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Radiation Death From Cardiovascular Shock Following a Criticality Accident

Report of a Second Death From a Newly Defined Human Radiation Death Syndrome

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Two case histories of nuclear radiation victims are similar and reflect radiation-induced hypotension, vascular damage, shock, and death within two days. Pathologic changes in one patient are described which show these two cases to represent a lethal subsyndrome of the acute radiation syndrome, occurring in the dosage range between the acute gastrointestinal and neurologic subsyndromes. Because meningeal and cortical changes occur as part of the vascular damage, terminal neurologic symptoms occur that lead to the suspicion of neurologic damage. Only minimal neuronal damage and glial reaction were present, however, and death apparently resulted from increased intracranial pressure, cerebral anoxia, cardiac failure, and massive peripheral edema.

THREE MAJOR mechanisms of fatal termination have been recognized in humans after lethal radiation exposure: central nervous system injury; gastrointestinal mucosal loss; and hematopoietic failure.[1] At radiation exposure levels (300 to 800 R) which are known to result in death of animals within 30 days or man within 60 days, death occurs as a result of hemorrhage, infection, and anemia secondary to hematopoietic injury. Radiation between 1,000 and 3,000 R denudes the mucosa of the small intestine, and results in septicemia and electrolyte imbalance causing death within five days in animals and within two weeks in man. At exposures higher than 3,000 R, deaths in animals or man within 24 to 48 hours are considered secondary to cerebral and cerebellar damage. After exposure to more than 5,000 R, most animals manifest a neurologic syndrome; malaise, weakness, ataxia, and prostration are progressive. Finally, such animals become unresponsive and die with convulsive manifestations.[2] Pathologic changes in such instances include meningeal leukocytic exudates, necrosis of cerebellar granular cells, oligodendroglial and cortical neurone lysis, and progressive cerebral edema.[3,4] This syndrome and its pathologic basis has been defined in monkeys[5] but not in man.

In man the hematologic syndrome has been documented by clinical and pathologic studies of cases of intentional[1] and accidental exposure to ionizing radiation.[1,6] The sequence of hematologic events is almost identical with that in animals, except for temporal differences in the nadir and recovery of peripheral while blood cell counts. These phenomena are delayed in man, so that his acute hematologic syndrome lasts 60 days instead of 30 days.[6-8] These observations have been verified in normal man by extensive study of the Hiroshima and Nagasaki atom bomb casualties,[9] and the Los Alamos,[5,10] Oak Ridge,[11] and the Vinca accidents.[12]

The occurrence of the gastrointestinal syndrome, on the other hand, is documented in man by only two cases: Accident Case LA-3[6] and the 1960 Russian suicide.[13] In these instances the total-body depth-dose distribution of 1,350 and 1,910 rads, respectively, was extremely uneven, but death occurred in nine to ten days as predicted, coincidental with intestinal mucosal denudation.

No human deaths have been attributed per se to the neurologic syndrome as it is known in animals. Although the early

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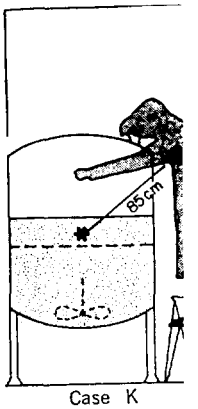

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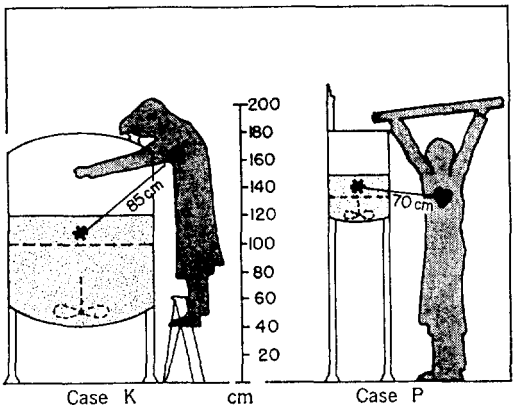


Fig 1.—Positions of the two men, relative to stirring tanks (approximate relative scale) in which the criticality excursions accidentally occurred, showing the activities and bodily orientation of the men to epicenters of the criticality excursions (asterisks). Estimated distances from the reaction to the anterior surface of the heart are shown. There was greater moderation of the neutron flux by water in the total-body exposure in patient K.

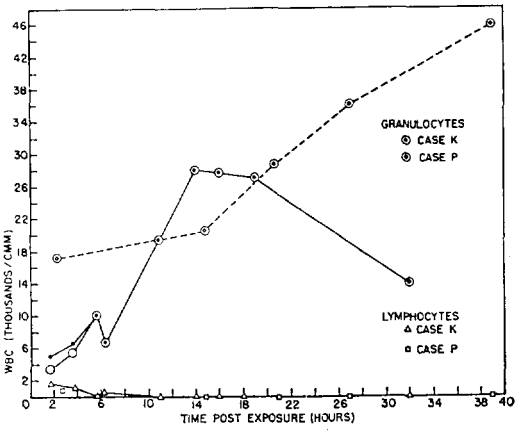


Fig 2.—Changes in peripheral white blood cell count and differentials in the two patients showing the early complete disappearance of lymphocytes and extreme leukocytosis.

deaths of some Hiroshima and Nagasaki victims may possibly have occurred in this manner, clinical observations during the first two days and postmortem examinations during the first week after the detonations were not made.[9]

Until the death of the man (P) described in this report, only one other person (K)[10] had been involved in a radiation accident in which exposure was known to exceed 4,000 rads, and had survived sufficient time to manifest clinical symptoms of a two-day death syndrome.[10] (The three victims of the Idaho Falls Reactor Test Site accident who received instantaneous doses of 1,000 kilorads or more were killed instantly by blast or died shortly after medical aid reached them.[14] The 1958 Los Alamos accident victim (patient K) survived 34 hours and failed to manifest signs of neurologic damage until immediately before his death, although he had received approximately 10,000 rads exposure to the front of the head. Just before death he suddenly became irrational, uncontrollable, and made convulsive movements. In spite of hypotensive clinical course and because of an estimated average whole-body dose in excess of 4,500 rads, autopsy findings of the so-called neurologic syndrome were anticipated. Instead, only minimal changes of mild meningeal vasculitis and perivascular edema were seen, while severe cardiovascular changes and generalized edema seemed to account for his death and to explain the protracted irrevocable shock from which this man suffered.[15] The absence in patient K of definitely primary neurologic injury similar to that previously described in animals after massive doses of radiation[2,3,5] suggested that the two-day death syndrome in man might be cardiovascular.[10]

Pathologic Details

The pathologic details of the Rhode Island radiation accident victim of 1964[16] are reported here at length, because they support the hypothesis that the neurologic syndrome in man, if it exists as such at all, is a terminal or secondary event in another death syndrome involving the cardiovascular system. A primary neurologic radiation death syndrome in man apparently requires an integrated total-body dose in excess of 10,000 rads and such a death is yet to be observed. The Rhode Island patient (P) received an estimated integrated whole-body dose of about 8,800 rads,[17] roughly twice as much as the Los Alamos man (K),[10] more radiation than considered necessary to produce cerebellar granule cell necrosis in experimental animals within 24 hours of exposure.[1,10]

The accidents in which the two men were involved were basically similar criticality excursions, which occurred when fissionable material in process of being reclaimed was unintentionally caused to flow into unsafe geometric volumes (Fig 1). In both accidents the man was close to a tank containing the extracting fluid. In Rhode Island, the tank was open at the top,

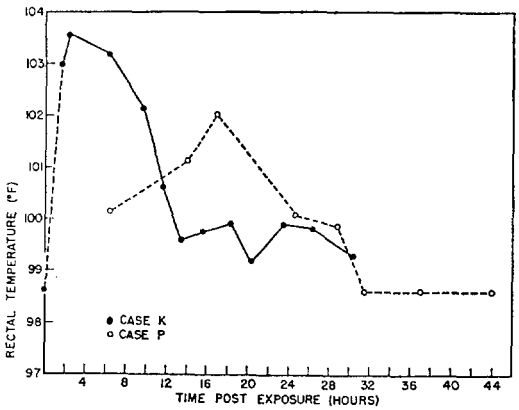


Fig 3.—Fluctuations in rectal temperatures of the men. The early high fevers rapidly subsided.

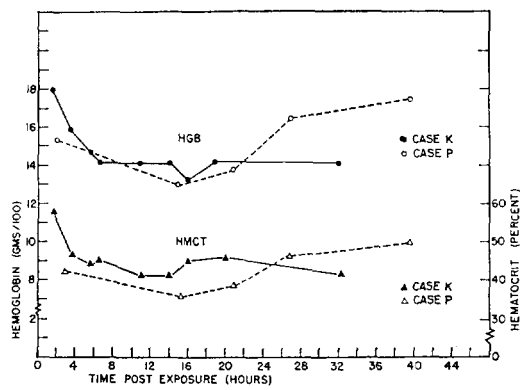
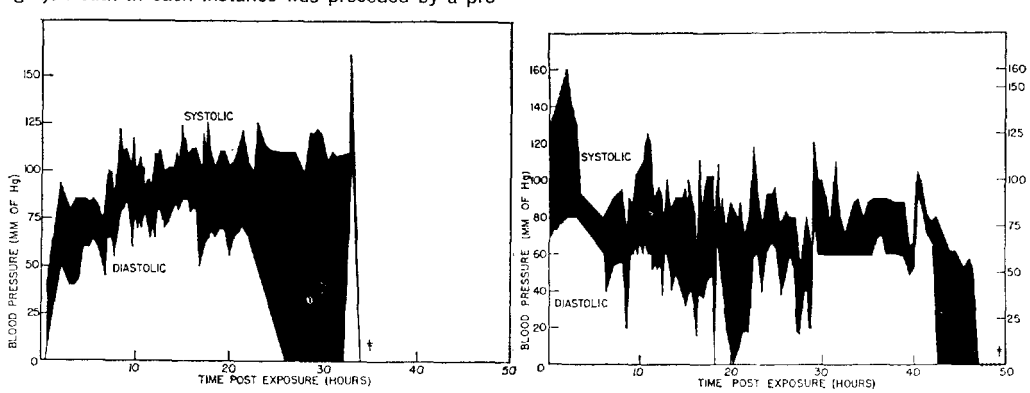


Fig 4.—Parallel changes in peripheral blood hematocrit and hemoglobin values in the two patients. An initial hemoconcentration was corrected by intravenous fluids in both patients and recurred only in patient P.

a propeller was stirring the contents, and criticality occurred as the contents of an elongated polyethylene bottle 10 cm in diameter were poured into the tank. This nuclear criticality accident occurred at a United Nuclear Corporation Plant at Wood River Junction, RI, on July 24, 1964. In Los Alamos, the criticality was initiated when the operator (K) activated an electric stirrer, which created a circulation in the tank that concentrated fissionable material (dissolved in a floating layer of solvent immiscible in water) in a vortex around the propeller shaft. Although this tank was enclosed so that none of its contents escaped, the blue flash of ionized oxygen, the shock wave, and an immediate burning sensation made patient K assume that he was injured by acid released from an explosion. The patient P was knocked down when he saw the blue flash and was showered with solutions containing fission products. He did not suffer any illusions of being burned and did not experience immediate prostration, but correctly interpreting the meaning of γ-ray alarms, ran down three flights of stairs, went through the proper building exit, and ran to an egress in the perimeter fence. Upon reaching this station, he shed all his clothing contaminated with radioactive material, laid his film badges down, and ran 150 yards across a field to an emergency shack. These actions required only a few minutes. When a security guard met him at the shack, the victim showed no signs of distress other than those usually expected from excitement and exertion. Five to ten minutes after the accident, however, the patient developed severe griping abdominal pains, accompanied by nausea, vomiting, and bloody diarrhea. At about the same time the guard noted that the whites of patient P's eyes were turning bright red and his skin began to appear acutely "sunburned.". During the next 15 minutes he vomited and had diarrheal stools about five times. During one of these episodes, as he was going away from the shack to relieve himself, he ran head-

Fig 5.—Temporal fluctuations in systolic and diastolic blood pressures in patient K (left), and patient P (right). Death in each instance was preceded by a prolonged period in which a diastolic pressure could not be discerned.



on into a sapling four inches in diameter, although the twilight was still more than adequate for the other men to distinguish objects. About 30 minutes after the accident occurred, an ambulance arrived. Patient P was then speaking coherently, and was only incapacitated during violent cramping evacuations. He helped himself onto the stretcher and was placed in the ambulance. At the first hospital inadequate facilities and staff directed the ambulance to the largest general hospital of the region where he arrived about 30 minutes later. During this trip he suffered from recurring episodes of nausea, vomiting, diarrhea, and cramping pains. The details of his subsequent hospital course and therapy has been reported at length.[16] By the time of his admission to the emergency room, the frequency and intensity of his gastrointestinal colic had largely subsided but were quieted completely with intramuscular morphine.

Initial Geiger-counter readings four inches from the body recorded a maximum radioactivity of 80 mr/hr, which was reduced by a bath to 45 mr/hr. Some of this residual radioactivity was due to induced ^{24}Na activity in the blood and interstitial fluids, but most was due to fission-product contamination of his skin and hair. The induced radioactivities of his whole-body sodium and hair sulphur were used to estimate the integrated whole-body dose, the thermal neutron flux, and bodily orientation to the criticality center at the time of the accident.[16,17]

Comparative Clinical Courses.—The two accidents occurred about five years (and 2,500 miles) apart and resulted in integrated total-body doses that differed by a factor of two (dose of patient K ⌣ 4,900 rads; dose of patient P ⌣ 8,800 rads). The clinical courses were so similar that they are contrasted here to support the thesis that these two patients represent a previously undescribed human lethal radiation syndrome. The possibility that this syndrome is due fundamentally to widespread vascular rather than primary cardiac damage as suggested in the reports on patient K[15,10] is raised by the gross and histopathologic observations in the second patient P. For the sake of brevity the two courses have been summarized under the headings of Hematology and Blood Pressure and Therapy.

Hematology.—The changes in total white blood cell, granulocyte and lymphocyte counts are shown in Fig 2 for patients K and P. Both showed the progressive leukocytosis and lymphopenia typical of heavily irradiated mammals. The early disappearance of lymphocytes shown by both these men has become well

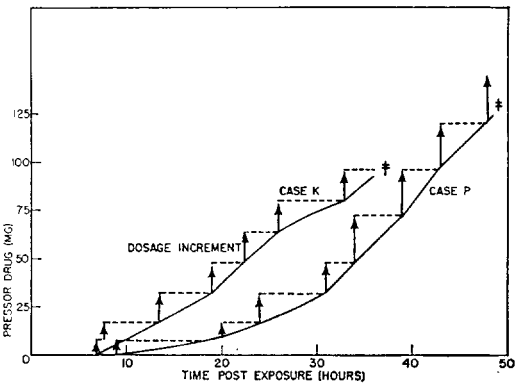


Fig 6.—Comparing the rate of infusion of pressor drugs into the two patients. Height of each arrow indicates the amount of drug injected at that time into fluids that were running intravenously at various rates. The curving solid lines sum the amount of pressor drugs infused.

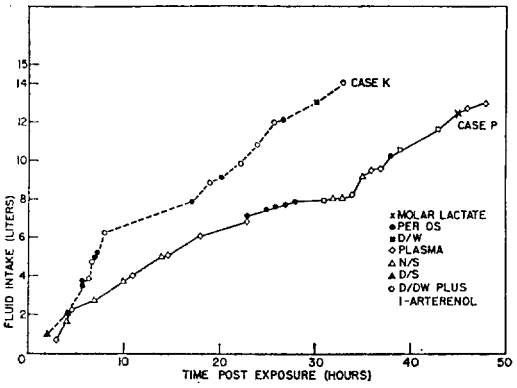


Fig 7.—Amount of various fluids administered per os or intravenously in relation to time after radiation exposure of the two patients.

Fig 8.—Temporal course of amount of fluid lost after exposure on the assumption that fluid loss in the immediate prodromal radiation reaction of the two men was similar and approximated two liters. Oliguria in patient K was more extreme, but in both fluid loss failed to balance fluid intake (Fig 7).

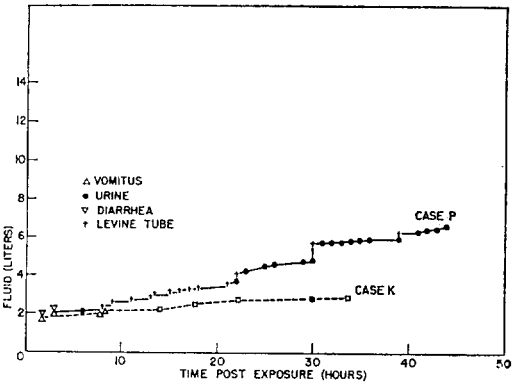


Fig 9.—Right ventricular myocardium showing interstitial leukocyte exudation and edema (hematoxylin and eosin, × 400).

Fig 10.—Subepicardial myocardium from the anterior portion of the base of the right ventricle showing granularity caused by interfibrillar edema of the cardiac muscle (hematoxylin and eosin, × 400).

known as an ominous prognostic sign of supralethal total-body irradiation.[1] Both men showed the granulocytosis thought to be due to an outpouring of these cells from bone marrow and other tissue reserves in response to widespread tissue damage. Increase in temperature as shown in Fig 3 may be another reaction to circulating protein breakdown products and postdiarrheal loss of fluid. The progressive changes in hematocrit and hemoglobin are shown comparatively in Fig 4. The major cause of the different initial levels of the blood values in the two men may be related to the altitudes at which they lived and died—7,000 feet at Los Alamos and sea level in Rhode Island. Both, however, showed postexposure hemoconcentration. This was followed by a return to normal hematocrit levels, but in spite of 14 liters of fluid administration to patient K and 9 liters to patient P, neither man showed signs of hemodilution but tended to hemoconcentrate. This progressive leakage into expanding extravascular spaces was particularly obvious clinically.

Blood Pressure Changes and Therapy.—The severity of the shock syndrome from which these men suffered is illustrated graphically in Fig 5-8. These figures show the blood pressure changes, fluid output, and fluids and vasopressor drugs administered in attempts to combat the hypotensive and oliguric courses. Patient K initially had an extremely low blood pressure (40/10) which never reached normotensive levels (Fig 5, *left*). Patient P was hypertensive (Fig 5, *right*) on hospital admission but within six hours required vasopressor drugs to combat the steady decline in his blood pressure (Fig 6). In both men, a relatively stable, but lower than normal, systolic pressure was maintainable during the first postirradiation day chiefly by vasopressor drugs and intravenous fluids (Fig 7), but diastolic pressures were often difficult to measure. After their initial fluid losses in their attacks of vomiting and diarrhea both men were oliguric (Fig 8) during the first day in spite of large amounts of intravenous fluids. Patient P regained some urinary function during the second day. Electrocardiographic changes in both men were similar,[15,16] reflecting (retrospectively) a developing relative left ventricular preponderance, pericardial effusion, and myocarditis. Terminally, both men had low unstable blood pressures, which were difficult to measure. Patient P had no discernible blood pressure for five hours before death.

Postmortem Observations

Lushbaugh[15] has previously reported the

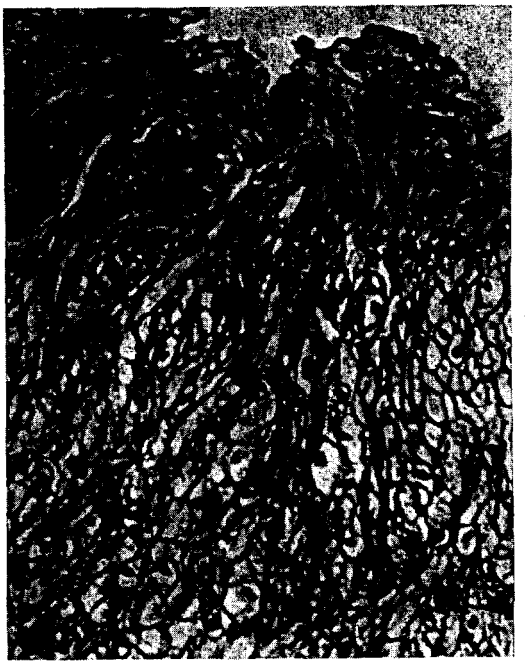


Fig 11.—Typical medium-sized artery showing extreme intracellular edema of the smooth muscle (hematoxylin and PAS, × 400).

Fig 12.—Small meningeal vein collared by exudated polymorphonuclear leukocytes (hematoxylin and eosin, × 400).

autopsy findings of patient K. The autopsy of patient P was performed seven hours post mortem. The most conspicious gross findings related to the cardiovascular, lymphopoietic and hemopoietic systems, and interstitial tissues and spaces. The following descriptions are limited to only pathologic alterations considered important. External inspection revealed a thick set, exaggerated muscular appearance, which proved due to massive subcutaneous and interstitial edema of skeletal muscle. Cutaneous incisions exuded a copious flow of clear fluid. The left forearm and hand, which were closest to the source of radiation (Fig 1), were maximally swollen, turgid, and cyanotic up to the elbow. Pitting edema overlay the olecranon process. In addition to extensive extravascular interstitial accumulations of fluid, there were bilateral hydrothorax and pericardial effusion. Ascites was present but unexplainably minimal.

Cardiovascular System.—A serofibrinous pericarditis was manifested by 100 ml of yellowish fibrin-flecked fluid and fibrin deposits on the right atrium and ventricle. This fluid clotted on standing in vitro. There was an abrupt transition from faint vascular injection of the upper anterior right ventricular pericardium to vivid hyperemia of the adjacent root of the aorta. Microscopically, fibrin and polymorphonuclear leukocytes were scattered in patchy fashion in the epicardium of the right ventricle, auricle, and atrium. Polymorphonuclear neutrophils were dispersed singly and in groups between muscle fibers, usually near blood vessels, and there was slight interstitial edema (Fig 9). Muscle necrosis was not observed. Mesothelial cells varied in appearance, being sometimes swollen and prominent, or shrunken and having pyknotic nuclei. Subepicardial myocardial cells were finely reticulated or granular as though the myofibrils were dispersed in the sarcolemmal sheaths by intracellular edema (Fig 10).

Most of the medium-sized arteries appeared pale histologically, because of swollen smooth muscle layers (Fig 11). This intracellular edema in smooth muscle was also seen in the muscle coats of the small and large intestine where the ganglionic cells of the intramuscular plexuses were similarly affected. The irregular staining and vacuola-

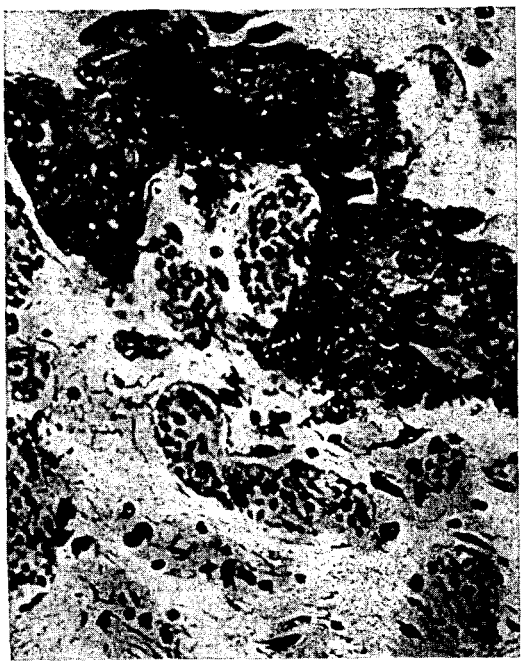


Fig 13.—Esophagus with extreme hyperemia and interstitial edema of connective tissue, and acanthotic appearance of desquamating epithelial lining. Basal cells are less evident than normally (hematoxylin and eosin, × 400).

Fig 14.—Autoradiogram of the skin showing abundant tracks in the emulsion from α-particles emitted from fission-product contaminants entrapped in the keratinized horny layer (hematoxylin and eosin, × 200).

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tion of the intestinal smooth muscle was most suggestive of hydropic degeneration or fluid imbibition. A possible fatty change was looked for, but the Sudan III fat stain was negative. Persistent alkaline phosphatase activity of capillary endothelium of small intestine was demonstrable 15 hours after death.

In many areas, polymorphonuclear leukocyte exudation was found where it could be considered only evidence of primary endothelial damage. The small venules of the meninges are an excellent example of this change,[18] for they were collared by neutrophils in the absence of demonstrably damaged tissue (Fig 12).

Hyperemia was especially prominent in subepithelial capillaries of the respiratory tract and esophagus (Fig 13) where the capillaries were enormously dilated with blood in which crenated and fragmented erythrocytes could be demonstrated. Thrombi containing erythrocytes were not found anywhere but leukocytic "thrombi" occluded small venules in central portions of the cerebral white matter.

Respiratory Tract.—Congestion of the trachea, bronchi, and lung parenchyma was accompanied by intra-alveolar and interstitial edema. Microscopic examination showed an irregular desquamation of epithelium of the airway passages and hypersecretion of their mucous glands. Necrosis and desquamation of the tracheal epithelium was prominent and the denuded basement membrane was irregularly widened and hyalinized. Macrophages, which were rarely multinucleated but occasionally vacuolated, were frequently dispersed in alveoli and contained black particulate debris in a brown cytoplasm. In some pneumatocytes, the PAS stain demonstrated material resistant to salivary amylase. Tests for metachromasia with toluidine blue at pH 2.5 and pH 4.5 were negative as was the Sudan III fat stain. The ferric ferrocyanide reaction inconstantly demonstrated hemosiderin. Smooth muscle cells in the media of the pulmonary arteries were vacuolated and edematous. Surprisingly, a terminal aspirative bronchopneumonia could not be demonstrated. Contamination of the respiratory tract by inhaled fission produ
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Fig 15.—Mucosa and submucosa of descending colon. The most superficial epithelial cells have been desquamated. Lamina propria appears to have lost its lymphoid complement and to be contracted but edematous. No mitotic activity is present. Remarkable submucosal edema is evident (hematoxylin and eosin, × 100).

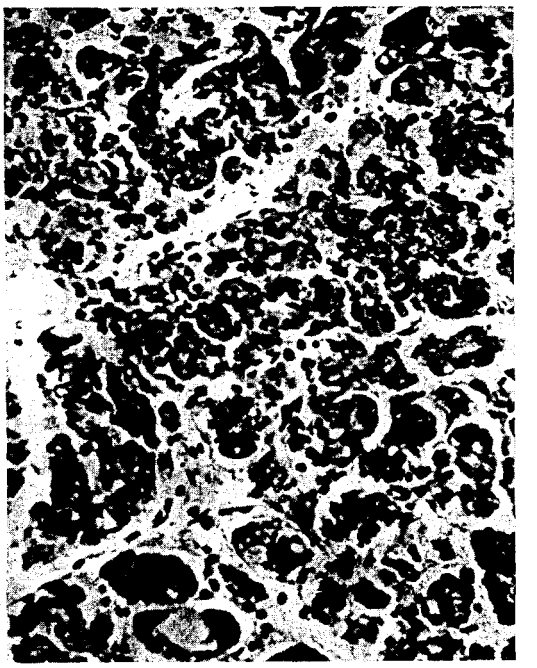


Fig 16.—Pancreas showing edematous interstitial connective tissue and a focus of necrotic and degenerating acini with infiltrating leukocytes (hematoxylin and eosin, × 128).

haled fission products was not demonstrated but autoradiograms of the skin (Fig 14) showed abundant tracks from α-particle emitting substances in the epidermal horny layer.

Gastrointestinal Tract.—The mucosa at the cardioesophageal junction was congested (Fig 13) and a few petechiae were found in the stomach. Submucosal edema produced prominent gastric rugae and a remarkably thickened colonic mucosa (Fig 15). Microscopically, the epithelium had desquamated to a variable depth from the esophagus down to the rectum. This was confirmed by a smear of intestinal contents that revealed numerous epithelial cells. No mitotic activity was found at any level. Histiocytes, polymorphonuclear neutrophils, eosinophils, and large lymphocytes occurred with variable but reduced frequency in the mucosa of the intestinal tract; but small lymphocytes were completely absent.

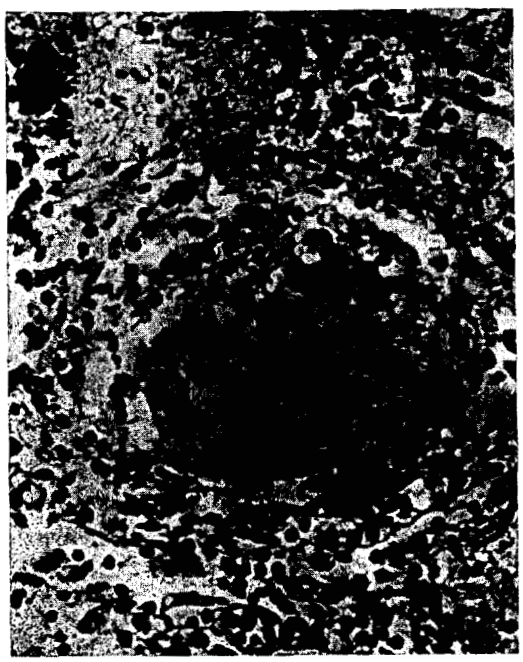
As in other sites, lymphoid follicles were denuded of lymphocytes and consisted of a reticuloendothelial skeleton containing a small residual amount of nuclear debris.

Liver.—The liver was enlarged and heavy (weight 2,370 gm), owing to congestion, confirmed microscopically. In addition, there was fatty metamorphosis and rare necrosis of individual liver cells. The sinusoids contained increased numbers of polymorphonuclear neutrophils with nuclei frequently altered by increased lobulation, pyknosis, and irregular outline.

Pancreas.—Although grossly not abnormal, the histologic changes were impressive. A patchy alteration of pancreatic acinar epithelium was manifested by shrinkage of cells, pyknosis of nuclei, and eosinophilia of cytoplasm (Fig 16). In some acini there was vacuolization of cytoplasm, as well as karyorrhexis and complete disappearance of cells. Duct epithelium was rarely desquamated and a few polymorphonuclear neutrophils appeared in duct lumen. The islets of Langerhans were uninvolved, except for a rare cell showing nuclear pyknosis. Polymorphonuclear neutrophils and monocytes in small numbers had infiltrated the edematous interstitial tissue. Leukocytes were present within necrotic acinar cells in some areas.

Fig 17.—Thymus gland showing epithelial remnant resembling a basalar layer differentiating into squamoid cells (hematoxylin and eosin, × 400).

Fig 18.—Reticuloendothelial follicular center in a mediastinal (hilar) lymph node, appearing as the "tubercle" of a heavily irradiated lymph node. Pyknotic nuclear remnants surround it. Anthracotic pigment-laden macrophages are at upper left, and granulocytes and erythrocytes are in a sinus at upper center and right (hematoxylin and eosin, × 400).



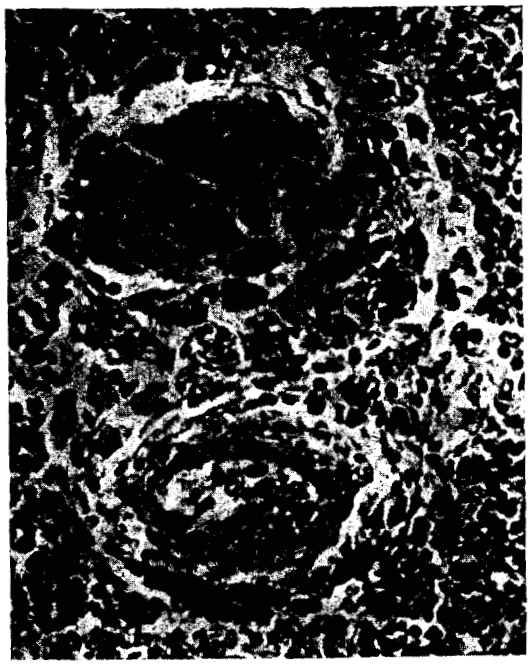


Fig 19.—Spleen shows former site of lymphoid nodule consisting of a periarterial tuberculoid nodule in condensed reticulum containing pyknotic lymphoid nuclear partcles and phagocytic cells of the sinusoidal reticulum (hematoxylin and eosin, × 400).

Thymus.—Although the thymus gland was not distinguishable grossly, and microscopic sections revealed extensive fat replacement and atrophy commensurate with the patient's age, lymphocyte depletion was impressively complete. Polymorphonuclear leukocytes were present in minute cystic foci. Hassall's corpuscles and epithelioid cells were intact. The denuded peripheral epithelial layer was so condensed that it appeared arranged in columnar palisade fashion, and looked remarkably like a basal epithelium differentiating into a squamoid epithelium (Fig 17).

Lymph Nodes.—Hilar lymph nodes were of average size and anthracotic pigment discolored them. Lymph nodes in the mesentery were calcified. Microscopically, there was a markedly diminished lymphocyte content. The sites of the follicles consisted of hypertrophied reticuloendothelial nodules surrounded sparsely by shrunken, pyknotic lymphoid cells and nuclear debris. Reticuloendothelial cells were intact throughout the lymph nodes and evidenced phagocyto-

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Fig 20.—Vertebral bone marrow showing cellularly depleted sinusoids dilated with erythrocytes, containing only a few accumulations of pyknotic nucleated cells, an occasional megakaryocyte, and reticular macrophage (hematoxylin and eosin, × 200).

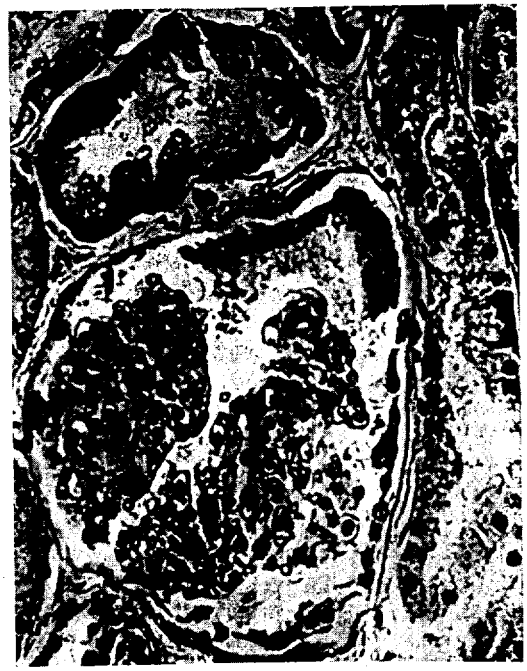
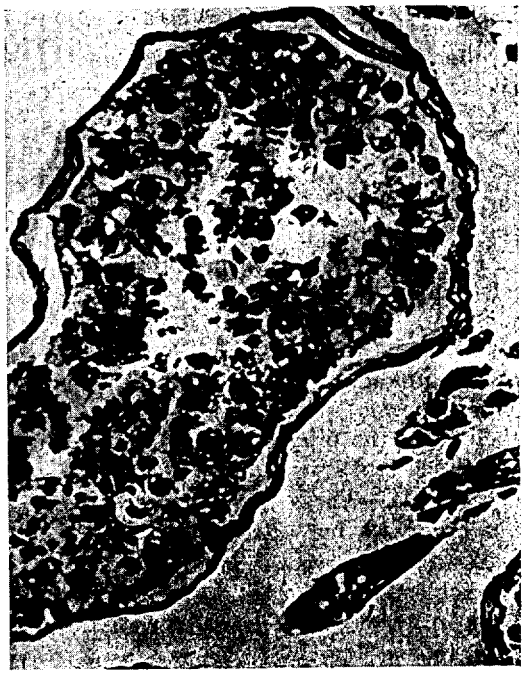


Fig 21.—Kidney showing infraglomerular epithelial reflux, a histologic finding associated with terminal oliguria and hypotension[19] (hematoxylin and eosin, × 400).

Fig 22.—Testicular tubule in distorted edematous intertubular connective tissue. Germinative epithelium appears to have an embedding artifact but changes typical of necrosis of spermatogonia and chromatolysis and injury of the chromatin of spermatocytes and chromatids are present (hematoxylin and eosin, × 400).



sis. Sinusoids contained polymorphonuclear neutrophils and eosinophils (Fig 18).

Spleen.—The spleen weighed 110 gm and was flabby grossly. Its appearance was that of acute massive blood loss. Malpighian corpuscles could not be identified and, correspondingly, their usual complement of lymphocytes was missing. The central arterioles were adjacent to prominent nodules of well-preserved hypertrophied reticuloendothelial cells (Fig 19). Only a few shrunken or disrupted lymphocytes were among the remaining pyknotic nuclear debris. Interspersed were eosinophils, polymorphonuclear neutrophils, plasma cells, histiocytes, and reticular cells. Phagocytosis varied in frequency and erythrophagocytosis was rare. Central arterioles showed hyaline intimal thickening. Occasionally hyalinized connective tissue was present in the center of the altered follicles. The sinusoids and red pulp were poorly defined by nucleated cells. Patchy areas were congested appearing like hemorrhage, but in most areas the reticular supportive connective tissue of the spleen

was condensed, especially, as seen with the PAS stain. Polymorphonuclear neutrophils were frequent in the blood of both the red pulp and large blood vessels.

Bone Marrow.—Grossly the bone marrow of the sternum, ribs, vertebral bodies, and femoral heads was thin, liquid, and a clear, bright red. Former islands of erythromyelopoiesis (Fig 20) were identifiable chiefly by the presence of fixed reticular phagocytes containing small amounts of nuclear debris. Megakaryocytes with pyknotic distorted nuclei could also be seen adjacent to sinusoids dilated by erythrocytes and to interstitial spaces filled by stainable edema fluid. A few cells appearing like primitive stem cells were found along with scattered small cells with pyknotic nuclei. Mitoses were absent and no accumulations of cells that suggested continuing cellular proliferation could be found. Fat cells were unaltered.

Thyroid.—The gross appearance of the thyroid was normal except for a minute calcific nodule in the left lobe. Microscopically, a rare acinus contained polymorphonuclear leukocytes in the colloid and brown pigment in the epithelial cells.

Parathyroid.—The parathyroid glands showed no abnormality except ectopic thymic tissue showing changes similar to those in the mediastinal thymus.

Kidneys.—The kidneys were moderately swollen but otherwise not abnormal and showed only slight degenerative changes. The glomeruli were normal but displaced by proteinaceous fluid that distended the glomerular space. Reflux of proximal tubular epithelium[19] into Bowman's space overlying the capsular epithelium were found (Fig 21). Epithelium in proximal convoluted tubules and rarely in other parts of the nephron, showed isolated foci of necrosis and nuclear degeneration. Small amounts of an unknown yellowish-brown pigment (? lipochrome) were present within the epithelium of the proximal convoluted tubules and thick loops of Henle.

Adrenals.—These glands were congested but otherwise not altered.

Testes.—Grossly the testes were not remarkable. A review, by a biologist specializing in histologic evidence of radiation injury in the human testes, revealed great damage in spermatids and spermatocytes, evidenced by nuclear pyknosis and cytoplasmic vacuolization. The spermatogonia were pyknotic, swollen, or unidentifiable as to type. The germinal epithelium was separated from the basement membrane and interstitial edema was massive (Fig 22).

Brain.—Grossly the brain was normal and microscopic changes were minimal. There was acute swelling of Penfield. Oligodendroglia and astrocytic nuclei showed clear spaces around them with wisps of stainable cytoplasm bridging them. Occasional fields showed more microglia than usual. The endothelial cells of capillaries sometimes were prominent. Cerebellar granule cells did not show necrosis or any decrease in number. Diffusely scattered extravascular polymorphonuclear leukocytes were increased in the meninges and around some of the cortical blood vessels (Fig 12), slightly greater in amount than the infiltrations seen in the viscera.

Review of these sections was made by a panel of consultants in neuropathology: Samuel P. Hicks, MD, Ann Arbor, Mich; David Sohn, MD, New York; F. Stephen Vogel, MD, Durham, NC; Harold W. Williams, MD, Providence, RI; Mary Ambler, MD, Providence, RI; and Wolfgang Zeman, MD, Indianapolis. All were in general agreement that cytologic evidence for primary neuronal and granule-cell damage was minimal or questionable, while vascular changes and meningeal leukocytic exudation were present but mild in comparison to the degree of these changes in monkeys[18] and lower animals irradiated at the level of this patient's exposure.

Comment

Pathologic changes are described here in a man who died 49 hours after receiving the highest estimated neutron-γ whole-body radiation dose (8,800 rads) in human experience.[16] They confirm and extend those previously reported in a man who died 33 hours after about half as large a radiation in the range where some previous animal experimentation suggests that the mode of death in both patients should have resulted exposure in a similar nuclear criticality accident.[10,15] The exposures of both men were

from primary radiation damage to the central nervous system, the so-called neurologic subsyndrome of the acute radiation syndrome of mammals.[1] Although death in both men occurred within the expected time for this lethal mechanism, the clinical courses and pathologic findings do not support the conclusion that these deaths are examples of the neurologic radiation syndrome. Both patients terminally did evidence symptoms referable to cerebral disease, but the absence of a significant amount of neuronal lysis or granule-cell pyknosis in contrast to the presence of meningeal vascular inflammatory changes, perivascular cellular exudates and edema—all changes found widespread elsewhere throughout the whole bodies—suggest that the neurologic symptoms in these patients resulted from vascular damage and cerebral circulatory impairment rather than primary radiation effects upon the central nervous system.

Severe intractable shock and accompanying histologic cardiac changes[15] in the previous study of a human death in this radiation dosage range suggested that *primary* cardiac damage might have been the etiologic lesion responsible for death.[10] This hypothesis, however, was based on the assumption that the myocardium may be more radiosensitive than the blood vessels themselves, although studies on the effect of total-body γ-irradiation on the cardiovascular system of animals fail to lend this idea support. In recent studies in a primate, Kundel[20] demonstrates that the widely accepted concept of the subdivisions of the acute radiation syndrome into hematologic, gastrointestinal, and neurologic syndromes fails to emphasize the "dominance" of peripheral vascular damage at doses greater than 3,000 R. Cardiovascular collapse can occur from such total-body doses before gastrointestinal mucosal ulceration has time to cause massive loss of fluid and electrolyte and before neurologic lesions are demonstrable. Furthermore, experiments in dogs[21] and rabbits[22] show that doses of radiation capable of causing hypotension when administered to the entire body are ineffectual when confined to the heart with the body shielded. Although irradiation of the head alone can induce hypotension in dogs and rabbits, a tenfold increase over the required total-body dose is needed.[23,24]

The findings in this human case study and the previous Los Alamos one of massive peripheral interstitial edema, cavitary effusions, random organ edemas, and inflammatory states leads us to the conclusion that peripheral and organic vascular damage was the dominant radiation lesion underlying the hypotensive shock and rapid death within two days. Although these two patients provide the only human medical evidence for it, this study, along with evidence from animals[20] of severe vascular damage after total-body exposure to 1,000 to 10,000 R, suggests a "vascular radiation subsyndrome" should be inserted into the radiobiologic concept of modes of death in the acute radiation syndrome. The occurrence of early transient hypotension at doses that cause death later because of hematopoietic and intestinal mucosal failure suggests that systemic vascular damage may play a role in these subsyndromes as well. The absence of well defined central nervous system neuronal damage in these patients (K and P) suggests that for the neurologic subsyndrome in man to be due, as implied, to direct cerebral or cerebellar damage, a prompt dose to the brain greater than 10,000 rads must be necessary. This opinion finds some support in the precise studies of Zeman et al[25] on the histologic and enzymatic effects of micro beams of deuterons upon individual neurones and glial cells. It lends credence also to Brown's[26] explanation for the anomalous cerebral radiosensitivity of the burro, that dies a "neurologic" death according to Trum[27] after exposure of its head to as little as 200 R. Brown[26] describes in these animals extraordinary cerebral vascular damage with the production of meningeal vasculitis, cerebral edema, and intracranial pressures in excess of 800 mm Hg, while histologic evidence of primary cerebral neural cellular damage is minimal. Acute intracranial vascular damage may thus be an important pathologic complex within the vascular radiation syndrome and explain in part the past confusion of this syndrome complex with a neurologic one.

The development of a radiation vascular lesion that leads acutely to fluid leakage and cellular exudation or remotely to sclerosis,

atrophy, and chronic circulatory impairment obviously depends upon some synergism of total dose and rate of exposure. In these patients (K and P), the total dose requirement was exceeded instantaneously and length of survival was determined by the acute vascular damage and the rate of accumulation of intolerable amounts of extravascular fluid. The use of plasma in patient P instead of as much electrolyte solution as in patient K may be the reason P survived longer after a greater dose. The primary vascular lesion itself, however, was not definable by light microscopy nor by limited histochemistry. The congested capillaries were lined by endothelial cells that were rarely pyknotic or disrupted. These changes, difficult to distinguish from artifact, were seen in the subcutaneous tissues of the left hand and abdominal wall of P and the omentum of K,[15] and rarely at other superficial sites in both.

Alkaline phosphatase, an enzyme that might be concerned with the transport of osmotically active molecules[28] was demonstrable in capillary endothelial cells for at least 15 hours after death, attesting to the radioresistance of this enzyme or the endothelial cell, or both. This "hardiness" might be related to enzyme survival, intact ribosomal function capable of enzyme synthesis, or continuous production of messenger ribonucleic acid and message transcription, or several of these possibilities. On the other hand, this enzyme might not reflect the molecular level of the radiation damage, which could conceivably be appraised better by measuring lysosome development using acid phosphatase as a marker for hydrolytic enzyme activity.[25]

The vacuolation of subepicardial myocardium and smooth muscle in the intestines and media of arteries was considered similar and probably was produced by the same basic mechanism. Although similar changes are due to postmortem artifact, these alterations of intracellular architecture can be caused by altered osmolality, cell-membrane permeability, and intracellular imbibition of fluid. Similar changes in muscle, although rare, have been previously described. Hartman[29] observed granular and vacuolar degeneration of myocardium in animals and humans exposed to localized radiation of the thorax. Warren[30] cited a case reported by Schweitzer of heavy dosage of radiation over the thorax with globules noted in the "myoplasm." Gassman[31] and Wolbach[32] have independently observed vacuolation of smooth muscle cells in the media of arteries secondary to radiation exposure. Warren and Friedman[33] have observed vacuolation of smooth muscle in the irradiated intestinal tract. In radiation accidents, Latarjet[34] has suggested that tissue changes in the heart might be biochemically induced by toxic tissue-breakdown products indirectly from whole-body damage. What total effect this intracellular change in hydration may have upon myocardial and vascular contractility and Purkinje fiber conductivity is of course unknown. Electrocardiographic changes, however, were minimal and seemed to reflect chiefly pericardial inflammatory changes. In support of this observation, in animals radiation doses that cause hypotension are not accompanied by reduction in myocardial contractility[20] or electrocardiographic changes. The relative ineffectiveness of angiotensive drugs in these patients is paralleled by the unresponsiveness of the heavily irradiated animal to levarterenol[20]

The degree of pathologic changes in the other organs was, for the most part, as expected from previous experience. The early disappearance of circulating lymphocytes was correlated with the almost complete absence in any tissue of cells recognizable as normal small or medium-sized lymphocytes. The peripheral granulocytosis during life was recognizable at death and its reflections were seen as leukocytic inflammatory exudates in many organs, leukocytic thrombi, and bone-marrow depletion. Although Liebow et al[35] noted frequent mast cells and erythrophagocytosis in lymph nodes and spleens in atomic bomb casualties, this was not the present experience. Phagocytosis of nuclear debris was considerable, but erythrophagocytosis was rare. Most impressive was the efficiency of the reticuloendothelial system in cleaning up cell debris. Only scant nuclear fragments remained, either in lymphoid tissue or in bone marrow.

The extreme damage to the bone marrow was consistent with previous experience in severe radiation exposures. Cell population was notably depleted, especially of immature hemopoietic cells. Yet there was a scat-

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The well-known vulnerability of germinal epithelium to radiation was borne out in the present patient with changes manifested in such a short time after exposure. In addition to the degeneration of germinal epithelium, its separation from basement membranes was of interest as an additional example of the loss of cell adherence due to radiation.

Among the atomic bomb casualties, epithelial cells in the gastrointestinal tract frequently became distorted with enormous nuclei, coarse chromatin network, and atypical mitoses, but comparable changes were not found in the present patient because death supervened. The Los Alamos patient[15] demonstrated desquamated necrotic parietal cells in the lumina of the gastric glands, but only equivocal changes in this tissue were observed in the Rhode Island accident victim.

It is especially difficult to ascribe the pancreatitis of the present patient to direct radiation damage, since the occurrence of pancreatitis has been observed rarely even after severe radiation exposures. The cytologic alterations seen in the pancreas, however, do not resemble the pancreatitis occasionally observed with shock and must be a direct effect of massive radiation dose. Case and Warthin[36] described such pancreatic changes in a patient who died weeks after heavy doses of roentgen radiation over the epigastrium. Acinus cells were atrophic, duct epithelium showed vacuolar degeneration and necrosis, and there was lymphocytic infiltration.

The other epithelial lesion of special note is that of the renal proximal convoluted tubule. This lesion, originally described by Councilman[37] and named infraglomerular epithelial reflux by Waugh,[19] apparently occurs when oliguria and hypotension are extreme shortly before death, as in patient P. Since it has not been described previously in a death from radiation damage and was not present in patient K, it must be correlated in patient P with the five hours before death during which no blood pressure was measurable, and can not be attributed to primary radiation damage.

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Mrs. Gretchen Humason, Oak Ridge Institute of Nuclear Studies, Medical Division prepared special histologic preparations; Paul E. Steiner, MD, University of Pennsylvania, critically reviewed histopathology of these case studies; Arthur F. Jacques, photographer, and Barbara R. Barker, PhD, Rhode Island Hospital, prepared the photomicrographs and autoradiographic studies. Miss Mavis Rowley, Research Associate, Pacific Northwest Research Foundation, Seattle, reviewed histologic evidence of injury to testes. Hospital records of Robert S. Grier, MD, Los Alamos Medical Center, NM, and of Joseph S. Karas, Rhode Island Hospital, contributed materially to this study. The Medical Division, Oak Ridge Institute of Nuclear Studies, Inc., under contract with the US Atomic Energy Commission, gave permission to reproduce Fig 1-22.

Generic and Trade Names of Drug

Levarterenol—*Levophed.*

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