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FOLDER ACUTE & LONG TERM
HEMATOLOGICAL EFFECTS

FINAL REPORT

To Dr. S. Warren,
CHAIRMAN OF PANEL ON PATHOLOGIC EFFECTS OF ATOMIC RADIATION
for the National Academy of Sciences

BY
THE PANEL ON ACUTE AND LONG TERM HEMATOLOGICAL EFFECTS OF ATOMIC RADIATION

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On January 7 and 8, 1956, the panel convened. All members were present. A preliminary report was written by Dr's. Bond and Cronkite and distributed to panel members. The comments of the subpanel members have been incorporated into this report.

INTRODUCTORY COMMENTS BY CHAIRMAN OF PANEL

Mankind has always lived in an environment suffused with radioactivity from natural and unavoidable sources such as radioactive minerals and cosmic rays. Natural radioactivity varies greatly in degree throughout the world. Intensities tend to be much lower at sea level and on small islands, with the exception of Baltic islands, throughout the world. At high altitudes cosmic ray activity increases significantly. Similarly natural radioactivity from minerals increases significantly in some mines, and in the water supplies of some areas. For example, water in the Joliet area in Illinois contains relatively large quantities of radium and its daughter products. Since the discovery of x-rays by Konrad Roentgen and natural radioisotopes by Becquerel and the Curies, there has been a steady increase in the amounts of radiation to which segments of mankind are being exposed. With the development of nuclear weapons and the spread of atomic energy by industrial activities, the levels of world wide radiation will unquestionably continue to increase.

At the present time there is confidence that the increment to the naturally existing radioactivity is but a small fraction of that believed to exist prior to the testing of atomic weapons and the presently developed atomic energy industry. However, when one specifies the diverse sources of radiation to which large numbers of mankind are being exposed, it is quite evident that serious concern must be felt by physicians and scientists for the possible influence of such radiation upon individuals, selected groups, and whole populations. In the course of the deliberation of this panel attention was called to the existence of the following types of exposure to radiation to which human beings were exposed, voluntarily and involuntarily:

1. Natural sources
2. World wide low-level fallout
3. Roentgenographic surveys of large segments of the population for tuberculosis and cancer
4. Dental x-rays
5. Industrial fluoroscopy and radiography
6. Fluoroscopy of infants
7. Fluoroscopy for shoe fitting
8. Diagnostic x-rays
9. Medical and scientific use of tracers in human beings
10. Therapeutic use of radioisotopes and x-ray
11. Tracer radioisotopes in agriculture and industry
12. Research and power reactors
13. Ionizing radiations for food sterilization
14. Experimental accelerators

During the early years when the diagnostic and therapeutic uses of x-ray were being developed, heavy and repeated exposure to physicians, physicists, nurses and technicians resulted in serious injuries. Historically, the occurrence of leukemia and aplastic anemia as late sequelae of exposure to x-ray and radioactive substances was well documented in the medical literature prior to 1937. Presumably Madame Curie died from an aplastic anemia. In recent years, while great care has been taken to avoid heavy radiation exposure, there is little knowledge on the hazards of repeated smaller doses, especially in regard to late effects on the blood forming organs.

The record of the atomic energy development, which involved the handling of large amounts of dangerously radioactive material is an example of the effectiveness of a controlled environment.

Dose dependence and correlation of other effects with hematologic effects:

In order to set the acute and chronic hemopoietic effects of radiation into the proper perspective with regard to overall radiation effects, the whole body radiation syndromes as a function of dose of radiation are summarized:

After very large doses of radiation delivered in a short time, a typical clinical syndrome is produced in animals. On the basis of observed symptomatology, it has been useful to name this symptom complex the central nervous syndrome (CNS). In animals, doses in excess of many thousands of r, are necessary to produce this complex. There are species variations. The "threshold" for this syndrome in man is not known and this syndrome has not been observed in man. Symptoms referable to the nervous system and GI tract appear promptly. Death may occur "under the beam" or within a few hours. In laboratory animals this syndrome invariably results in death either promptly, or later as a result of the next clinical syndrome which results in death at a later time. If the nervous symptom complex subsides, or if the dose has been smaller (in the region of 900 - 5,000 r for laboratory animals; dose for man not known), a symptom complex termed the gastrointestinal syndrome (GIS) appears. Nausea and vomiting appear shortly after exposure. Diarrhea and tenesmus become severe. The GI symptoms may be intractable or may subside for a variable period. Fluid and electrolyte loss from the GI tract progressively produce dehydration and eventual vascular collapse, and death that may occur during the 1st and 2nd weeks. This picture was observed in the Japanese casualties and has been well studied in laboratory animals. Death from this syndrome has been prevented experimentally in some dogs by adequate fluid and electrolyte replacement; in addition spontaneous recovery may occur after the lower doses in this range. However, the survivors then experienced another symptom complex that may result in death. It is this third symptom complex characterized by signs and symptoms referable to bone

marrow depression which characterizes the lethal dose range*. By custom, the mortality from this syndrome has been tabulated as of 30 days after exposure. There are reasons, to be discussed later, why a 30 day tabulation may be too short for human beings.

A fourth phase of deaths was observed during the 2nd and 3rd months after exposure in the Japanese casualties in which in some instances the causes of death were not clear; however, pancytopenic sequelae were still present. Hemopoietic recovery was in progress but defects in proliferation and maturation were observed in the pathologic sections of marrow. Following the third month, deaths are infrequent and it becomes increasingly difficult to ascribe deaths to the effects of radiation since phenomena observed are those which may result in death in any non-irradiated population.

There is evidence that large single doses, or repeated small doses of radiation can produce diverse neoplasia, genetic defects, and shortened life span in select controlled animal populations. However, attempts to ascribe a specific role to irradiation in neoplasia in human populations becomes an exceptionally complex biometric study because of the increasing contamination of the atmosphere by industry with potential carcinogens, and the introduction and widespread use of an array of clinically useful drugs, whose long term effects in man are imperfectly understood, but which in some cases have produced severe blood dyscrasias. Accordingly, in all of the discussions on the long term effects of single doses of radiation on man, and the effect of repeated or low level exposure, one must be especially cognizant of the fact that the "effects" are deduced by statistical correlations, and cannot be proved by controlled experimentation, nor can other causative factors be eliminated. In this era of awakened public interest to the hazards of radiation, it is especially important that preoccupation with the hazards

*Sublethal refers to the lower doses of radiation that will produce no deaths within a given period of time, usually taken as 30 days in animals. The lethal range extends from the threshold dose at which only rare deaths occur in this time interval, to the level at which virtually all exposed will die (the LD 1 to LD 99 range). Doses above the LD 99 level are termed supralethal. In all ranges, however, ultimate longevity is reduced to some degree.

of ionizing radiation does not becloud the searching mind of the scientist or the responsible citizen to the presence of other hazards of equal importance. This is not an attempt to minimize the hazards of ionizing radiation with respect to the development of blood dyscrasias and other late effects. It is most important to bear in mind that the incidence of bone marrow failure* and leukemia has increased significantly in the United States in groups in whom there is no known overexposure to ionizing radiations. Today no informed physician believes that exposure to ionizing radiation has either a beneficial or stimulating effect on the blood.

In the course of the deliberation of this panel, attention was focused upon the known effects of nuclear explosions, the immediate and long term effects of single exposures from all causes, and the long term effects of intermittent and continuous exposure to radiation of diverse types. In the latter category, the panel felt that a reasoned judgement could not be made because of the paucity of realistic quantitative data on the degree of exposure.

ACUTE HEMATOLOGICAL RESPONSE TO SINGLE DOSES OF PENETRATING RADIATION

Although the available sources of hematological data on human beings exposed to total body external radiation have serious limitations, they were considered to be reasonably consistent among themselves to allow characterization of the time course of change in peripheral elements following exposure. The sources of data included the reports of the Japanese exposed to immediate radiation from atomic weapons, the account of the human beings accidentally exposed to fallout radiations at the Pacific Proving Grounds in March, 1954, the reports of human beings exposed to reactor accidents in the laboratory, and data on patients with incurable neoplastic disease exposed to therapeutic total body irradiation. The pattern of response of the peripheral blood elements changes

*Synonymous with aplastic anemia, refractory anemia, hypoplastic anemia. Aplastic anemia has been observed to terminate in leukemia. The occurrence of aplastic anemia after use of diverse drugs is common clinical knowledge.

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with increasing radiation dose. In the following description, changes are divided into those that occur in the sublethal range, and those that occur in the lethal range (doses that result in some mortality within 60 days of exposure). This division is arbitrary, since the patterns of change merge imperceptibly, and each category covers a range of doses and thus degree of effect. When the dose is increased from sublethal levels to lethal levels, the lag period between exposure and depression is progressively shortened.

Response after sublethal doses:

The neutrophil count shows an initial rise in the first 12 to 48 hours followed by a sharp drop, to or below, the pre-exposure level. The count then fluctuates around or slightly below the pre-exposure level until the 3rd or 4th week, following which definite depression is observed. The time of maximum depression occurs during the 5th or 6th week or even later, and is followed by a gradual return to pre-exposure levels. Complete recovery may require several months or more.

The drop in lymphocytes is early and profound. Little or no evidence of recovery in the high sublethal range may be apparent several months after exposure, and return to former levels may not occur for months or years. The total white count parallels closely the change in neutrophil count.

The platelet count shows little or no change over the first three weeks following exposure. At approximately the end of the 3rd week the platelet count falls. The time of maximum depression is remarkably constant at sublethal dose levels, and occurs on the 28th to the 32nd day of post-exposure.

No trend in eosinophile, basophile, or monocyte counts can be definitely ascertained. This may result in part from the larger errors inherent in counts of these cells. In the absence of hemorrhage, the hematocrit may show slight depression. This effect is probably due to a combination of inhibition of erythropoiesis and shortened life span of the red cell.

Response after doses in the lethal range:

The neutrophil count may rise during the first two days following exposure. The count then falls steadily to reach values below 1,000/mm³ by the 5th to the 10th post-exposure day, depending on dose. In survivors, recovery begins during the 5th week, but may not be complete for several months.

The lymphocyte count drops to vanishing levels within 12 to 24 hours of exposure; recovery is not apparent for several weeks; and it may not be complete for several months, or for a year. The total white count parallels the neutrophil count.

The platelet count in the lethal range, in marked contrast to that at lower doses, may drop precipitously, starting approximately on the 4th day, and platelets may virtually disappear from the peripheral blood by the 10th day.

Changes in the eosinophiles, basophiles, and monocytes counts cannot be characterized definitely at this time. The hematocrit* is not appreciably affected until hemorrhage occurs, severe gross external or occult internal bleeding may occur as early as the 9th day, depending primarily on the time at which the platelet count reaches dangerously low levels. This may occur from the second to the fifth week, with peak incidence in the 4th week in the low and mid-lethal dose ranges. The degree of response as a function of dose varies for the several blood elements. The platelet and lymphocyte counts are affected by very small doses of radiation, and are reduced to minimal levels before the lethal dose range is reached. The neutrophil count, however, does not reach minimal values until the lethal range is reached.

Comparison of man and other mammals:

The time course of changes in the leucocyte and platelet counts in human beings is definitely different from that observed in lower animals. In

*Admittedly the hematocrit can be misleading since it represents both changes in plasma volume and red cell mass. However, in general decreases in hematocrit represent a diminution in red cell mass for one reason or another (loss, hemolysis, or no new production).

man, severe depression of these elements occurs later, and recovery is more delayed. Similarly, the time of deaths in man resulting principally from hematological depression differs from that of laboratory animals. In most laboratory species, essentially all animals alive on the 30th post-exposure day will remain alive for several months, although the life span is shortened. In man, however, the peak incidence of death from marrow depression occurs during the 4th and 5th post-exposure week (Hiroshima and Nagasaki data). Thus an LD 50, 30 day consideration is inadequate to characterize the acute lethal dose response of man, and an LD 50, 60 days would be preferable*. The extensive serial blood counts obtained in human beings exposed to fallout gamma radiations were relied on heavily in characterizing the hematological responses of human beings exposed to external radiation. Admittedly the dose rate with fallout was much lower than with prompt radiation and may have reduced the effectiveness somewhat. These individuals received, in addition to gamma radiations, beta radiations of the skin, and probably a minimal degree of internal contamination. It was the consensus of the subpanel that neither the beta lesions nor the low level of internal contamination significantly contributed to the pattern of change observed. This view was supported by the general agreement of these data with other less extensive data on human beings who did not receive additional skin lesions or internal contamination; and the lack of correlation between the severity of hematological change and the extent of beta lesions in those exposed to fallout radiation. The reservation was held, however, that data are inadequate to establish this view with certainty, and that synergistic effects cannot be ruled out.

Mortality and morbidity from whole-body radiation:

The pan-hemopoietic depression contributes in large measure to morbidity and mortality following total body irradiation. In the sublethal and low lethal

*The reservation must be made here that the exposed Japanese population were heterogenous with respect to age, sex, physical condition and degree of added trauma from burns or blast. The extent to which these factors affected survival time has not been determined. In studies on laboratory animals the converse is true--homogeneous populations are studied.

0016992

ranges, the response observed is consistent with other clinical pancytopenic states. Neutrophil depression increases the susceptibility to infection and platelet depression contributes to the bleeding tendency. Correction or treatment of these defects during the first few weeks may permit survival in some individuals who might otherwise have succumbed. The concept of total body x-radiation as primarily a pancytopenic state, while useful, is probably an oversimplification, particularly in low and high lethal ranges.

Susceptibility to infection is well established and the pathogenesis may well involve interference with specific immune mechanisms, phagocytosis, and migration of leukocytes in addition to simple neutrophil depression.

Susceptibility to bleeding is well correlated with platelet depression. However, additional factors may be involved such as lipid antithromboplastins (Tocantins) or disturbances in the β lipoprotein transport mechanism (Nickson and Bane). In some instances, the latter changes are similar to changes induced by heparin administration to rabbits. The relation of these alterations to the bleeding tendency has not been established. It was the consensus that frank heparinemia is not a contributing cause of bleeding.

After higher doses, death ensues even if hemorrhage and infection are corrected. Germ free rats die at dose levels moderately higher than the lethal dose for rats in the natural state. These animals die later with severe hemorrhage and anemia. At dose levels in excess of the LD 100, 60 day level, individuals die within the first week presumably from fluid imbalance and vascular collapse correlated with marked damage to the intestinal epithelium. It is clear that at all dose levels, poorly known and little understood biochemical changes* occur which may contribute to mortality in the exposed individual. Our knowledge is inadequate to determine at the present time to what extent such biochemical changes may prove lethal in themselves even when infection and hemorrhage can be treated adequately.

*Apparently decreased respiratory quotient (RQ) in animals; increased excretion of amino acids in irradiated human beings, etc.

Lethal dose for man:

No data are available to allow adequate characterization of the LD 50 value for man. The degree of hematological depression observed in patients receiving total body x-radiation indicates that the current estimate of 450 r is a reasonable estimate for x-radiation as employed in the clinic. A recent re-evaluation of the data from Hiroshima and Nagasaki indicated a value higher than this for immediate gamma radiation from the bomb. Geometrical and depth-dose considerations can be interpreted to indicate that the LD 50 for man exposed to immediate gamma radiation and fallout gamma radiation from the atomic bomb may be lower than this figure. A large degree of uncertainty exists in both approaches, and more biological and physical data are required to settle the issue. The situation is complex, and it became evident that it is not possible to extrapolate with confidence from one condition of radiation exposure to another, or from animal data to man.

Threshold dose for detectible effects:

There appears to be no threshold* dose for changes in the peripheral platelet count and possibly for other elements of the blood. Changes at very low dose levels, however, can be detected only in a relatively large population. Nothing is known about subtle changes in the blood forming organs at dose levels so small that changes in the blood picture cannot be detected.

Diagnosis of radiation exposure and its severity:

The diagnosis of exposure to radiation and its severity is made on the basis of the history and physical and laboratory examinations, as with any disease. Available estimates of air roentgen dose received obtained by physical means should be considered in evaluating the degree of exposure, but should never in themselves be taken as an index for disposition or treatment since tissue dose and distribution

*The threshold concept may be incorrect since inability to detect effects at lower doses may only be a manifestation of inadequate criteria for effect. For practical purposes a threshold might be classified as that dose where statistically significant differences are detected. For many effects this may necessitate extremely large samples.

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of absorbed energy ultimately determines effect not dose in air. Any degree of radiation exposure should be avoided if possible. If exposure is necessary under emergency conditions, severe hematological depression may be expected at doses of 100 r or more measured in air, from immediate radiation from the bomb or from the gamma radiation from fallout material. With human exposure a wide spectrum of ages and of state of health is likely to be involved. Thus it is not possible to predict accurately the severity of response that might be expected for a population exposed at various dose levels. There is evidence from the human beings exposed to fallout radiation that children may be more severely affected than are young adults. Whether this is due to inherently greater sensitivity or to an increased depth dose due to smaller size is not known. From animal data, it has been postulated that elderly individuals may be more seriously affected than young adults.

Therapy of Radiation Injury:

Recommendations for therapy are given for 1) conditions where exposed individuals can be carefully and individually handled because they are limited in number and adequate facilities exist for taking care of them, and 2) exposures at the catastrophic level where adequate medical observation and care are impossible. In the first category, of cardinal importance in therapy is careful observation, good nursing care, and treatment on an individual basis of any condition that may arise. Antibiotics in general should not be given prophylactically, and should be administered only if infectious processes develop that would be treated with antibiotics in the absence of radiation. Prophylactic use of antibiotics may be considered if the neutrophil count drops below $1,000/\text{mm}^3$. Prophylactic use of antibiotics may be considered particularly where severe wounds or other complications may be present. If antibiotics are used, they should be given in large doses and the broad-spectrum drugs should be employed. Fluids should be given as indicated clinically. Blood should not be given prophylactically, but only as indicated from clinical and laboratory findings. Fresh

whole blood by direct silicone multiple syringes without anticoagulant or collected in plastic bags or platelet transfusions may be of some value in controlling purpura and other hemorrhagic manifestations. The use of drugs without clear indication is discouraged because of their unknown and possibly harmful effects on the irradiated individual whose metabolism is deranged. Parenteral administration of drugs should be held to a minimum because of the added trauma in an individual susceptible to purpura and infection. At present there are no specific prophylactic or therapeutic agents* that should be stock-piled for use in the hematological depression and the resulting disease state following exposure to total body irradiation.

Under catastrophic conditions it of course will not be possible to adhere to the above regimen. The principles of therapy remain the same, except that here there is a much better potential case for widespread and empirical antibiotic dispensation, particularly to individuals in which burns, mechanical wounds or other added trauma exist.

RECOMMENDATIONS WITH RESPECT TO THE ACUTE HEMATOLOGICAL RESPONSE
OF HUMAN BEINGS TO RADIATION

- 1) The Japanese data from the Hiroshima and Nagasaki bombings should be further analyzed in respect to:
 - a) Duration of depression of leukocytes as a function of distance and shielding (dose).
 - b) Leukocyte counts at various intervals in relation to ultimate survival.

*Antibiotics of great value in the therapy of infection in the exposed individual are not considered here as specific drugs. Such prophylactic agents known to this panel such as sulfhydryl compounds, hypoxia inducing drugs, spleen or bone marrow preparations, etc., claimed or shown to favorably modify acute radiation injury in animals, have no place as yet in the treatment of human radiation injury.

- c) Survival time as a function of distance and shielding (dose), and of age.
 - d) The degree of initial blood count depression in relation to the later development of leukemia and other late disease.
- 2) Additional and intensive studies should be initiated on human beings receiving radiation to the whole body or large portions of the body in the therapy of malignant disease. Particular attention should be given to the time course of peripheral blood counts for several weeks following exposure to different doses, and the nature of the clotting defect*.
- 3) Initiate studies on the cause of death in animals in which death from hemorrhage and infection have been prevented. This refers to deaths within the first few weeks, as opposed to the much later deaths from nephritis, neoplasia, etc.
- 4) Although nothing of practical value is now available for the specific therapy of acute radiation injury, it is urged that further research be pursued on the fundamental defects produced by ionizing radiation on mammalian systems. Medical experience has shown that rational therapy is only developed when the basic physiologic defects are understood. With this in mind further research is needed. However, it would be unfair to the public to imply that effective therapy can be expected in the near future or indeed that overwhelming doses are ever likely to yield to therapy.

LONG TERM EFFECTS ON THE BLOOD OF A SINGLE EXPOSURE TO IONIZING
RADIATION

The best single source of information on this subject is the Japanese

*One member of the panel reactivated the heparinemia concept of radiation hemorrhage by describing the cessation of bleeding in an irradiated individual with thrombopenia following injection of protamine, an antiheparin agent.

0016997

survivors exposed at Hiroshima and Nagasaki in August, 1945. Of necessity, data on the immediate radiation effects are fragmentary and data on the exposed individuals between the 16th week and the 2nd year are not available. In 1954 a statistical analysis of the hematological data obtained by studies on Hiroshima survivors and a control population, carried out from 1950-1953 (ABCC Program ME SS) showed that there was no evidence for an increase in leukopenia, leukocytosis or anemia in the exposed as compared to the control population. During this period several cases of aplastic anemia were encountered among the Nagasaki survivors. However, it cannot be definitely stated that these cases were due to atomic radiation. Up to late 1953, no cases of aplastic anemia had been found in the Hiroshima survivors. It should be noted that "aplastic" anemia is not an uncommon blood dyscrasia in the Japanese.

Incidence of leukemia:

In contrast, an increased incidence of leukemia among survivors has been clearly established. It has long been known that repeated or single doses or radiation could increase the incidence of leukemia under controlled experimental conditions in laboratory animals. Accordingly, an intensive investigation of the incidence of leukemia in the irradiated survivors in Hiroshima has been carried out by the ABCC. This study is continuing and a statistical analysis, based on the varified cases of leukemia occurring in the Hiroshima survivors, establishes beyond reasonable doubt that the incidence of leukemia was significantly increased in exposed individuals. During 1955-1956, 22 new cases were discovered in Hiroshima. The following table is based on the six year incidence from 1948-1953, not an annual incidence.

0016998

Distance from Hypocenter In Meters	Incidence in Survivors Who Had Acute Symptoms Referable To Radiation
0 - 999	1/50
1,000 - 1,499	1/150
1,500 - 1,999	1/583
2,000 - 2,499	1/950
> 2,500	1/12,000

Particularly germane to the above table is the fact that spontaneous incidence of leukemia in Japan at large during this time was 1:16,000. Data indicate that the incidence of death from leukemia in Japan is about one third that of other countries.

Analysis of the incidence of leukemia by the ABCC teams at Hiroshima reveals certain inconsistencies which are disturbing:

- a) Some of the people who were 2,000 to 2,500 meters from the hypocenter developed unquestionable signs of irradiation sickness: epilation, purpura or oropharyngial lesions, where, according to available published sources of information*, the dose received was between 8 and 35 r gamma radiation.
- b) The incidence of leukemia among these people at 2,000 to 2,500 meters who had irradiation sickness is statistically greater than is the incidence among people who at the same distance, had no irradiation illness. This further indicates that some individuals in this region received significant exposure.

These considerations make the observers suspect that the available information about the amount of irradiation exposure may be incomplete. The members

*The Effects of Atomic Weapons, Page 235, U. S. Government Printing Office, Washington, D. C., 1950.

of the panel find it difficult to evaluate the data because of these inconsistencies and would like to recommend that the known data on exposure of the Hiroshima group be made available to those who were responsible for the leukemia data and its interpretation. Furthermore, without precise knowledge of the doses received, it becomes impossible to establish levels of single exposure at which the incidence of leukemia will not be increased, if in fact a "threshold" exists. Such information is vital to the future welfare of human beings who may be forced to live in contaminated areas. In addition, with the growing belief that there may not be threshold levels for radiation effects, it becomes absolutely essential to obtain the most reliable estimate of the exposure wherever observable effects have been detected.

In Japanese atom bomb survivors the leukemias have been predominantly myeloid. However, Dr. Furth of this panel emphasizes that radiation induced lymphatic leukemias in Europeans have been observed. In this connection it is of interest that lymphatic leukemia is a rarity in Japan suggesting that radiation is prone to induce the type of leukemia that might occur spontaneously.

Hematologic changes preceding development of obvious leukemia:

In the course of studies on Japanese atomic bomb survivors, observations on hematologic changes preceding development of overt chronic myelogenous leukemia were made in a number of cases. In routine surveys, blood studies revealed evidence of a generalized proliferative effort by the bone marrow, many months before obvious evidence of leukemia. These manifestations were the presence of a small per cent of myelocytes and metamyelocytes, and a very striking increase in absolute numbers of basophils, in the peripheral blood. These changes were accompanied by increased numbers of platelets and occasional normoblasts. Beginning in November, 1952, biochemical studies on the separated leukocytes demonstrated that in these early pre-clinical cases of leukemia, the polymorphonuclear

leukocytes contained very little alkaline phosphatase. These alkaline phosphatase values were similar to those reported by Valentine et al. for neutrophiles in well established cases of chronic myelogenous leukemia.

Subsequent studies in chronic myelogenous leukemia, employing histochemical as well as biochemical methods, have shown that 2 per cent or less of segmented polys contain even small amounts of alkaline phosphatase. In contrast, in other conditions with increased polymorphonuclear leukocytes, such as infection and myeloid metaplasia, the alkaline phosphatase values are high and practically all segmented neutrophiles contain large amounts of alkaline phosphatase.

It has been postulated that the leukemic cell is deficient and in the precursor stage of development of leukemia, two populations of cells are present with the leukemic type increasing in number until a typical leukemic blood picture is evident. It has been the experience of some of the panel members that cases of "bone marrow failure" may terminate in leukemia.

Recommendations:

1) Periodic hematologic surveys should be performed on the Marshallese and Americans exposed to fallout radiation in March, 1954. Careful study for cytological changes mentioned above, especially basophilcytosis and immature leukocytes, and routine histochemical studies for alkaline phosphatase (using peripheral blood smears and either Gomori's Cobalt technique or the azo dye method) should be carried out. In suspicious cases, biochemical determinations for alkaline phosphatase on separated leukocytes should be done. In view of the long "latent period", studies for many years after exposure if not for life, are essential.

2) The cytologic and histochemical-biochemical studies might well be employed in surveys of radiologists and other chronically exposed groups.

3) The present concepts of leukemoid reactions and myeloid metaplasia, and the relationship of these disorders to leukemia are obscure. Further studies

on the enzyme and metabolic activities of leukocytes in these disorders may lead to a better understanding of radiation effects on myeloid cells and the role of irradiation in leukemogenesis.

4) It is generally recognized that routine hematologic studies of potentially exposed individuals are wasteful and unproductive. However, studies on select groups by routine and newer techniques are highly desirable, e.g., radiologists, physicist.

5) It was the consensus that it would be desirable to know the incidence of leukemia in WW I soldiers who were exposed significantly to mustard gas.

6) Pediatricians have fluoroscoped newborn babies, and a considerable dose of whole body radiation may have been received. A long term follow-up on these exposed children is needed.

EFFECTS OF REPEATED LOW LEVEL EXPOSURE

Increasing numbers of human beings are exposed to repeated doses of radiation frequently at very low dose levels. Thus in industry and in AEC installations, in radiologists and radiological technicians, public health surveys and particularly those using fluoroscopy, and in repeated roentgenograms in medical and dental diagnosis, large populations are exposed to radiation at levels well in excess of background.

There are several studies on radiologists and radiological technicians, indicating that statistically the blood counts of such individuals may be altered. Similarly from the vast number of counts on individuals exposed to low level radiations at AEC installations, there is evidence that the so-called maximum permissible dose may result in statistical alteration in the blood count. The possible significance of these small changes is not clear. The slight decrease in neutrophils or lymphocytes count has little or no significance in itself. It would appear that its significance in relation to the later development of

leukemia or other disease that shortens life span should be investigated. Recommendations to this effect are given below. Data are available on the hematological effects of exposure to radiation up to 10 times background. The drinking water of prisoners at Joliet prison in Illinois contains 20 times the radium content of the drinking water of neighboring communities. Extensive study has failed to detect differences ascribable to the increased radium content of the drinking water. In the course of radiotherapy for relatively benign conditions, it seems clear that serious late effects can result from a single exposure or a series of exposures to x- or isotopic radiations. Thus thyroid cancer has resulted in children given x-radiation for thymic enlargement. Similarly, leukemia has been reported in individuals receiving repeated x-radiation therapy for spondylitis, and in patients receiving repeated I-131 for thyroid cancer.

Recommendations:

- 1) Since there are geographical locations in which the known radiation intensities vary considerably, it is felt that the incidence of leukemia should be established in:
 - a. Island populations (low background except Baltic Islands)
 - b. Andes (high background)
 - c. Prison and civil population in Joliet (radium content in water higher than normal)

- 2) It was the consensus that a ceaseless search should be continuously made for other harmful agents in the atmosphere and our modern diet. It is genuinely felt that preoccupation with radiation may obscure other equally hazardous factors in man's environment.

USEFULNESS OF HEMATOLOGIC STUDIES IN CONTROL OF RADIATION INJURY

A large effort at great expense was made by the AEC during the development of atomic energy to determine if routine hematologic studies would detect low level exposure to radiation. It was the consensus that frequent routine

0017003

studies on personnel exposed to low levels of radiation have a limited value that does not justify the expense. Physical control of the environment by radiation monitoring is an effective means of maintaining a safe environment, and nothing is gained by widespread hematologic studies on personnel. However, it would not be wise to dispense completely with hematologic studies since it is important to have pre-exposure levels in the individuals who may be exposed to radiation such as with those accidentally exposed to fallout radiation. Had base line studies been available relative depression and recovery time as a function of dose could have been more precisely determined. Accordingly it is believed that periodic, perhaps annual hematologic studies should continue on limited groups of individuals who run a greater risk of accidental over-exposure. Certainly, all individuals who have been exposed so accidentally at dose levels of 25 r or more of essentially whole body radiation (single exposure) should have periodic systematic studies to determine the degree of hematologic depression and the recovery rate. These individuals should remain away from an environment where further overexposure is likely until the dose received has been amortized at the rate of 0.3 r/week. The latter is suggested because clinical radiation therapy experience indicates that individuals who have been exposed previously as a result of local therapy or whole body exposure show greater hematologic depression following further whole body radiation. A more fruitful field of hematologic study in relation to chronic radiation exposure would appear to be the periodic study of phosphatase content of the neutrophils and number of basophils, on limited populations, who are known to be exposed chronically, such as radiologists, urologists, orthopedists, x-ray technicians, and dentists.

CONCLUSIONS

At the commencement of the deliberations there was some question in the minds of the panel as to the objectives and the reasons for the establishment of

the panel. However, in the course of the discussions it became apparent that in addition to the confusion in the minds of the public there also exists some large gaps in knowledge essential for the understanding and quantification of radiation hazards in the world of today let alone the world of the future. The immediate effects of direct exposure to high intensity radiation are well documented and the relation of dose to effect is known with some degree of confidence, even though certain hiatuses exist that are listed in the general discussion and recommendations. In the realm of chronic exposure it was recognized that the unavoidable background level of radiation was known to vary with seasons of the year, geographic location, and altitude above sea level. However, world-wide levels do not seem to be known with sufficient accuracy to determine when a rise in atmospheric level of radiation is definitely occurring. Since there is little quantitative information on the relation of dose to effect under conditions where harmful effects were observed it becomes vital to ascertain natural levels of radioactivity and to try to establish the level of atmospheric radioactivity at which detectible chronic effects might conceivably occur. However, with all of the recommendations contained in this report, it is believed that a "crash-type" research program to obtain needed information is not indicated.

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