University of Pittsburgh

GRADUATE SCHOOL OF PUBLIC HEALTH
Department of Radiation Health
Office of the Chairman

November 23, 1983

Ms. Jenny M. Johansen
Radiation Specialist
U.S. Nuclear Regulatory
Commission Region I
631 Park Avenue
King of Prussia, PA 19406

Dear Ms. Johansen:

In accordance with your recent request, I have reviewed your draft report #030-03053/83-01 and its appendices. On the basis of the data provided in the report there is no convincing evidence that this individual's illness and death could be ascribed to the manifestations of the acute radiation syndrome elicited by an acute whole body radiation exposure of 300-600 rads.

Sincerely yours,

Niel Wald, M.D.

NW/rcg

8402270435 840

RC510 SCAIFE HALL PITTSBURGH PA 15261

NOV 2 9 1983

Cecil Textbook of Medicine, Eds. J.B. Wyngaarden and L.H. Smith, Jr., Philadelphia: W.B. Saunders, 1982, pp. 2228-2234.

520. RADIATION INJURY

Nirl Wald

DEFINITION Radiation energy from sources of ionizing radiation produces a variety of clinical manifestations, depending on the magnitude and duration of radiation exposure and on the size and function(s) of the body area irradiated. The source of the radiation may be external, such as an x-ray machine, or internal from a radioactive isotope inhaled, ingested, injected, or absorbed through the skin or a wound.

Clinical manifestations of radiation energy absorption may be acute, with or without late sequelae, or they may be delayed and chronic. The acute manifestations include the acute

radiation syndrome which typically follows whole body radiation exposure; local tissue or organ injury with little or no systemic manifestations after partial body exposure; and growth and developmental disturbances after exposure of the fetus. The clinical effects of intermittent or constant low level radiation exposure may present as chronic progressive impairment of certain tissues or organs, or solely as the relatively late appearance of one or another of the long-term sequelae of radiation exposure, such as cancer and leukemia. In addition, any exposure of the gonads may produce germ cell changes or mutations with sequelae in subsequent progeny.

Tissue injury may be produced by cellular interactions with radiations of any part of the electromagnetic spectrum, including the output of the sun, lasers, or microwave equipment. Some of these, such as x-rays, gamma rays, and neutrons, are capable of penetration, and can produce internal tissue damage. Other radiations, such as alpha rays and low energy beta rays, have a very limited range in tissue and are injurious only when given off within the body by incorporated radioactive isotopes. The radiations *emitted* by ionizing radiation sources are quantitated in roentgens (R) of exposure, whereas the radiation energy *absorbed* by tissues is quantitated in rads. The same absorbed dose delivered at different rates will produce very different effects.

ETIOLOGY. Typical radiation injury is caused by exposure to *ionizing radiations*. Since the recognition of man-made radiation by Roentgen in 1895 and of natural radioactivity by Becquerel the following year, occupational and medical exposures have been the most common sources of radiation injury, although the use of nuclear weapons in World War II produced a major addition in clinical cases. Injury from external sources occurred among the early x-ray workers, the employees of the nuclear weapons project, and subsequent nuclear energy research and industrial organizations. In addition, unavoidable injury has been produced in some radiation therapy patients through exposure of normal tissues adjacent to the lesion under treatment.

Internal radionuclide exposure resulted in injury to employees of the radium watch dial painting industry in the 1920's. More recently, fallout from nuclear weapon tests has produced some internal radionuclide deposition in the general public. In the medical patient population, the uses of radium as a therapeutic agent and thorium as a diagnostic x-ray contrast medium have resulted in clinical sequelae decades after administration. Also, there have been instances of diagnostic and therapeutic radioisotope misadministration producing acute injury and occasionally causing death.

INCIDENCE AND PREVALENCE. The frequency with which radiation injury occurs is closely related to the availability of sources for radiation exposure and the understanding and care with which they are maintained and used. The largest potential source of radiation casualties is the military use of *nuclear weapons*. The Joint Commission for the Investigation of the Effects of the Atomic Bomb in Japan estimated the incidence of radiation injury in Hiroshima to be about 40 per cent and in Nagasaki about 50 per cent in the injured survivors. In Hiroshima about 30 per cent of the deaths in those who survived longer than one day were ascribed to radiation injury either alone or combined with blast and/or burn damage. In the survivor study population of 82,244, 144 cases of leukemia developed between 1950 and 1974. It is probable that modern nuclear weapon effects would exceed these results. In nuclear weapon tests, some 300 people have inadvertently been exposed to local high levels of radioactive fallout, with resultant clinical manifestations in about 25 per cent.

Early peacetime uses of radioactivity led to an initial high incidence of injury. Within seven years of the demonstration of x-irradiation by Roentgen in 1895, some 200 cases of x-ray injury had been reported. After recognition of the hazard, radiation protection standards were developed internationally. There has been a marked reduction in this type of injury, although hand injuries will occur occasionally in industrial radiographers and users of x-ray analytic equipment.

The discovery of natural radioactivity by Becquerel in 1896 led to the purification of radium by the Curies in 1911 and its use in medicine and industry. About 5000 watch dial painters, industrial chemists, and medical patients were involved. In 2500 of these, in whom medical information was compiled by A. M. Brues at Argonne National Laboratory through 1975, there were 408 malignant tumors, with the excess over the expected frequency involving bone and the air cavities of the head. The development of man-made radioactive material during and after World War II led to a nuclear industry population of several hundred thousand workers, but only 138 cases of clinical radiation injury had developed by 1979. Although data collection concerning medical misadministrations of radioactive isotopes designed for diagnostic and therapeutic purposes has not been systematic, several deaths and a number of injuries are known to have occurred in the very large American patient population, estimated at over 8 million annually, receiving these materials.

EPIDEMIOLOGY. The manifestations of acute or of late radiation injury are not produced solely by irradiation. It is therefore essential to utilize epidemiologic methodology in order to establish the relationship of the etiologic agent to the clinical symptomatology. Two most helpful features have been the temporal relationship of the exposure to the development of clinical effects and the quantitative dose-response relationship.

The etiologic role of radiation in the clinical syndrome of *acute* radiation injury has been shown in epidemiologic studies of the Japanese atomic bomb survivors, the Marshall Islanders and Japanese fishermen exposed to fallout from a nuclear weapon test, several groups of radiation therapy patients, and the workers involved in various industrial radiation accidents. Epidemiologic studies relating *late* radiation effects such as neoplastic diseases and life-shortening to radiation exposure have dealt with radiologists and other physicians, the Japanese population under long-term follow-up by the Atomic Bomb Casualty Commission and its successor since 1975, the Radiation Effects Research Foundation, the radium watch dial painters, therapeutically x-irradiated patients (particularly those receiving thymic irradiation in infancy), patients receiving radioactive iodine therapy, and nuclear industry employees.

PATHOGENESIS. The basic pathology begins with the interaction of the radiation with tissue within the first second of exposure. The radiation energy in photons or particles penetrating the protoplasm may interact at the atomic level to produce ion pairs. These ions combine radiochemically with cell water, producing free radicals such as H and OH, which further react to produce such forms as H_2O_2 and HO_2. These, in turn, may interact with critical molecules of the cell protoplasm such as nucleic acids or enzymes. If the dose is high and interactions are numerous, the cell may be killed directly by the radiation. At lower doses, the ability of the cell to divide may be impaired permanently or temporarily. If the DNA is involved, sublethal damage to this molecule may result in reproduction of the alteration (i.e., mutation) in daughter and descendant cells. Direct cell killing begins with exposures of one or more thousands of rads, in general, although some cells such as lymphocytes and spermatogonia are affected at much lower doses. Those cells which are rapidly dividing and differentiating are most vulnerable. Mitotic arrest occurs after several hundreds of rads and is characterized by continuing function of the existing cells but no new divisions. The continuing synthesis of proteins and enzymes, despite an irreversibly impaired mitotic apparatus, leads to "giant cells" which die after several weeks because their excessive size interferes with nutrition and metabolism. At doses of about 100 rads or more, mitotic delay results from temporary impairment of the mitotic mechanism. At still lower doses transient chromoso-

final "stickiness" is seen, presumably caused by denaturation of the DNA-histone molecules. Also, beginning at exposures as low as a few rads, are chromosome aberrations, i.e., breaks, deletions, gaps, and abnormal forms such as ring and dicentric chromosomes.

The effects of these cellular abnormalities depend on the rate of proliferation of new cells required. In high turnover tissues such as the blood-forming tissue and the gastrointestinal tract, the relatively short life span of the predominant cells leads to rapid depletion before the onset of mitotic recovery and new cell production. In the period of mitotic inhibition of the blood-forming tissue, for example, the consequent depletion of mature cells results in increased probability of infection and hemorrhage. The resultant pathologic manifestations are nonspecific, although the inflammatory changes accompanying infection are deficient in polymorphonuclear cells.

In tissues which have little or no continuous proliferation, such as the liver or brain, this type of radiation injury is not apparent; however, functional impairment may be detected by appropriate means. In very slow turnover tissues, such as the lens of the eye or the thyroid gland, the manifestations of acute radiation effects may require months to years before becoming evident. Also, the small arterioles damaged by local radiation injury may show a compensatory increase in cell production, leading to endothelial thickening, obliterative endarteritis, and extensive fibrosis over a prolonged period of time.

Chromosomal abnormalities produced in injured cells may be reproduced and perpetuated for decades. A long-lived component of the lymphoid cells may even carry the original radiation damage for many years before dividing. Clones of cells with the same specific chromosome abnormality may develop over a period of years as well.

CLINICAL MANIFESTATIONS. Clinical manifestations of radiation injury can be subdivided into three major forms: the acute radiation syndrome, acute local radiation injury, and delayed effects. External penetrating irradiation, as well as external and internal radionuclide contamination and local traumatic injury with radionuclide contamination, may produce these manifestations.

Acute Radiation Syndrome. This syndrome is seen typically after exposure of most or all of the body to external sources of penetrating ionizing radiation, although high doses of ^{32}P, ^{131}I, and ^{198}Au have also evoked it. It appears in three major forms, in ascending severity of injury. These are the hematologic, the gastrointestinal, and the central nervous system–cardiovascular forms. Four discernible clinical stages can be recognized. These are the initial or prodromal stage which subsides into a latent stage, followed by a stage of manifest or overt illness, and a recovery stage. The duration of each stage is inversely related to the severity of injury.

Typical manifestations of the *hematologic form* are seen after an exposure in the midlethal range (about 300 rads without treatment). Prodromal anorexia, nausea, and possibly vomiting may commence within several hours and generally subside within 48 hours. Transient waves of skin erythema and conjunctivitis may be observed over the same period or longer. The patient may be asymptomatic after the prodromal stage for one to three weeks. Then the increasing inadequacy of the body's defenses against infection and hemorrhage becomes manifest, with development of fever, oropharyngeal lesions, abscesses, petechiae, purpura, and bleeding from body orifices. Other findings include scalp pain and epilation in the third postexposure week, and recurrent anorexia and nausea accompanied by weakness, fatigue, weight loss, and emaciation. Gradual recovery ensues, beginning about the fifth to sixth week after exposure and possibly requiring several months.

The earliest laboratory finding is lymphopenia, reaching absolute lymphocyte levels below 1000 per cubic millimeter within the first 48 postexposure hours. The reticulocytes may disappear in the same time period. A gradual fall in granulocyte counts begins during the first two weeks, reaches a plateau, or even shows an abortive rise, followed by a steep fall to a low point at about 30 days postexposure. The platelet count nadir occurs at the same time, after a more continuous fall. If the individual survives, an abrupt increase in all the cell lines mentioned, except the lymphocytes, will occur within the next week and the counts will rapidly reach normal levels. An initial increase in granulocyte count in the first 24 hours may occur on the basis of a nonspecific "alarm reaction," and should not mislead one to exclude radiation injury on this basis. Blood biochemical analyses may show nonspecific indicators of major cell and tissue damage such as creatinuria, increased excretion of DNA breakdown products such as deoxycytidine, beta-aminoisobutyric acid, and various other amino acids. Serum enzyme values such as LDH, SGOT, and SGPT may be elevated, and an early transient slight hyperbilirubinemia observed. Within 24 hours chromosome breakage and abnormal forms can be seen in peripheral blood cytogenetic preparations, the frequency being related to the magnitude of the radiation exposure.

The *gastrointestinal form* is associated with anorexia, nausea, vomiting, and diarrhea within the first few hours after exposure. These may be of sufficient severity to require active treatment but usually subside within 48 hours. A latent period follows which may last only a few days to a week before there is a major recurrence of all the gastrointestinal symptoms as well as those of infection and hemorrhage as described above. These patients generally die with a fulminating enterocolitis before the full appearance of epilation and other slower developing radiation sequelae.

Laboratory abnormalities in the gastrointestinal form of radiation injury are similar to those of the hematologic form but occur more promptly and with greater magnitude. In addition, the hematocrit may be increased as a result of hemoconcentration caused by fluid loss, which, together with hypoglycemia and electrolyte imbalance, results from the loss of a functional intestinal mucosal lining.

In the *central nervous system and cardiovascular form*, immediate nausea, projectile vomiting, and explosive diarrhea are characteristic. These may be accompanied by disorientation, hyperesthesia, ataxia, sweating, prostration, and shock. There may be some improvement after several hours, but alternations develop between central nervous system hyperexcitability, including convulsions, and CNS depression, such as somnolence and coma. This is accompanied by hypotension which becomes irreversible, as does oliguria, leading to a fatal outcome in 24 to 48 hours.

Laboratory observations in the central nervous system and cardiovascular form of acute radiation injury show marked telescoping of the previously described injury syndromes with abnormalities occurring sooner and with greater severity. Complete lymphopenia and an initial granulocyte level as high as 40,000 may be present within the next few hours. Prompt chromosome examination may show marked increase in aberrations, but as the circulating lymphocytes disappear, it may become difficult to find dividing cells. The biochemical evidences of tissue damage are much more striking in this form of the syndrome. In addition, azotemia secondary to hypotension becomes prominent.

Local Radiation Injury. Localized radiation injury may occur with acute and/or chronic clinical manifestations, depending on the total dose and dose rate at which exposure takes place.

The early changes result in three major clinical findings: erythema, epilation, and transepidermal injury. *Erythema*, erythema, comparable to a mild sunburn or a thermal burn of the first degree may appear on exposure to more than 200 to 300 rads. A transient first wave may be present within hours after exposure, associated with hyperesthesia, burning, or itching. The major redness appears two or three weeks later, the

interval depending on the dose. In the lower dose range no further changes other than tanning may occur, and medical care is not necessary. A counterpart to this reaction has been described in the conjunctiva and in the anterior chamber of the eye, with inflammatory changes observed promptly after exposure.

Epilation, or loss of hair, may occur after exposure to any form of radiation, beginning with exposures to the skin of about 300 rads. It generally does not become apparent until the third week after exposure. Associated skin or scalp tenderness may occur one or two days preceding the actual hair loss. With doses greater than about 500 rads, epilation may be complete. If the exposure is much greater than 600 rads, hair may not regrow.

Transepidermal injury (dry or wet dermatitis) is comparable to a thermal second-degree burn with erythema, blistering, and pain. Confluent bullae may develop in about one and one half to three weeks, depending on the dose (usually exceeding 1000 rads). These may rupture, leaving open, weeping lesions vulnerable to infection.

With higher doses, probably on the order of 5000 rads, a more serious version of transepidermal injury occurs, in which the lesion resembles a third-degree burn. Pain occurs promptly and is intense. The raw areas may be very slow in healing, or may not heal until surgical resection and skin grafting are performed. Epilation is permanent.

Still higher doses may produce immediate tissue damage to structures below the skin. Such injuries, which have occurred in the abdominal wall, male genitalia, and extremities, are irreversible, requiring surgical excision and further reconstructive management.

Delayed Effects. Delayed effects of radiation exposure are of two varieties: those finally appearing in organs whose cells received the radiation exposure and are relatively slow in responding, and those late effects occurring in organs and tissues in which descendent cells ultimately express the initial radiation injury after a latent period which may be many years in duration. The first type of delayed effect can be seen in the male gonad, for example. Doses as low as 15 rads will produce *impairment in fertility* owing to moderate oligospermia beginning about 50 days after the exposure. Azoospermia will occur with doses of more than 200 to 300 rads for a period of roughly one to two years. Doses of 500 to 600 rads may produce permanent sterility in male or female survivors.

The lens of the eye is another late-responding tissue, with opacities appearing in the posterior subcapsular region in months to several years after exposures of about 200 rads or more. *Cataracts* of the posterior lens may develop in the majority of patients who receive more than 600 rads. *Hypothyroidism* may gradually develop several years after exposure of several hundred rads. *Skin changes* constitute another late response to either acute injury or repeated low level radiation exposure. There may be loss of the detailed finger-ridge pattern and hair, abnormalities of the fingernails, and dryness of the skin. Localized hyperkeratosis may be seen, as well as breakdown of previously healed but atrophic skin, and, ultimately, neoplastic skin changes may develop in such areas.

In the *fetus* the clinical manifestations will depend largely on its age and the magnitude of exposure. If the exposure takes place in the first one to two weeks, resorption of the conceptus is probable. Between the second and sixth weeks, the effect will be on the particular organs under development at the time. Further along in gestation, there will be more subtle generalized effects ultimately expressed as deficits in growth and development, including microcephaly and mental retardation.

The most common *late effects* of radiation exposure are *neoplastic diseases*. The earliest to appear are the acute leukemias and chronic granulocytic leukemia, with a peak incidence about eight to thirteen years after the radiation exposure. Chronic lymphocytic leukemia is not increased by radiation exposure. Other neoplasms whose induction appears significantly increased by radiation exposure include cancer of the thyroid and salivary glands, lung, bone, and female breast tissues. Internally deposited radionuclides have been associated particularly with malignant neoplasms of bone and reticuloendothelial tissues such as liver, spleen, and lymph nodes. Radium deposition has involved the mastoid bones and those surrounding the paranasal sinuses in particular, whereas internally administered thorium dioxide has produced an increase of hemangiosarcomas of the liver. In addition, a generalized increase in incidence of all forms of cancer has been documented in the Japanese atomic bomb survivors. *Shortening of life expectancy* through somewhat earlier death from all causes has been demonstrated in the radiologist population but not yet in the Japanese A-bomb survivors.

Diagnosis. Acute Radiation Syndrome. The manifestations of acute radiation injury are not unique to this causative agent. Therefore the diagnosis rests on the history and the evolving clinical pattern defined by time of onset and duration of the clinical signs, symptoms, and laboratory abnormalities, particularly the hematologic changes.

In the absence of an adequate history of radiation exposure, the diagnosis may be elusive. The various manifestations may suggest a wide range of conditions. Prodromes suggest psychoneurosis, food poisoning, or gastrointestinal viral infection; symptoms in the period of manifest illness may mimic aplastic anemia, leukemia, infectious gastroenteritis, typhoid fever, and even mumps (for radiation parotitis). When a radiation exposure history is elicited, hematologic and cytogenetic examinations may be used as well as physical dosimetry data obtained by personnel monitoring equipment, if any, and by reconstruction of the exposure situation, in order to obtain confirmatory and quantitative information concerning the potential severity of the injury. However, the evolving clinical pattern is the final diagnostic criterion for the recognition and management of this form of injury.

Local Injury. Local radiation injury, particularly as it appears on the upper extremities, is often confused with thermal and chemical burns. Differentiating features are absence of waves of erythema in the latter as well as the more severe prolonged pain and slower healing associated with radiation. Recurrent tissue breakdown after healing is also suggestive of radiation injury as opposed to the other possibilities.

Delayed Effects. No clinical characteristics of the late effects of radiation exposure are unique to this etiologic agent.

Radionuclide Contamination. Radionuclides deposited on the surface of the skin may be absorbed, inhaled, or ingested into the body where they may act to produce delayed effects. In order to prevent such sequelae, the recognition of their presence is essential even though no immediate clinical manifestations are present. Such diagnostic procedures must involve close collaboration between the physician and the health physicist, the professional trained to recognize and quantitate radiation exposure in order to prevent deleterious effects of radiation. Radioactivity surveys of the suspected individual with appropriate radiation detection equipment should be carried out. It is most important to collect all urinary and fecal excretions in separate containers until sufficient data of the nature and magnitude of contamination are obtained. Some radionuclides such as radon may be sought in breath samples. An early postexposure blood sample should also be collected and preserved for radionuclide analysis. Finally, it may be necessary to carry out chest or whole body low-level radiation counting in an appropriate facility, i.e., a so-called "whole body counter."

If a traumatic wound is present, radionuclide contamination may be sought by measuring radioactivity of swabs used in cleaning the wound as well as by surveying over the surface with appropriate detectors. If the wound is the sole contaminated area, excreta samples will show whether the contaminant has been absorbed into the body and therefore is suffi-

quately soluble for circulation and translocation to sites remote from the wound.

TREATMENT. *Acute Radiation Syndrome.* The treatment of acute radiation syndrome is based on an understanding of its pathophysiology. The prodromal symptoms in the acute radiation syndrome are self-limited, but sedatives and antiemetics may be used if needed. Throughout the syndrome it is important to reduce anxiety by keeping the patient informed about the nature of his injury, the expected transient health impairment, and its anticipated duration and treatment. The prolonged weakness associated with this syndrome even during convalescence may be in some measure secondary to the prolonged anxiety and fear of the unknown often associated with radiation injury.

In the *hematologic form*, the inhibition of mitosis responsible for the overt illness is self-limited. Thus management is directed toward maintenance of the patient through the period in which his defenses against infection and hemorrhage are deficient. This is best achieved by conservative means. The threat of exogenous bacterial and viral infection is reduced by strict reverse isolation of the patient with maintenance of a clean environment by use of a laminar air flow or "life-island" methods. Attendant personnel must be screened for potential pathogens and treated prophylactically if necessary.

Prophylactic oral antimicrobial drugs to clear pathogenic bacterial and fungal organisms from the gastrointestinal tract have been used when the total granulocyte level falls below 1000 per cubic millimeter. Various blood elements may be given to replace deficiencies when needed. Donors should be limited in number and tissue typed to minimize systemic reactions to and inefficacy of transfused cells. Red cells are needed only if significant bleeding has occurred. Fresh platelets should be available for use if significant hemorrhage develops. Their use has been advocated even in the absence of bleeding when the platelet count falls below 10,000 per cubic millimeter. If available in concentrated form, normal granulocytes may be administered in the face of overt infection during the granulocytopenic phase. If not available, in the presence of a clearly life-threatening infection the use of the much greater numbers of granulocytes of patients with chronic granulocytic leukemia has been suggested, because they are capable of phagocytosis. On recovery, it is assumed that the patient's immune system will rid the body of such donor cells.

In the situation in which both biologic and dosimetric indicators suggest the high probability of a fatal outcome, bone marrow transplantation may be warranted. The transplantation procedures developed by Thomas et al. for managing leukemic patients after therapeutic whole body irradiation are potentially helpful in accidental radiation injury patients also. Recent improved results with leukemic patients treated in remission and in the use of unrelated donors may increase the applicability of this approach in high radiation exposure cases. Because transplanted marrow requires about two weeks to correct the deficit in circulating blood cells, such a decision should not be delayed much beyond the first postexposure week.

Management of the *gastrointestinal form* of acute radiation syndrome has not been successful thus far in the few human occurrences. Animal studies by Bond and Cronkite suggest that the vigorous and early utilization of adequate anti-infection agents, blood components, nutrients, electrolytes, and fluid may influence mortality favorably.

In the few human instances of the *central nervous system–cardiovascular form*, the progressive hypotension has not been improved by the administration of pressor agents, and the fluid administration involved has augmented the congestive heart failure which has ensued.

Local Radiation Injury. The treatment of local radiation injury is generally similar to that of thermal burns of the same severity. This includes the maintenance of asepsis, eventual removal of devitalized tissue to the degree necessary, and the use of skin grafting to cover nonhealing ulcerations. An additional feature in management is very careful and prolonged observation for possible early neoplastic changes of the skin.

Delayed Effects. Clinical management of the delayed effects of radiation exposure does not differ in any way from the management of similar pathologic conditions not caused by radiation.

Radionuclide Contamination. In the event of an accident in which radionuclide contamination is likely, only urgent first aid should be given and the patient evacuated from the site. Contaminated skin and wounds should be washed promptly, and all excreta collected.

Useful preparations for skin decontamination include soap and water, surgical and laundry detergents, and oxidizing agents. These should be accompanied by brushing and rinsing, with care taken not to abrade the skin.

Contamination of the eyes, nose, and mouth is treated initially with copious water washing as soon as possible. Isotonic irrigants may be substituted as soon as available.

For definitive wound care, the usual surgical principles apply, with modifications only in the aseptic procedures and debridement in order to avoid introduction of skin contamination into the wound. Prior to surgical treatment it may also be desirable to give intravenous diethylenetriaminepentaacetic acid (DTPA), a chelating agent available from the U.S. Department of Energy for investigational use, to minimize the retention of any contaminant which may get into circulation during surgery.

If radioactivity measurements of excreta and of the whole body suggest a residual body burden of a larger quantity than seems acceptable on the basis of medical and health physics judgment, various treatments may be used to minimize the absorption and enhance the excretion of the radionuclide.

To minimize respiratory absorption, the use of irritants, expectorants, and pulmonary lavage is under current investigation. Inhalation of DTPA aerosol mist is also currently being tested for transuranic isotope contamination.

To minimize gastrointestinal absorption, the simplest measure is to accelerate excretion with a mild laxative. For strontium-90, sodium alginate and aluminum hydroxide gel have been used orally to prevent uptake from the gut. For cesium-137, Prussian blue (ferric ferrocyanide) does the same. To promote excretion of nuclides already within the body and to reduce deposition in target organs, such as bone, a variety of agents are available. For plutonium, americium, yttrium, lanthanum, and fission products, intravenously administered chelating agents are useful, DTPA being the most effective. For strontium, the combination of high calcium intake and acidification of the blood with ammonium chloride has effectively reduced bone absorption.

In the event of potential contamination of the public by deposition of radionuclides from nuclear industrial or weapons accidents, ameliorative measures may achieve a reduction of radiation exposure and health impairment. The simplest is to stay indoors in the building area most shielded from the outside, usually the basement, and to minimize outside air exchange, as well as intake of air-exposed food and water. Temporary evacuation from the affected geographic area may be appropriate, especially when preplanned and in the light of information concerning the nature, location, and direction of travel of the radioactivity. If radioiodine, a common fission product, is present, reduction of thyroid uptake has been recommended for consideration when the anticipated total thyroid absorbed dose exceeds 10 rads. This can be accomplished by administration of potassium iodide, 130 mg daily (65 mg. for those under one year of age), during the emergency period, probably no longer than ten days.

PROGNOSIS. Acute Radiation Syndrome. The estimated short-term radiation exposure which would be lethal for 50 per cent of an untreated human population in 60 days ($LD_{50/60}$)

is about 300 rads mean midline absorbed dose. This exposure would be expected to produce the hematologic form of the acute radiation syndrome, with half the exposed population dying within 60 days. However, an accidentally irradiated worker survived an estimated 600 rads absorbed whole body dose, with postexposure treatment, including isogeneic marrow transplantation, by Wald, Thomas, and coworkers, despite tissue damage severe enough to necessitate subsequent amputation of all four extremities. Also, Thomas et al. and others have used pre- and postexposure treatment, including isogeneic marrow, in over 100 acutely ill leukemic patients receiving 1000 rads of whole body exposure with about 20 per cent early post-treatment fatalities. Recent experience with patients treated while in leukemic remission suggests that such fatalities are even less frequent.

Thus it appears that successful management of the hematologic form of acute radiation injury is possible under good therapeutic circumstances. Wald and Watson have suggested that active supportive treatment can raise the LD_{50} to over 500 rads and heroic therapy, such as bone marrow transplantation, to over 1000 rads in accidentally exposed individuals. Clearly, such prognostic optimism would not apply to the large-scale population exposure situation such as occurred in Hiroshima and Nagasaki. Furthermore, even the best clinical management has not yet succeeded in allowing the survival of those few individuals who accidentally have received exposures resulting in major gastrointestinal or central nervous system-cardiovascular damage.

Local Radiation Injury. The outlook for good recovery from local radiation injury depends in part on the adequacy of management of the acute changes, including the removal of devitalized tissue and the prevention of secondary infection. However, the main determinant of the ultimate outcome will be the severity of injury to the underlying blood vessels.

Delayed Effects. The likelihood of a radiation-exposed individual's developing a late effect of the exposure is increased in some relation to the magnitude of the exposure. Since most radiation exposure above the natural background is due to human activities and therefore presumably controllable, increasing recent effort has been given to quantitative risk assessment for radiation carcinogenesis to facilitate better benefit-risk judgments. In 1977, both the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and the International Commission on Radiological Protection (ICRP) reviewed human epidemiologic data and published risk approximations for radiation-induced cancer based on human epidemiologic data. In 1980, the National Academy of Sciences Committee on the Biological Effects of Ionizing Radiations (BEIR) published a revision of its similar effort of 1972.

Although the risk estimates cannot be determined with great accuracy, it is possible, in some instances in which mutually consistent epidemiologic data are obtainable from several different sources, to estimate the overall radiation-related cancer risk or to classify different tissues into groups with different degrees of sensitivity to induction of malignancies by radiation. It is important to note that most of the information is derived from actual exposures of 100 rads or more of x- or gamma radiation at high dose rates, and then extrapolated to exposures of a few rads or less delivered at very low dose rates, such as received by the occupationally exposed radiation worker population. Thus, these risk estimates are greatly influenced by the extrapolation model used. For example, the change from a linear model (1972 BEIR estimates) to a linear-quadratic model considered more appropriate (1980 BEIR estimates) lowered the estimated range of radiation-related cancer deaths per million persons per rad (in excess of the normally expected 164,000 cancer deaths from all causes) from about 117 to 621, to 77 to 226. The latter range agrees well with that of the 1977 UNSCEAR report.

The approximate risk of induction of radiation cancer in various tissues estimated by UNSCEAR can be summarized in terms of the number of cases expected per million persons so exposed per rad of absorbed radiation exposure. In descending order of sensitivity, with the approximate number of cases per million per rad given in parentheses following each tissue, they include thyroid (100); female breast (100); lung (25 to 50); leukemia (20 to 50); stomach, liver, large intestine, brain, and salivary glands (10 to 15); and bone, esophagus, small intestine, urinary bladder, pancreas, rectum, lymphatic tissues, and mucosa of cranial sinuses (2 to 5). These estimates are very broad generalizations, and for each tissue there are differing effects of such factors as sex and age at exposure, in addition to the kind of radiation, dose, and dose rate. For example, the pediatric population is more sensitive to thyroid cancer induction, female breast cancer is induced primarily by exposure during the early reproductive period, and lung cancer does not appear to be increased in males exposed while under 35 years of age. Also, the induction of cancer in the fetus is distinctly elevated, estimated roughly as 50 fatal cases per million per rad per year for the first decade.

The duration of the period at risk also varies with different tissues. The mean interval between exposure and leukemia development is about ten years, for example, whereas the other malignancies typically appear in an exposed population with a mean of 25 years of latency. In a population exposure, the earlier appearing leukemia may serve as an indicator for the eventual total of all fatal malignancies, which ultimately may occur in four to six times as many individuals as developed leukemia.

The prognosis for the various delayed effects of radiation exposure is similar to that of the same pathology in the absence of such exposure. For this reason many of the radiation-induced cancers would be expected to respond to treatment. The ICRP therefore derived maximum risk rates for fatalities from radiation-induced cancers. In descending order of risk, with approximate numbers of fatal cases per million exposed per rad in parentheses, they are female breast (50), leukemia (20), lung (20), thyroid (5), bone (5), and all other organs together (50).

Prevention. Since the foregoing discussion has indicated that there are no specific methods of reversing the course of events initiated by radiation exposure, the best measure against radiation injury is prevention. The largest potential source of radiation exposure to the general population is the nuclear weapon. It is therefore essential that all measures be taken to minimize the possibility of any human population receiving such an exposure again. Another potential source of population exposure, the widespread and increasing utilization of nuclear energy as a source of electric power generation, has been controlled successfully thus far. Despite the great amount of anxiety evoked by the 1979 accident at the Three Mile Island nuclear power plant in Pennsylvania, the resultant public radiation exposure was well below any biologic detection limit.

The largest actual source of population exposure consists of users of radiation in the healing arts. Such use of ionizing radiation has produced untold benefit to the same population. Nevertheless, it is incumbent on the users of medical radiation sources to minimize the exposures needed to obtain the necessary diagnostic information. This requires not only optimal operation of existing equipment by current techniques but also a continuing research and development effort to improve the efficiency of such equipment to allow reduction of exposure while obtaining the necessary biomedical information. Adequate specialized education of all users of radiation sources in the philosophy and methods of radiation protection is another factor in the preventive approach to radiation injury.

Basic Radiation Protection Criteria. NCRP Report No. 39. Washington, D.C., National Council on Radiation Protection and Measurements, 1971. Presents the technical and philosophic basis for radiation protection standards in this country.

Cameron GW. Radiation Histopathology. 2 Vols. Boca Raton, Fla.: CRC Press, 1980. A detailed presentation of human radiation pathology.

Chaoui M. Biological effects of electromagnetic and radiofrequency radiation. In: Brusch CP [ed.]: Critical Reviews in Environmental Control. Vol. 7, Issue 3. Cleveland: CRC Press, 1977. p. 111. A review of surviving radiation effects as distinguished from those produced by ionizing radiation and described in the general chapter.

Heal EJ. Radiotherapy for the Radiologist. 3rd ed. Hagerstown, Md.: Harper & Row, 1979. An excellent text for the physician interested in a general but detailed overview of human radiotherapy.

Hansen JA, Clift RA, Thomas ED, et al. Transplantation of marrow from an unrelated donor to a patient with severe leukemia. N Engl J Med 303:565, 1980. The possibility of transplantation from unrelated human donors expands the potential application of this technique to life-threatening human radiation injury.

Hearne RJ, Fry SA. The Medical Basis for Radiation Accident Preparedness. New York, Elsevier-North Holland, 1980. The printed age of a recent international conference includes detailed follow-up information on virtually all of the world's serious clinical radiation injury cases, as well as population risk assessment and medical preparedness for nuclear accidents.

Management of Persons Accidentally Contaminated with Radionuclides. NCRP Report No. 65. Washington, D.C., National Council on Radiation Protection and Measurements, 1980. A manual to assist physicians in the management of accident involving radioactive contamination of radionuclides of various natures, ranging from short reference tables to scientific literature review (20 pages of references) and specific treatment recommendations.

Medical Radiation Exposure of Pregnant and Potentially Pregnant Women. NCRP Report No. 54. Washington, D.C., National Council on Radiation Protection and Measurements, 1977. Guidance on radiation exposure of women of reproductive age.

Protection of the Thyroid Gland in the Event of Releases of Radioiodine. NCRP Report No. 55. Washington, D.C., National Council on Radiation Protection and Measurements, 1977. Prophylaxis therapy information for nuclear releases.

Radiation Protection. ICRP Publication 26. Recommendations of the International Commission on Radiological Protection. New York, Pergamon Press, 1977. Basis for risk assessment for cancer and other late effects of low-level radiation exposure.

Robertson DAF. Surgical problems in the excision and repair of radiation injury. Reconstruct Surg 56:41, 1975. Management of the acute radiation injury.

Sources and Effects of Ionizing Radiation. United Nations Scientific Committee on the Effects of Atomic Radiation, 1977. Report to the General Assembly, with annexes. New York, United Nations, 1977. Detailed data on worldwide radiation exposure sources and their effects, including risk assessment for late effects.

The Effects on Populations of Exposure to Low Levels of Ionizing Radiation. Report of the Committee on the Biological Effects of Ionizing Radiations. Washington, National Academy of Sciences-National Research Council, 1980. A very complex presentation of the basis and results of attempts at assessment of the health risk of very low levels of radiation exposure. Some background in epidemiology and biostatistics is useful.

Thomas ED, Buckner CD, Clift RA, et al. Marrow transplantation for acute nonlymphoblastic leukemia in first remission. N Engl J Med 301:597, 1979. Current methodology for bone marrow transplantation.

Weiss N. Medical Management of Radiation Accidents. In: Bradley A, ed.: Handbook of Radiation Measurement and Protection. Vol. II, Sect. B.24. Boca Raton, Fla.: CRC Press, 1982. Diagnostic and therapeutic information for initial management of radiation injury presented in tabular and figure form for the information of radiation protection personnel.

Weiss N, Watson J. Medical modification of human acute radiation injury. In: Proceedings 19th Congress Pan American Radiation Protection Association, 1977. p. 1183. Discussion of the influence of diet and hormones in survival after acute radiation injury.

University of Pittsburgh

GRADUATE SCHOOL OF PUBLIC HEALTH
Department of Radiation Health
Office of the Chairman

November 23, 1983

Ms. Jenny M. Johansen
Radiation Specialist
U.S. Nuclear Regulatory
Commission Region 1
631 Park Avenue
King of Prussia, PA 19406

Dear Ms. Johansen:

In accordance with your recent request, I have reviewed your draft report #030-03053/83-01 and its appendices. On the basis of the data provided in the report there is no convincing evidence that this individual's illness and death could be ascribed to the manifestations of the acute radiation syndrome elicited by an acute whole body radiation exposure of 300-600 rads.

Sincerely yours,

Niel Wald

Niel Wald, M.D.

NW/rcg

NOV 2 9 1983

[illegible] PITTSBURGH PA 15261

8402270435 XA