-ray exposures in infancy, the frequency of two other post-natal events, acute pulmonary infections and severe injuries, was significantly increased in children who subsequently died of leukemia.

Recently, Stewart[184] extended the survey to incorporate the records of 1638 dead children (of whom 780 died of leukemia and 858 of cancer) as well as those of 1638 live children. The dead children encompassed 86 per cent of all children who died of cancer and leukemia before the age of ten in England, Scotland and Wales during the three years 1953 to 1955, including all the children considered in the previous report. She used the data to test a hypothesis that malignant diseases are initiated by x-rays and other mutagens either before conception (prezygotic), during gestation (prenatal), or after birth (postnatal). For various reasons, not all of which are fully substantiated,[185] she considered that most childhood cancers and leukemias are prezygotic; that the recent increase in incidence of childhood leukemia is due to the prezygotic form, and that the maximum incidence of that form occurs earlier than the maximum incidence of prenatal leukemias.

Based on various estimates of the maturation phase, Stewart expected the peak incidence of prezygotic leukemias to occur sometime between the second and fifth years of postnatal life, the years that do indeed show a peak of leukemia mortality. Division of her cases and controls into two-year age groups revealed a rise in the ratio of cases to controls for prenatal x-ray exposure from 1.02 for children whose age at the onset of symptoms was below two years, to 3.23 for children whose age at onset was between eight and nine years. Similarly a rise in this ratio was found with increasing age at death. It appears that, in proportion to the number of children who are x-rayed, the cases of cancer and leukemia were more common between five and ten years of age than between birth and five years of age. These findings are in keeping with those of her earlier study as well as with the apparent latent period for radiation leukemogenesis.[164]

Among the various objections raised concerning this work is the fact that the mothers of the dead children had more abdominal x-ray examinations before marriage or conception than did their controls, and that the reason for the increased incidence of such x-ray may have influenced the results. Another problem is that about 40 per cent of the randomly selected controls who were initially chosen in the first study were not available, primarily because they had moved away, and thus, the control population may not have been a suitable one. The possibility has been suggested that mothers whose children died of neoplastic disease might have a better recall of their medical and radiographic history. Subsequent studies described below have answered some of these objections. These investigations and the most recent one of Stewart are summarized in table 4.

The case histories of all children under ten years of age in Louisiana who were certified to have died of leukemia and other malignant diseases during 1951 through 1955, and a group of 608 control children who died from other causes in the same period were reviewed by Ford et al.[186] Cases actually analyzed totaled 78 leukemic children, 74 with other forms of cancer and 306 controls. In this series, information concerning radiation exposure was obtained from the physicians who delivered the mothers and from appropriate hospital records when available. In this way, the question of maternal recall was eliminated. The

TABLE 4.—*Frequency of Abdominal Irradiation During Pregnancy of Mothers of Cancer Children and Mothers of Control Children: Summary of Published Data* (modified from Court-Brown et al.[191])

Reference	Cancer Children: Description of Group	Cancer Children: Proportion of Mothers Who Received Abdominal Irradiation During Pregnancy	Control Children: Description of Group	Control Children: Proportion of Mothers Who Received Abdominal Irradiation During Pregnancy
Stewart, A.[184]	Children dying of leukemia under 10 years of age in England, 1953–55, (86% of total)	96/780 (12.3%)	Matched for age, sex, and location	117/1,638 (7.1%)
	Children dying of cancer under 10 years of age in England, 1953–55	115/858 (13.4%)		
Ford et al.[186]	Children dying of leukemia under 10 years of age in Louisiana, 1951–55:		Children dying of causes other than cancer under 10 years of age in Louisiana, 1951–55:	
	(a) white	20/70 (28.6%)	(a) white	48/247 (19.4%)
	(b) colored	1/8 —	(b) colored	8/59 —
Kjeldsberg[187]	Children with leukemia seen at Rikshospitalet, Oslo, 1946–56	5/55 (9.1%)	Healthy children	8/55 (14.5%)
Kaplan[188]	Children dying of acute leukemia in California, 1955–56	37/150 (24.7%)	(a) Closest sibling	24/150 (16.0%)
		34/125 (27.2%)	(b) Most habitual playmate	27/125 (21.6%)
Polhemus and Koch[177]	Children with leukemia seen at the Children's Hospital, Los Angeles, 1950–57	72/251 (28.7%)	Children attending the Children's Hospital, Los Angeles, 1950–57, with other selected conditions	58/251 (23.1%)
Murray et al.[170]	Children dying of leukemia under 20 years of age in Monroe County, New York, 1940–57	3/65 (4.6%)	Children dying of non-malignant disease under 20 years of age in Monroe County, New York, 1940–57	3/65 (4.6%)
			Siblings of leukemias	7/93 (7.5%)
			Siblings of deceased controls	2/82 (2.4%)
MacMahon[189]	Children dying of cancer under 10 years of age in New York City, and born in a specified maternity hospital, 1947–57	8/114 (7.3%)	1% sample of children born in one of 11 specified maternity hospitals, 1947–57, residents of New York City	173/2,520 (7.3%)
Lewis[190]	Children dying from leukemia from 1953–58, who had been born at Queen Charlotte Hospital, London	1/7	All children born at Queen Charlotte Hospital, London, 1943–58	(25.3%)

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diagnostic x-ray examinations in this study consisted of abdominal or pelvic x-rays taken for obstetric reasons during the last trimester of pregnancy. The findings of these workers were very similar to those of Stewart, and the similarity is enhanced when only the white children are considered. The ratio of cancer cases receiving fetal irradiation to controls was 1.8 to 1, as compared to Stewart's ratio of 2.06 to 1. Another similarity is in the distribution of cases and controls irradiated in utero classified according to the number of abdominal x-ray examinations reported to have been made during the relevant pregnancy. In this instance the ratio for cases over controls was doubled when four or more x-rays were taken. In addition, the disproportion of incidence of prenatal x-ray exposure in leukemics compared to that of controls was larger in the five to ten year age group than in the zero to five year group, as was found by Stewart.

Somewhat different results were reported in several other similar studies. Kjeldsberg[187] reviewed the history of antenatal x-ray exposure in 55 of the total of 68 leukemic patients at a pediatric clinic at Oslo and found that the percentage of these patients who had such exposure was slightly less than in a similar number of control patients. A pertinent fact is that the control patients were born at a different time from the leukemic children and thus did not experience the same likelihood of antenatal x-ray examination.

Several other groups carried out questionnaire or interview surveys of families of children who had died of leukemia in relation to the frequency of prenatal maternal abdominal roentgenographic examinations. Kaplan[188] found a slightly higher incidence of such examinations in the leukemics than in a control group of the closest siblings and a less striking difference in such examinations as compared to the most habitual playmates. Polhemus and Koch[177] used as controls a group of consecutive surgical admissions matched for age, socioeconomic and geographic factors and found essentially equal percentages of pelvimetric studies in the two groups. The work of Murray et al.[170] was carried out in connection with the above mentioned review of thymic radiation, and showed no increase in the percentage of children who had received prenatal irradiation when compared with a group of deceased controls or with the siblings of the leukemic patients.

Another approach to this problem was employed by several other workers. MacMahon[189] took a 1 per cent sample of all live births in eleven New York City maternity hospitals between 1947 and 1954. The percentage of this large group of children that had received prenatal radiation exposure was the same as that in the total number of cancer and leukemia patients under ten years of age who had been born in one of the same hospitals. Lewis[190] carried out a somewhat similar survey of all of the leukemia patients who died before ten years of age between 1953 and 1958 and who were born in a particular hospital in London. In this hospital the general incidence of prenatal irradiation was approximately 25 per cent but only one of the seven leukemic patients was in the irradiated group.

An extensive study was reported by Court-Brown et al.[191] Women who were irradiated during pregnancy between 1945 and 1956 were identified from the records of the radiological departments of four hospitals in Edinburgh and four in Northwest London. The subsequent deaths from leukemia of the children of these pregnancies were then determined, and the observed mortality compared with that expected on the basis of the national mortality rates. Among 39,166 live-born children who received antenatal irradiation, nine died of leukemia before the end of 1958. The expected number was estimated to be 10.5. None of the children of the 750 women irradiated in the first three months of pregnancy developed leukemia during an average follow-up of over six years. No correlation was found between incidence of leukemia and the amount of antenatal exposure. It was felt that the magnitude of any increase in incidence of leukemia from prenatal irradiation in these hospitals was unlikely to be more than 50 per cent of that incidence normally incurred irrespective of radiographic examination.

In view of the evidence that the time of maximum incidence of the onset of radiation-related leukemia is about four to eight years after exposure,[159] and that the incidence of leukemia in in-utero irradiated children rises progressively with age in the first decade,[184] the interpretation of the last three investigations might be open to some question. In all of them a significant portion of the population used for comparison was not observed for a sufficient length of time to determine the occurrence of leukemia after a latent period of the length which might be expected in the radiation-related disease.

For example, unpublished data supplied by Court-Brown et al. to Stewart[184] indicates that one-third of the children the former group studied were born before 1950 and two-thirds during 1950 through 1957. In the one-third born before 1950, the youngest cohort which was born in 1949 was at risk for ten years. On the other hand, in the two-thirds born from 1950 through 1957, the number of years at risk for each year's cohort ranged from one to nine. Although the numerical distribution of cases over these years is not given, it can be determined that 33 per cent of the cases were born in the first 38.5 per cent of the time period, and 66 per cent of the cases were born in the remaining 61.5 per cent of the time period. It therefore appears that the distribution was assymetric and that the annual increment of study cases was increasing in the more recent years. Thus, a significant proportion of the total population may have been at risk for less than five years. If the most likely duration of the latent period is from four to eight years, this may account in part for the fact that seven leukemia cases, including three over the age of five, were found in the population born before 1950 while only two, both under the age of five, were found since 1950.

There are no exact measurements of the doses received by the patients in any of these studies. Estimates have been made ranging from 86 to 600 mr per x-ray film when measured at the gonads of the fetus,[192] to 1 to 2.5 r[193] and in one extreme instance, 25 r.[194] In general, it is clear that no quantitative conclusions concerning dose and response can come from these studies. In fact, even the qualitative observations do not provide a definite cause-effect relationship between radiation exposure of such low levels and subsequent leukemia development. Clearly, sufficiently large prospective study populations, valid and perhaps multiple control populations, and appropriate observation time periods are essential to resolve the question of possible radiation leukemogenesis from antenatal exposure to very low levels of diagnostic radiation.

d) *Medical internal radiation exposure. Iodine-131.* Among a relatively small number of patients treated for carcinoma of the thyroid with doses of I^{131} ranging from 50 to several thousand millicuries, at least six cases of leukemia have occurred.[195-200] In addition, four instances of "leukemia or aplastic anemia"

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have been reported.[201] The I^{131} dose to these patients ranged from 250 to 1710 mc. It is estimated that the radiation dose to the hematopoietic system from orally administered I^{131} is of the order of 0.5 to 1 rad per mc.[202] In all but one case the leukemia appeared between two and four years after the initial therapy. In the other case the latent period was less than one year.

Recently, Pochin[203] has attempted to determine the incidence of leukemia among the conservatively estimated 60,000 patients treated for thyrotoxicosis with radioiodine during the last 20 years. Using an estimate of 59,200 patients treated as of mid 1960 in the main clinics of the United Kingdom, United States, Canada and Austria (an estimated 221,900 patient years at risk) and the appropriate national leukemia rates, it was determined that an expected number of 21 cases of leukemia would arise by chance in such a population, with a range of 14 to 28 cases. Pochin collected the eight published cases and ten others, as well as one case of lymphosarcoma. In addition, Solomon and Rubenfeld[204] reported one case of leukemia and another of lymphoblastoma following iodine therapy for hyperthyroidism. Also, Burns et al.[205] reported two cases of acute leukemia following I^{131} therapy, one of which appears to be included in the Pochin report as a case of chronic monocytic leukemia (Case 16, Table VIII of Pochin's report[203]). This makes a total of 20 cases of leukemia and two cases of other lymphomas. These are summarized in table 5.

In view of the low doses of radiation to the blood forming organs resulting from treatment with eight millicuries or less of I^{131}, the lack of an increase over the expected incidence of leukemia in this study population is not surprising. There are certain atypical features about the small leukemia group itself, however. Of the 19 cases in which the type of leukemia is known, 15 were diagnosed as acute. This proportion is higher than would be anticipated in a normal population of this age and sex distribution. Also, it is estimated that only about 20 per cent of the hyperthyroid patients treated with I^{131} were males. In contrast, over 70 per cent of the cases of leukemias in this group occurred in males. The atomic bomb exposure data also suggest a heightened sensitivity of males to radiation-related leukemia.

The mean age of this group is above that of hyperthyroid patients in general. This probably reflects the conservative use of I^{131} in the younger population. Finally, eight of the 20 cases were diagnosed in less than two years after iodine therapy, and only five were diagnosed more than four years later. This latent period distribution differs from the four to eight year peak previously discussed in association with radiation leukemogenesis. These facts would suggest either that these cases of leukemia occurred by chance or that under these clinical circumstances the latent period of radiation-related leukemia was shortened. Further clarification will have to come from studies of larger populations.

Phosphorus-32. Patients treated with P^{32} for polycythemia vera comprise another large group exposed to internal therapeutic radiation. P^{32} was first used for the treatment of this disease in 1936 and since that time it has become the agent of choice. In table 6 are summarized the recent series reported in which all or most of the patients received this form of therapy. Among the 1238 cases collected, there have been 308 deaths. Approximately one third of these deaths have been from hematologic complications, 41 of which were acute leukemias. Since

TABLE 5.—*Leukemia Following Radioiodine Therapy for Hyperthyroidism*

Case	Author	Age at Time of 1st Dose	Sex	Total Dose (mc)	Latent Period in Months-1st Dose to: Symptoms	Latent Period in Months-1st Dose to: Diagnosis	Type of Leukemia
				Acute			
1	Pochin et al.[206]	41	F	7.1	19	24	Acute
2	Abbatt et al.[207]	67	F	17.0	18½	19	Acute myeloid
3	Childs[208]	46	M	5.3	?	14	Acute granulocytic
4	Werner and Quimby[209]	28	F	2.1	17	18	Acute granulocytic
5	Blomfield et al.[210]	50	F	4.9	17	17	Acute monocytic
6	Vetter and Hofer[211]	50	M	7.1	18	18	Acute stem cell
7	Kennedy and Fish[212]	38	M	5.5	22	22½	Acute granulocytic
8	Burns et al.[205]	64	F	8	6	12	Acute monocytic
9	Burns et al.[205]	67	M	14.0	64	84	Acute monocytic
10	Pochin[203]	65	M	3.9	>38	43	Acute
11	Pochin[203]	73	M	8.9	35	36	Acute
12	Pochin[203]	64	M	8.5	?	60	Acute
13	Pochin[203]	?	M	4	?	(4 yr.)	Acute blast cell
14	Pochin[203]	54	M	3.5	52	54	Acute myeloblastic
15	Pochin[203]	58	M	46	32	33	Acute monocytic
				Chronic			
1	Chapman[213]	65	M	4	?	26	Chronic monocytic
2	Solomon and Rubenfeld[204]	66	M	7.5	31	31	Chronic lymphocytic
3	Pochin[203]	60	M	14.3	?	86	Chronic monocytic
4	Pochin[203]	60	M	28	0?	3	Subchronic lymphocytic
5	Pochin[203]	?	?	?	?	(4 yr.)	?
				Lymphoma			
1	Solomon and Rubenfeld[204]	65	F	11.4	40	40	Giant follicular lymphoblastoma
2	Pochin[203]	69	F	12.5	?	51	Lymphosarcoma or aleukemic lymphatic leukemia

nearly 75 per cent of the patients in these combined series were still alive at the time the reports were made, these incidences will undoubtedly change in the future. On the basis of the present data it is not possible to state the exact role that P^{32} played, if any, in the development of leukemia in these patients.

The principal obstacle to determining whether there is a real increased incidence of leukemia related to the radioisotope therapy in this population is the lack of sufficient data to allow statistical analysis and conclusions concerning the natural incidence of terminal leukemia in nonirradiated polycythemia patients. Prior to the advent of radiophosphorus, as well as since, x-ray therapy has also been used frequently in this disease. In the various recent large series presented

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in table 6, the number of patients who were not treated with any form of radiation is extremely small, totalling only four. However, two cases of acute leukemia in patients treated by phlebotomy alone were observed by Dameshek.[226] It is possible that a complete compilation, currently in progress[227] of all polycythemia vera cases reported in the literature, when added to these recent cases may provide a large enough series for valid comparison.

In the various recent series, those polycythemic patients who were not treated with P^{32} sometimes developed a terminal leukemoid blood picture. The leukemias that did occur were usually chronic. Vascular complications, especially thrombosis, were a more frequent cause of death. In many cases these were related to inadequate control of the peripheral blood abnormalities.

By affording better control of hematologic abnormalities, and thereby reducing the incidence of thrombotic and hemorrhagic episodes, P^{32} has extended the life expectancy of the polycythemia patients. This longer life span may allow the late development of a terminal leukemic state in patients who would otherwise have succumbed to a vascular accident at an earlier stage. Another possibility is suggested by the finding of Masouredis and Lawrence[219] that the patients in their series who subsequently developed leukemia showed apparently significant differences in their pretreatment clinical and hematologic picture compared with the nonleukemic group. The former, therefore, may have had a different form of the primary disease. The relatively high incidence of acute leukemia in the P^{32} treated group may indicate that P^{32} precipitates the acute form of leukemia in the patients whose basic disease predisposes them to a leukemic termination.

In the absence of an adequate control group of nonirradiated patients it is not possible at this time to resolve the question of the leukemogenic effect of P^{32} in polycythemia vera. It has been suggested[228] that such a control group might be the polycythemic patients treated with Myleran.[229] It would, of course, have to be assumed that Myleran itself is not leukemogenic in man. This might be difficult to prove since most of the experience with this drug has been gained during its administration to patients who already have leukemia.

Thorium. Thorium dioxide in a suspension, known as thorotrast, was first used clinically in 1928 in diagnostic radiology, primarily for the visualization of the liver, spleen, and cerebral arteries. It was widely used, particularly in Europe, in the period from 1930 to 1945. Since then, its carcinogenetic potential has become recognized and its use restricted. No definite epidemiologic study has yet been carried out in the population of patients receiving this substance. This is due, in part, to the extreme difficulty of estimating the dosage resulting from the varied localization of this material and the complex series of radioactive daughters that are produced in the body.

Various case reports and follow-up studies have resulted in the accumulation of about ten instances of leukemia following thorium injection, but several of these are not too well substantiated. In six of the cases for which detailed data were available, the time between thorotrast administration and the occurrence of leukemia was 12 ± 7 years.[230] It is clearly impossible to draw any conclusions about the leukemogenic effect of thorium from these data, although animal studies suggest the possibility.

Radium. The internal therapeutic use of radium and its daughters enjoyed a

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TABLE 6.—*Leukemia Deaths in Patients with Polycythemia Vera Treated with P^{32}*

Series	Period of Observation	Treatment	Number of Cases	Number of Deaths	Leukemia Deaths: Acute	Leukemia Deaths: Chronic	Leukemia Deaths: Myeloproliferative State	Leukemia Deaths: Total	Remarks
Wiseman et al.[214]	10 yrs.	P^{32} + Ph	108	6	1	0	0	1	
Stroebel[215]	12	P^{32} + Ph	241	39	8	0	9	17	Myeloproliferative states were reported by author as "anemia with leukemoid reaction."
Wassermann[216]	>10	P^{32}, X, TEM, Ph	150	64	7	0	9	16	All acute leukemia received p^{32} and/or X-ray.
Erf[217]	15	P^{32} + Ph	40	17	2	1	4	7	
Osgood[218]	>7	P^{32}	71	12	2	0	1	3	
Masouredis and Lawrence[219]	17	P^{32} + X + ?	179	58	5	9	1	15	
Reinhard and Hahneman[220]	14	P^{32} + Ph	98	35	9	5	5	19	
Chodos and Ross[221]	10	P^{32} + Ph and/or PHH	7	3	1	0	0	1	Subacute granulocytic leukemia.
Calabresi and Meyer[222]	12	P^{32} + Ph	97	28	0	6	2	8	
Szur, Lewis and Goolden[223]	10	P^{32} + Ph	90	19	1	1	1	3	
Ledlie[224]	11	P^{32} + X + PHH + ?	117	21	5	1	2	8	
Rigby and Leavell[225]	18	P^{32} + Ph	50	6	0	0	2	2	
Totals			1,248	308	41	23	36	100	
% of Deaths					13.3	7.5	11.7	32.5	

Ph = Phlebotomy
X = X-ray
TEM = Triethylene Melamine
PHH = Phenylhydrazine

great vogue from about 1915 to 1929. In addition, hundreds of persons ingested or inhaled significant amounts of radium in the luminous dial painting industry from about 1917 to 1925. Despite the extensive follow-up epidemiologic studies of this population now in progress, at the Argonne National Laboratory and Massachusetts Institute of Technology in particular,[231] it is interesting to note that there has not been a report of a case of leukemia in which both the validity of the diagnosis and the presence of a significant body burden of radium have been well established.

e) *Environmental external radiation exposure.* Another approach to the role of radiation in the production of leukemia has been to seek large populations exposed to somewhat elevated levels of environmental radiation and determine the increase, if any, in the incidence of leukemia. Clearly, the difficulty in finding suitable control populations of the necessary size and with identical characteristics to those of the study population except for the radiation exposure level are formidable indeed. Comparative studies have been considered of the inhabitants of cities at sea level and at 6000 feet altitude where the level of cosmic radiation is much higher. Buck[233] pointed out that the total excess radiation received in this manner by age 65 would be 1.5 r. Using the data of Court-Brown and Doll[163] to derive a dose-response relationship, a dose of five roentgens accumulated from birth to age 34 would require a minimum of six million persons years at risk from ages 35 to 44 to demonstrate a significant difference in number of leukemia deaths. Examination of present records indicates that the incidence of leukemia in the 163 metropolitan areas of the United States bears no demonstrable relationship to differences in the amounts of cosmic radiations.[234]

Populations have also been considered whose environmental radiation exposure is augmented by natural radioactive materials in the ground, such as the monazite sand in the area of Travancore, India, and in Brazil.[192] The dose received over a 30-year period in Travancore is said to be somewhere between 10 and 30 roentgens. Since there are a hundred thousand people in the area, it is conceivable that such a study might be productive if the levels of leukemia morbidity and its diagnosis in the study area and in the suitable control areas are similar to those of the United States.

Court-Brown and Doll[235] considered the role of increased environmental radiation in the finding that mortality for leukemia was highest in Aberdeen and in Edinburgh in a study of the four principal cities of Scotland, five mainly rural areas, and the rest of Scotland from 1939 to 1956. In Aberdeen this was mainly due to an excess of acute leukemia and the chronic myeloid form, which are usually associated with radiation exposure, whereas the excess in Edinburgh was mainly due to chronic lymphocytic leukemia. In part it was felt that the excess mortality was due to better case finding in the large centers, but it was of interest that the average local gamma radiation background in Aberdeen was 90 mrad per year, almost twice as high as that of Edinburgh which was 57 mrad per year.

No definite results have emerged from this type of study and it is clear that the labor and costs involved are very great.

f) *Environmental internal radiation exposure.* Various natural environmental radioactive materials which might be considered as possible leukemogens, such as radium and thorium have been discussed above

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A relatively new source of environmental internal radiation exposure has been the atmospheric "fallout" of radioactive products produced by nuclear fission of uranium and plutonium during atomic bomb detonations. There has been no direct evidence in man that such internally deposited materials as Sr^{89} and Sr^{90} are leukemogenic. A few studies in rodents, discussed by Law,[232] suggest the possibility.

g) *Experimental animal radiation exposure.* Excellent reviews of radiation leukemogenesis in experimental animals have been published in recent years by Storer and Grahn,[137] Law,[232] Upton,[237] Loutit,[140] Mole[142] and others. Many of the phenomena observed in these experimental studies parallel the situation in man closely while other observations show great differences from those found in man. It is very difficult in the present state of knowledge of radiation leukemogenesis, or the lack of it, to be certain which data may be extrapolated to man and which may not.

2. *General Conclusions from Present Evidence*

a) *Causal relationship.* On the basis of the investigations of human radiation leukemogenesis which have been reviewed above, it can be accepted that an increased likelihood of leukemia follows a single, whole-body penetrating exposure of 100 rad or more, and a short-term series of exposures totaling 500 rad or more to a major portion of the human bone marrow. It also appears that a long-term, intermittent series of exposures may produce the same result. The leukemogenic effect of a single or short-term exposure to less than 100 rad, or of protracted internal exposure to ingested or parenterally administered radioisotopes has not yet been definitely established, although various human epidemiologic studies and much animal data suggest that the probability of such an effect is considerable. In summary, it appears well established that leukemia occurs in man as a late manifestation of radiation injury to the hematopoietic system received under a variety of exposure conditions.

It should be mentioned at this point that the demonstrated relationship between radiation exposure and an increased incidence of leukemia cannot be used as evidence that all leukemia cases are related to radiation exposure. Even employing the most pessimistic and unproven assumptions discussed below concerning dose-response relationships, the resultant calculated number of cases of leukemia produced by natural background or medical radiation levels has been variously estimated to be only 5 to 20 per cent of the actual total number of cases.[156,238]

b) *Dose-response relationship.* The desirability of determining a definite relationship between the magnitude of a given dose of radiation and the probability of the resultant occurrence of leukemia is evident. This is so whether one is concerned with a basic understanding of the mechanism of leukemogenesis or the details of the interaction of radiation with biological matter, or even the more prosaic problem of hazard prediction from the standpoint of occupational or public health. It must, nevertheless, be borne in mind that leukemia is a rare disease, even among those who have been irradiated. Some 226 radiation related cases currently comprise the world total of published and validated cases occurring among the hundreds of thousands of people with a definite history of exposure to ionizing radiation in the past half century.[138]

Inadequate dosimetric information further reduces the number of human cases usable in defining a dose-response relationship and only the data of the atomic bomb survivors and the patients with ankylosing spondylitis have been helpful for this purpose. Pertinent information has therefore been sought from more adequately controlled laboratory animal experiments. Here the numbers of animals needed, the variety of exposure conditions requiring testing, and the validity of extrapolation of results to man are major problems. Thus, definitive data are lacking with which to determine the shape of the dose-response curve at low exposure levels. In addition, in the present absence of an understanding of the fundamental mechanisms whereby the transfer of radiant energy at a molecular level results in leukemia years later, no conceivable experiment is likely to produce results which are not subject to more than one interpretation.

Despite these formidable unsolved difficulties, the pressing need for answers has resulted in the proposing of several concepts of dose-response relationship appropriate to the available data in the past few years. Among these are the "threshold" concept, in which it is considered that the incidence of leukemia does not rise until a certain level of radiation exposure is attained; the "linear" concept, in which it is expected that for every increment in radiation dose, a proportionate increase in the incidence of leukemia will occur; and the "curvilinear" concept which anticipates that increasing exposure doses will produce a rising incidence of leukemia, but one which increases in some manner that is not simply proportional throughout but is better described by an exponential, quadratic or other relationship to dose. Detailed discussions of this complex subject are available in recent publications of Bacq and Alexander,[4] Cronkite et al.,[138] Burch,[239] Mewissen,[240,241] Brues,[242,243] Lamerton,[244] Mole,[245] Court-Brown,[141] Kimball[162] and Lewis.[156]

In the absence of direct evidence concerning the lower end of the dose-response relationship, most groups concerned with radiation protection have used the "linear" concept as a prudent and conservative guide.[136,246] Based on the unproven assumptions implicit in such an approach, one can hypothesize from the data of the atomic bomb survivors that the annual incidence of leukemia per rad of radiation exposure is about one or two cases per million persons at risk in the first fifteen years after a single short-term exposure to 100 rad or more.[138] Similarly, the spondylitic therapy series has been analyzed in the light of such assumptions and a dose of 30 to 50 rad to the whole body has thereby been considered capable of doubling the incidence of leukemia.[141] It is evident that many factors such as sensitivity differences due to age and sex, and the differing effects of the same dose given at different rates, externally and internally, are not considered in this hypothetical approach.

A better definition of the dose-response relationship of radiation leukemogenesis, must await more fundamental knowledge about the underlying mechanism itself, and the more precise epidemiologic and experimental studies which can then be designed and performed.

c) *Clinical characteristics. Type.* The data are quite clear that only the incidence of acute leukemia and of the chronic granulocytic form are often increased by irradiation. An "aleukemic" or pancytopenic onset was noted in the spondylitic series but this may only reflect earlier observations than in the Japanese cases in which this was not a frequent finding.

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Latent period. It appears that radiation-related leukemia begins to occur one or two years after short-term exposure and that the peak of increased incidence of radiation related leukemia occurs in from four to eight years. The increased incidence is probably of a limited duration and falls off in time, such that a majority of the cases may be anticipated within about a decade after radiation exposure of the short-term variety. It is difficult to determine such time relationships in the long-term exposure situation.

Age incidence. There is suggestive evidence in the data from atomic bomb survivors that younger persons are more susceptible to leukemogenesis. The spondylitic series points the other way and the in-utero exposure situation is not resolved. Accordingly, no conclusion may be drawn in this regard.

Sex incidence. A possible preponderance of leukemic males in the Japanese study is hard to evaluate. The unusually high proportion of males among the leukemia cases following I^{131} therapy for hyperthyroidism has already been pointed out. The fact that most of the other epidemiologically useful populations studied in this connection are predominantly male ones (spondylitics, radiologists) prevents any definite conclusion about sex related sensitivity to radiation leukemogenesis.

Clinical course. Lacking the means to identify an individual case of leukemia as being radiation-related it has not been possible to investigate possible variations in the clinical course statistically. No particular deviations from the usual pattern have been noted by the various hematologists who have observed the leukemia patients among the atomic bomb survivor population. Little uniformity of observations exists in the relatively few other instances where patients were studied whose disease had a reasonable probability of being related to radiation exposure.

d) *Estimation of probability of radiation-related etiology.* There has been no evidence that any clinical means exists to identify an individual case of leukemia as being related to radiation in the absence of a history of radiation exposure. Thus, the etiologic role of radiation is essentially a matter of statistical probability rather than a clinical judgment. However, there may be clinical characteristics which, if found in enough cases in which a definite exposure history makes the etiologic relationship probable, may themselves become useful guides in further defining the probability in a given instance.

For example, the foregoing information about clinical characteristics, and the conservative and unproven assumptions concerning a linear dose-response relationship can be combined in an attempt to determine the probability of radiation relationship in individual cases under certain conditions.[1] If the onset of acute leukemia or the chronic granulocytic type occurs within an appropriate time interval after a known single whole body radiation exposure to more than 100 rad, the probability of relationship is high. It can be estimated by considering the normal age group incidence and the probable increase due to the dose. The probability will increase to a maximum four to eight years after exposure and fall ultimately, perhaps, to that expected in the general population.

It must be borne in mind that this estimation of the probability of radiation leukemogenesis is no better than the validity of the assumptions on which it rests. Since even less definite information is available in other exposure circumstances, even a rough estimate of this type for such cases would be impossible.

B. *Other Myeloproliferative Diseases*

The general concept of myeloproliferative diseases developed by Dameshek[247] would suggest that the stimulus producing an increased incidence of one form of this type of disorder, i.e., granulocytic leukemia, might well be capable of the initiation of closely related clinical entities such as polycythemia vera, erythremic myelosis and myelosclerosis. In view of the much greater rarity of these other syndromes and the complexities involved in their diagnosis, it may well be that large scale prospective epidemiologic studies carried out with a continuous high level of diagnostic acumen will be necessary to arrive at any definite conclusions. In addition to the value of such surveys in connection with an understanding of the hematologic effects of radiation, they could also contribute notably to a better understanding of the interrelationships among the myeloproliferative diseases themselves.

1. *Polycythemia Vera.*

Reports of hematologic changes in the blood findings of the early roentgenologists[121] included the development of erythrocytosis in a number of instances. This was considered to be evidence of over-compensation for bone marrow injury. It was asymptomatic and required no therapy.

The possibility of an increased incidence of polycythemia vera following radiation exposure was considered by the Atomic Bomb Casualty Commission but none was found.[248] Recently, Yamazaki et al.[249] indicated in a preliminary report the finding of 18 cases of polycythemia vera among Hiroshima atomic bomb survivors. Eight of these were within 2000 meters of the hypocenter and eight cases showed acute radiation signs and symptoms in the immediate postexposure period. The disease was manifested in four of the patients within seven years after exposure, in ten from seven to nine years after, and in four it was not evident for more than nine years postirradiation. The 18 cases comprised 22 per cent of the 81 cases of polycythemia vera reported in all of Japan since 1950.

In the absence of full details, and with the knowledge of the many variables involved in this type of retrospective analysis, further evaluation of the relationship of polycythemia vera to radiation exposure must await more information.

2. *Erythremic Myelosis*

One instance of chronic erythremic myelosis was seen in a survivor of the Hiroshima atomic bombing.[250] As is frequently the case, this patient's course ended in typical acute granulocytic leukemia, under which category the case is included in the records of that study. Obviously, there is no adequate basis for any conclusion concerning a relationship between this extremely rare disease and radiation exposure.

C. *Aplastic Anemia*

The rapid development of generalized bone marrow aplasia following short-term exposure to high doses of external radiation has been clearly demonstrated.[6] Similar results, more gradual in onset, have been reported after intermittent long-term exposure to external radiation, particularly among the early radiologists.[14] Acute aplasia of the bone marrow has also been observed following internal radiation exposure from radioisotopes such as gold-198[23,25] and gallium-72.[28]

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Clear-cut evidence for the development of the clinical syndrome of aplastic anemia as a delayed effect of radiation exposure is more difficult to find. Lange et al.[251] have reported the occurrence of aplastic anemia in four individuals who had suffered severe radiation injury four to seven years before, in the atomic bombing of Nagasaki. The paucity of cases and the relatively high incidence of aplastic anemia in Japan make a causal relationship extremely uncertain. The Hiroshima study gives no conclusive supporting evidence in this regard. Although an incidence of anemia (hemoglobin below 10 grams) of about 10 per cent was found in the survivors studied, this was primarily of the iron deficiency type and related to inadequate dietary iron intake.[248]

Another population in which a few cases of aplastic anemia have been reported is that of the ankylosing spondylitics treated with short-term courses of x-radiation. Court-Brown[163] reported four cases, in two of which the aplasia developed within six weeks after therapy was begun. Van Swaay[252] found two such cases in his series.

The clinical syndrome of aplastic anemia has also been reported by Martland[253] in former radium dial painters with a constant radiation exposure to internally deposited radium, and by Looney et al.[230] in patients with significant body burdens of thorium. Bone marrow examinations have shown characteristic myelofibrotic and myeloproliferative appearances at various times. It is extremely difficult to determine the time of onset of these changes because of their insidious nature, but they do seem to appear as a delayed effect some years after a known internal deposition of the radioactive material.

A major problem in learning whether aplastic anemia is definitely a late effect of radiation exposure lies in the fact that, except among the radium workers, its appearance has been noted in populations known to be at increased risk for the development of leukemia. Since the onset of the latter disease is not infrequently characterized by a period of pancytopenia and bone marrow hypoplasia, it is very difficult to determine whether some of the patients who died with this clinical picture might not actually have been cases of radiation-induced leukemia. It is pertinent that Court-Brown and Doll[163] found that of 16 instances in which the diagnosis of aplastic anemia was made at death in patients with ankylosing spondylitis treated by radiation, eight were considered to be probable or definite instances of leukemia, and in four others the evidence for the diagnosis of aplastic anemia was considered insufficient, leaving only four patients in whom the diagnosis was acceptable. This demonstrates the difficulty in identifying this clinical syndrome with certainty.

For the reasons discussed above, it does not appear possible at this time to determine whether or not aplastic anemia is a delayed effect of radiation exposure in man. If it is, it certainly is an occurrence of considerably lower incidence than that of leukemia.

IV. Summary

The important advances made in the past half decade in our understanding of the hematologic manifestations of radiation exposure in man have been reviewed. The early changes produced by short and long-term exposure have been considered, with emphasis on the newer findings made possible by recent technical

developments such as radioisotope tracer kinetic technics, fluorescent microscopy and cytogenetic methodology. The clinical implications of these observations in relation to the diagnosis and prognosis of acute and delayed hematologic disease have been stressed. The late manifestations of radiation exposure with particular attention to leukemia and the present evidence for radiation leukemogenesis and other myeloproliferative diseases and aplasias have been reviewed in detail.

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