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___ FALLOUT RADIATION: EFFECTS ON THE SKIN

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FALLOUT RADIATION: EFFECTS ON THE SKIN

___.1 INTRODUCTION

Until recently it has been generally assumed that injury to the skin from ionizing radiation was not a serious hazard associated with the detonation of nuclear devices. However, in 1954 the importance of this hazard became apparent when widespread radiation lesions of the skin developed in a large group of people accidentally exposed to fallout radiation in the Marshall Islands following the experimental detonation of a large nuclear device. In addition to exposure of some 239 Marshallese people and 28 Americans, there were 23 Japanese fishermen exposed on their fishing boat. The radiation effects and skin lesions in this latter group have been described by Koyama et al. and others. Prior to that time, a limited number of skin lesions on the backs of cattle (Bird; Paysinger et al.) and horses (Atomic Energy Commission Report) has been noted from fallout following experimental detonations. In addition, exposure of the hands of several individuals who had carelessly handled fission product samples from a detonation resulted in the development of severe lesions (Knowlton et al.). Other cases of beta lesions in human beings of accidental or experimental nature have been described by Robbins et al.; Crawford; Low-Beer; Wirth and Raper; Conard and Tessmer; Kepp; Griffith et al. and Kepp, Miller and Reich; Nodle; and Witten et al. Some of the rather numerous studies on the effects of beta radiation on animal skin are reported by Henshaw; Raper and Barnes; Snider and Raper; Lushbaugh; Moritz and Henriques; Paysinger et al.; Brues; Cloudman et al.; Glucksmann; Kharchenko and Venolurov; Koletsky et al.; Minisov; Passonneau and Hamilton; Shubik et al. and Ungar et al.

The recent accident in the Marshall Islands affords the first example of large numbers of lesions of the skin in human beings from fallout. Studies of

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these lesions in the Marshallese and Americans exposed have been documented (Conard et al.) and will be referred to frequently in this chapter.

Lesions of the skin induced by fallout are primarily due to the beta radiation from the fission products adhering to the fallout material and are, therefore, frequently referred to as beta burns. So-called beta burns of the skin may also result from accidental exposure to, or contamination with, radioisotopes used in science and industry. The possibility of such accidents must be considered seriously in view of the increasingly widespread use of radioisotopes.

___.2 FALLOUT SITUATIONS RESULTING IN SKIN DAMAGE.

With detonation of nuclear devices, serious radiation injury to the skin is only associated with fallout situations where the radioactive material is sufficiently concentrated. Such concentrations are most likely to occur with close-in fallout, i.e., fallout that occurs within several hundred miles of the detonation. It seems probable that the fallout will be visible if serious acute skin damage is to result; however, this cannot be stated with certainty. In the Marshall Island accident, the extent and severity of the skin lesions were directly correlated with the amount of visible fallout. On the most distant of the contaminated islands, some 200 miles from the site of detonation, the fallout was not visible and no beta lesions of the skin developed among the inhabitants.

The world-wide deposit of fallout which occurs slowly from the troposphere or stratosphere does not result in skin injury since in this situation the fallout material is greatly diluted and reduced in amount.

Damage to the skin such as that seen with beta radiation does not result from the immediate penetrating gamma or neutron radiation associated with detonation of nuclear devices since the dose of such radiations necessary to severely

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damage the skin results in early deaths from damage to the bone marrow and the deep organs. Thus the skin burns observed in the Japanese casualties from the Hiroshima and Nagasaki bombs were not the result of ionizing radiation and were caused chiefly by thermal radiation. Fallout radiation associated with these bursts was insignificant.

___.3 CHARACTERISTICS OF FALLOUT MATERIAL.

The chemical and physical make-up of fallout will vary according to the type of terrain or soil over which the detonation occurs. All fallout is particulate in nature, but the size of the particles will depend to some extent on the physical and chemical characteristics of the soil. The fallout associated with the Castle detonation, March 1, 1954, was a white, powdery material largely composed of incinerated coral. Aside from the radioactive component, the calcium oxide of the material was in itself irritating to the skin due to its caustic nature. Moreover, it was probably partly dissolved in the perspiration on the skin, thus increasing its irritating action. This also may have enhanced the radiation to the skin by bringing the radioactive materials in closer contact with the skin. The presence of irritating chemicals on the skin is known to enhance the radiation effect (MacKee, Cipolarro and Montgomery). Fallout produced from other types of soil, not predominantly coral, might vary considerably in chemical and physical make-up and ability to irritate the skin. Color and particle size would also vary. For instance, siliceous type soils would probably form much less irritating fallout.

The particulate nature of the material results in a spotty distribution of lesions on the body. The Marshallese claimed that the material adhered closely to the skin and was difficult to brush off. This was borne out by the difficulties encountered in decontaminating the skin of the exposed individuals.

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___.4 SOURCES OF RADIATION FROM FALLOUT.

Fig. 1 is a rough diagramatic sketch showing the relatively uniform distribution of fallout on the ground, buildings, trees and personnel. The penetrating gamma radiation which is represented by the wavy, shaded areas penetrates many yards in air before it is attenuated appreciably, while the beta radiation represented by the stippling is completely attenuated in several feet. Damage to the skin results largely from the beta component of the fallout in view of the fact that all of the beta radiation entering the skin is absorbed in the skin and because of the high beta to gamma ratio. Estimates of this rationvary widely up to 1/150, depending on the exposure conditions. The skin does receive some radiation from penetrating and soft gamma radiation, but by far the greater part of the dose is contributed by the beta radiation. Alpha emitters are usually not present in fallout to any great extent and due to their very weak penetrating ability, they are not likely to add significantly to the skin damage.

The skin dose results from two sources of beta radiation: the fallout material in direct contact with the skin (contact hazard) contributes by far the largest part of the dose to the skin, and the material on the ground (beta bath hazard) contributes a much smaller amount. The fallout in contact with the skin will usually be spotty in distribution and due to the particulate nature will result in multiple point sources of radiation on the skin. Though radiation from these sources is largely from the skin surface, it is possible that some deeper radiation may result from percutaneous absorption as well as penetration into the dermal region via hair shafts, sebaceous and sweat glands. Some of the fission products are water soluble, and it is possible that some are lipid soluble, which would enhance this effect. Witten et al. have shown

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that thorium-x applied to the skin results in some percutaneous absorption and entry into the hair shafts and glands.

Beta dose to the skin from fallout on the ground will be largely confined to the lower parts of the body, particularly the feet and legs, since the beta particles are completely stopped in approximately two meters of air.

___.5 ESTIMATION OF SKIN DOSE

Measurement of beta doses to the skin from fallout is an exceedingly difficult problem due to the complicated spectrum of different energy beta emitters esent, the nonuniform distribution on the skin, and the fact that practical dose meters have not yet been perfected which will adequately discriminate between the beta radiation and the contaminating gamma component.

The penetration of beta particles into the skin depends, of course, on the beta energies of the component isotopes. Each radioisotope has its own characteristic spectrum of beta energies up to a maximum energy. Relatively few particles are of the maximum energy, however, and the average energy (roughl one-third of the maximum energy) and the 50 per cent attenuation thickness of tissue are more meaningful in estimating skin effects. Thus an isotope emitting low energy radiation, confined largely to the dead, horny layer of skin, would be relatively ineffective; more energetic radiation, penetrating through the epidermis could result in transepidermal necrosis; and deeper penetration into the dermis could result in more severe ulcerating lesions. Fig. 2 shows roughly the tissue depth necessary to produce 50 per cent attenuation of the beta particles from several isotopes.

In Table 1 data from animal studies from several investigators show the evergy dependence of beta particles from various isotopes in producing recognizable skin reactions. Note that the surface doses for threshold reaction (erythema, epidermal atrophy) are fairly dependent on the energy of the beta

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particles of the various isotopes. Thus it takes 20,000 - 30,000 rep from S^{35} (ave. energy 0.05 mev.) to produce a reaction, while it takes only 1,500 - 2,000 rep of Sr^{90} or Y^{90} (av. evergy 0.3, 0.7 mev.) to produce the same reaction.

The degree of skin damage therefore is dependent on the absorbed dose at a certain critical depth in the skin. Moritz and Henriques found that the dose at 0.09 millimeters depth of the pig skin (estimated to be the epidermal thickness) was constant within several hundred rep to produce transepidermal injury. Wilhelmy has also noted that it takes roughly the same dose of electrons and soft X rays at the level of the subpapillary layer to produce erythema. On this basis, Parker has advocated the use of beta-detecting instruments with chamber walls corresponding in milligrams per square centimeter to the thickness of the relatively inert epidermal layer. Thus in expressing skin dosage, it is probably more informative to use the depth dose at a level corresponding to the basal cell layer of the epidermis.

Table 1 also indicates the species difference in skin sensitivity to beta radiation. Rabbits and sheep required larger doses than mice to produce the same effect with roughly the same energy beta. Porcine skin, which is reputedly more like human skin than other animals, apparently is more sensitive than the rabbit or sheep skin. Some of these differences, aside from species differences, may be due to variation in thickness of the epidermis of different species and differences in techniques used.

Table 2 shows beta dosage data from some human experiments and accidents found to produce various effects on the skin. These data must be interpreted with great caution due to differences in experimental techniques and dosimetry. The authors have taken the liberty of interpreting the severity of the skin reactions given by these investigators in degrees. A first degree reaction implies erythema and/or dry desquamation; a second degree, transepidermal necrosi

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with ulceration; and third degree, lesions which show deeper dermal involvement with breakdown and the development of chronic radiation dermatitis. It can be seen that there is a considerable variation in dose reported to produce the various reactions.

In the Marshallese the dose to the skin could not be calculated with any degree of accuracy due to the aforementioned reasons. The majority of the beta radiation was of low energy (average 0.1 mev, Sondhaus et al.) and accounted for the fact that most of the lesions were superficial in nature. However, there was sufficient penetration of more energetic components at the level of the hair follicles to result in temporary epilation. Due to the rapid attenuation of beta particles in tissue, the skin surface dose may have been quite high. The contribution of beta radiation to the skin of the Marshallese from the ground has been estimated by Sondhaus et al. to have been about 2,000 rep to the feet, 600 rep at hip level and 300 rep to the head. These doses were insufficient in themselves to produce detectable lesions, though they probably contributed significantly to the severity of the foot lesions that occurred.

___.6 EFFECTS OF FALLOUT RADIATION ON THE SKIN.

___.6.1 ACUTE EFFECTS. In general beta radiation effects on the skin are similar to effects produced by more penetrating radiation such as gamma or x-radiation (Low-Beer; MacKee, Cipollaro and Montgomery; Warren; Nodl; and Walbach). However, the less penetrating beta radiation produces more superficial lesions with less damage to the dermis. The lesions are more like those produced by grenz-rays and ultra-violet rays (MacKee, Cipollaro and Montgomery; Ellinger). Consequently, they are usually less painful and heal more rapidly. The time sequence of beta lesions varies considerably with the dose to the skin A general description of the sequence of changes is presented below.

___.6.1.1 EARLY EFFECTS. During the first 24-48 hours after exposure, itching, burning, or tingling sensations of the skin are usually experienced.

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These symptoms may also involve the eyes with accompanying lachrymation. As pointed out earlier, fallout of an alkaline nature may contribute to this symtomatology. The above symptoms occurred in many of the Marshallese. In more severely damaged skin, erythema, edema and areas of blanching may be noted. Erythema was not observed in the Marshallese, perhaps due to the dark color of the skin.

___.6.1.2 LATENT PERIOD. The early signs and symptoms usually disappear within a few days and a relatively asymptomatic latent period ensues. The length of this latent period may vary from a few days to several weeks and is related to the dose to the skin; the higher the dose, the shorter the latent period. In the Marshallese, the more heavily exposed group developed lesions about two weeks after exposure, a week earlier than the less heavily exposed groups.

___.6.1.3 DEVELOPMENT OF GROSS LESIONS. Following the latent period the evidence of skin damage becomes apparent with intensification of signs and symptoms. A secondary wave of erythema may be seen along with gross changes in the skin. Such changes may be in the form of simple tanning or more marked pigmentation with the formation of macules, papules, or raised plaques of thickened pigmented skin. Mild lesions may cause only slight itching and burning and superficial desquamation from the center of the lesion outward, leaving depigmented thinned areas of epidermis which gradually repigment and heal the following week or so. In the more heavily exposed Marshallese group of 64 people, about 90 per cent developed multiple, spotty, pigmented lesions on exposed parts of the body. Most of these lesions were superficial in nature (see Figs. 3, 4, and 5). More severe exposure to the skin results in vesiculation and ulceration. Such lesions may be quite painful and secondary infection may occur. They require longer to heal and may result in some degree of atrophy

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and scarring of the skin. Repigmentation may be long delayed or may never be complete. Only about 20 per cent of the Marshallese group referred to developed ulcerating lesions and secondary infection occurred in a few cases. Lesions on the dorsum of the feet were generally the most severe, showing bullae formation followed by ulceration (Fig. 6). At three years after exposure some of these lesions continue to show incomplete repigmentation of the skin with atrophy or scarring in some cases (see Fig. 7).

Epilation may occur along with the development of the skin lesions. The head region is more sensitive to epilation than the axillary, pubic, or eyebrow regions. If the radiation dose to the follicles has not been too high, regrowth of hair commences in several months. Permanent epilation may result if the skin dose is high. Usually by five or six months, regrowth of hair is complete. In the Marshallese group, spotty epilation of varying degrees occurred in 90 per cent of the children and about 30 per cent of the adults (Fig.8). Regrowth of hair commenced in all cases about 3 months post-exposure and by 6 months, hair was of normal color, texture and abundance (Fig. 9). Though change of color of hair from black to gray has been frequently observed in animals (Hance and Murphy; Chase), regrowth is usually of normal color in the human being. However, Conard and Tessmer have reported a case in which regrowth of the hair of the eyebrows (previously black) regrew white in a lesion presumably due to fission product contamination.

___.6.2 CHRONIC EFFECTS, CARCINOGENESIS. Following large doses of beta radiation, imperfect healing may result. Damage to the vessels of the dermis may result in sufficient impairment of circulation to cause cycles of breakdown and repair of the epidermis or chronic, indolent ulcers may result. Also commonly seen are atrophy, scarring, keratosis and telangiectatic vessels. The hair follicles, sweat and sebaceous glands may be injured sufficiently to result

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in permanent epilation and dryness of the skin. Such lesions are fertile ground for the later development of malignant change. Lesions of the skin resulting from beta radiation are less likely to result in chronic radiation dermatitis than are the lesions produced by more penetrating radiation such as are sometimes seen following X-ray or radium therapy.

Malignant changes in the skin have been reported in animals following beta radiation (Raper et al. Brues, Glucksman, Kolotsky, Shubik), but so far as the authors are aware, such changes have not been reported in the human being. Though malignancy usually develops at the site of chronic radiation dermatitis, as a result of repeated exposures to radiation, it may develop as a sequel to mild exposures with little chronic changes in the skin. It has been reported to occur in animals following a single exposure to beta radiation with little or no chronic change in the skin. (Raper et al.)

In view of the superficial nature of most of the Marshallese lesions and the low evidence of chronic effects in the skin, the likelihood of skin cancer in this group seems diminished.

___.6.3 HISTOPATHOLOGY OF BETA LESIONS. By and large, the histopathological changes in the skin produced by beta radiation are much the same as those produced by gamma or X rays. Since histological changes induced by the latter radiations have been well documented (MacKee, Cipollaro and Montgomery; Warren; Bloom and Bloom; and Walbach, etc.), a detailed description of the changes induced by beta radiation will not be presented. A limited number of studies of the histological changes in the skin of animals (Snider and Raper; Moritz and Henriques) and in man (Low-Beer) from beta radiation have been reported.

In general the changes produced by beta radiation are more superficial than those produced by more penetrating radiations with relatively much greater damage to the epidermis than to the dermis. With fallout radiation

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the damage is spotty in character with areas of damage surrounded by relatively normal tissue.

The histopathological changes induced in the skin by fallout in the Marshallese lesions were studied in section of a number of biopsies taken during the first 7 weeks, at 6 months and at 2 years. Details of these changes can be found elsewhere (Conard et al.). Some of the major changes seen are summarized below. During the early,acute period of the lesions, the epidermis showed marked damage characterized by atrophy and flattening of the rete pegs with disorganization of malpigian and basal layers and marked cellular changes (pleomorphic nuclei, pyknosis and cytoplasmic halos). Additional features were atrophy or absence of the stratum granulosum, imperfect keratinization, and loose fibrillation and hyperkeratosis of the stratum corneum. Cells laden with pigment were frequently present throughout the epidermis. In the dermis the changes were largely confined to the upper part with edema, telangiectasis of vessels with perivascular infiltration of lymphocytes. Chromatophores filled with melanin were prominent. Fig. 10 shows some of these changes in a pigmented lesion biopsied 3 weeks after exposure.

By six months there was considerable improvement in the histological appearance of the lesions. The following changes were found to persist in varying degrees: focal atrophy of the stratum granulosum, slight focal pigmentary disturbances in cells of the basal layer, and slight disturbances in polarity of the epithelial cells in basal papiliary projections. In the dermis, telangiectasis of slight to moderate degree persisted.

At two years, biopsies at sites of persistent gross abnormalities revealed that none of the lesions were neoplastic or showed alterations suggestive of a precancerous condition. In some sections, acanthosis, absence

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of pigment in the basal layer and atrophy and benign dyskeratosis were noted in the malpigian layer of the epidermis. In the dermis degenerative changes in the collagen were noted frequently, and capillary dilation persisted. Some of these features may be seen in Fig. 11, which is a section taken at two years of a lesion on the back of the neck which showed gross pigment changes.

___.7 THERAPY OF BETA LESIONS

The treatment of beta lesions during the acute stage is very similar to the treatment of thermal burns. Mild lesions will only require daily cleansing and application of bland antipruritic lotions and ointments. Calamine lotion with 1 per cent phenol is soothing. Analgesic and anesthetic ointments are helpful in allaying more painful symptoms and in keeping the skin soft in lesions that are dry and thickened. Antibiotics applied locally and/or parenterally should be used if secondary infection occurs, or prophylactically if the lesion is associated with severe leukopoenia from whole body radiation. The above treatment proved quite adequate with the Marshallese lesions.

In severe lesions with the development of necrotic tissue, surgical debridement should be carried out. Use of pressure dressings, splinting and elevation of affected parts may be necessary. Early skin grafting should be considered in cases developing painful or progressive chronic radiation dermatitis (Brown et al.). For more detailed therapy of radiation lesions, the reader is referred to standard textbooks on the subject such as that of MacKee, Cipollaro and Montgomery.

Several agents have been reported in recent years to be beneficial in the treatment of radiation lesions of the skin. Among these are preparations of the Aloe Vera plant (Lushbough; MacKee, Cipollaro and Montgomery). The use of vitamins such as A and D are advocated by some investigators in the acute stages. The use of triiodothyronine preparations in such lesions

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appears to be beneficial from results of preliminary work (Nickson). Prednisone injections have been reported to reduce post-irradiation inflammation (Matthewson). Further clinical experience with these agents is necessary before they can be recommended for general use in the treatment of beta burns.

___.8.1FACTORS INFLUENCING SEVERITY OF SKIN LESIONS FROM FALLOUT

___.8.1 PHYSICAL FACTORS. Usually fallout material must be in contact with the bare skin to result in significant skin damage. Most of the lesions in the Marshallese occurred on exposed parts of the body, and protection was afforded by clothing, even a single layer of cotton material. Since clothing would probably not result in more than about 25 per cent attenuation of the beta particles, additional protection must have been afforded by the fact that the loosely-fitted clothing tended to hold the radioactive material away from the skin. Avoidance of skin contamination by taking shelter offers almost complete protection. No lesions developed in those Marshallese who remained in their houses during the fallout.

The ultimate dose to the skin depends on the radiation characteristics of the fallout material, the time after detonation that the fallout occurs, and the length of time that the material is in contact with the skin before contamination is accomplished. Due to the process of radioactive decay which is quite fast during the first few hours, the earlier the time of the fallout, the greater is the dose rate from a given sample. This fact emphasizes the importance of early decontamination of the skin, particularly if contamination takes place during the first day after detonation. The fact that thorough decontamination of the Marshallese was not accomplished until their evacuation some two days after the accident, resulted in an appreciable increase of their skin dose. Those individuals that bathed or went swimming during the early period developed few lesions.

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___.8.2 BIOLOGICAL FACTORS. There are certain biological factors known to influence the sensitivity of the skin to radiation. In addition to species differences referred to, it is known that the skin of certain parts of the body is more sensitive to radiation than that of others. In general, the thinner-skinned flexor surfaces of the body are more sensitive than the thicker-skinned extensor surfaces (MacKee, Cipolarro and Montgomery). This was found to be true in the Marshallese. Lesions were more prevalent on the front and sides of the neck, axilla and antecubital fossae. Another factor is associated with pigmentation of the skin. Darker-skinned people, brunettes, are known to be less sensitive to radiation than blondes or people with ruddy complexions, and Negro skin is the most resistant (MacKee, Cipollaro and Montgomery; Bloom and Bloom).

Areas of the body where perspiration is more profuse, such as the folds of the neck, axillae, and antecubital fossae tend to cause the fallout to stick and collect. It was found that skin lesions in these areas were more abundant in the Marshallese. This effect is increased in a warm, humid climate, such as in the Marshall Islands.

___.9 CONCLUDING REMARKS

As a result of the Marshallese accident, the potentialities of serious injury to the skin from fallout associated with the detonation of large nuclear devices are apparent. Of concern also is the occurrence of similar radiation injuries to the skin from accidental exposure to radioisotopes which are being used increasingly.

The skin hazards associated with fallout can be greatly reduced by taking simple precautionary measures. Much was learned from the Marshallese experience in this regard. This group of people was not aware of the hazards of fallout and only minimal, if any, efforts were made to protect themselves.

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This situation represents an extreme example, and the extensiveness of the skin effects could have been greatly reduced had proper measures been taken. Based on the experiences of these people during the critical fallout period and the skin lesions that developed on an individual basis, the following facts emerge:

1. Avoidance of contact of fallout material on the skin by taking shelter or covering the body with clothing virtually eliminates the possibility of skin effects.
2. Prompt, thorough decontamination of the skin and hair is of utmost importance. Repeated scrubbing with soap or detergent and water may be necessary. If contamination of the hair is severe, it may be advisable to clip the hair close or shave the head.
3. Areas of the body where perspiration is more profuse tend to cause the fallout material to collect. Such areas should be carefully checked for contamination. A warm, humid climate will naturally aggravate this effect.
4. Moderately severe beta lesions of the skin and epilation may result from fallout situations in which the whole body penetrating dose of radiation is sublethal. With such doses, the skin lesions do not appear to complicate the radiation syndrome.
5. In situations where skin lesions are associated with larger doses of whole body radiation with marked leukopoenia, such lesions might become secondarily infected more easily and afford portals of entry leading to bacteremia or septicemia.
6. Severe skin irradiation with minimal whole body irradiation might result in fallout situations where prompt evacuation from the contaminated area occurred, but skin decontamination was delayed.

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7. Early skin and eye symptoms might be mildly disabling during the first day or two after exposure to fallout and later symptoms associated with full-blown lesions might be quite disabling. Late effects on the skin in the form of chronic radiation dermatitis and malignancy are possible complications.

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LEGENDS

Figure 1. Diagramatic sketch showing distribution of fallout. Gamma radiation represented by wavy shaded areas, beta radiation by stippling.

Figure 2. 50% attenuation in skin of various isotopes.

Figure 3. Early hyperpigmented moculopopular neck lesions at 15 days. Case 39, age 15, F.

Figure 4. Extensive lesions in 13-year old boy at 46 days post exposure. Case 26.

Figure 5. Same case as in figure 4 six months after exposure showing healed lesions and regrowth of hair.

Figure 6. Hyperpigmented raised plaques and bullae on dorsum of feet at 28 days after exposure: One lesion on left foot shows deeper involvement. Feet were painful at this time.

Figure 7. Same case as in figure 6 six months later. Foot lesions have healed with repigmentation, except depigmented spots persist in small areas where deeper lesions were.

Figure 8. Epilation in 7-year old girl at 28 days after exposure. Case 72.

Figure 9. Same girl as in figure 8 six months after exposure showing complete regrowth of normal hair.

Figure 10. Section from beta lesion of neck at 3 weeks after exposure to fallout. (X 100) Epidermis: extensive transepidermal damage (with slightly less involved zones on either side). Loose lamination of stratum corneum, absence of stratum granulosum. Parakeratinization with exfoliation of pigment containing cells. Disorganization of the malpigean layer. Dermis: mild edema of pars papillaris with indistinct capillary loops. Pesivascular cellular infiltrate (lymphocytes and mononuclear phogocytes), in superficial corium with telangiectasis. Case 26.

Figure 11. Section (512 x) from lesion on back of neck at two years after exposure to fallout. Lesion showed mottled pigmentation and depigmentation grossly. Section shows some loss of pigment in the basal layers of the epidermis and telangietasis in the dermis. Case 39.

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Surface Doses Required to Produce Recognizeable Epidermal Injury				
Investigator	Animal	Isotope	Ave. Energy (mev.)	Surface Dose (rep)
Henshaw, et al.	Rats	P^{32}	0.5	1,500-4000
Snider and Raper	Mice	"	"	2,500
Raper and Barnes	Rabbits	"	"	5,000
Lushbaugh	Sheep	S^{90}	0.3	2,500-5000
Moritz and Henriques	Pigs	S^{35}	0.05	20,000-30,000
"	"	Ca^{60}	0.1	4,000-5,000
"	"	Cs^{137}	0.2	2,000-3,000
"	"	Sr^{90}	0.3	1,500-2,000
"	"	Y^{91}	0.5	1,500-2,000
"	"	Y^{90}	0.7	1,500-2,000

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Human Exposure to Beta Radiation			
Investigator	Radiation	Est. Dose (rep)	Reaction
Wirth and Raper	P^{32}	635	1st. degree (threshold)
"	"	1180	2nd degree (threshold)
Low-Beer	"	143*	1st. degree (threshold)
"	"	7-17,000	2nd degree
Robbins et. al.	Cathode rays (1200 Kv)	1-2000	3rd. degree
Knowlton et. al.	Fission Products	3-4000	2nd. degree
"	(1 Mev. Ave. Energy)	5-10,000	3rd. degree
"	"	5-10,000	3rd. degree
"	"	8-16,000	3rd. degree
* Estimated dose in 1st. mm. layer.			

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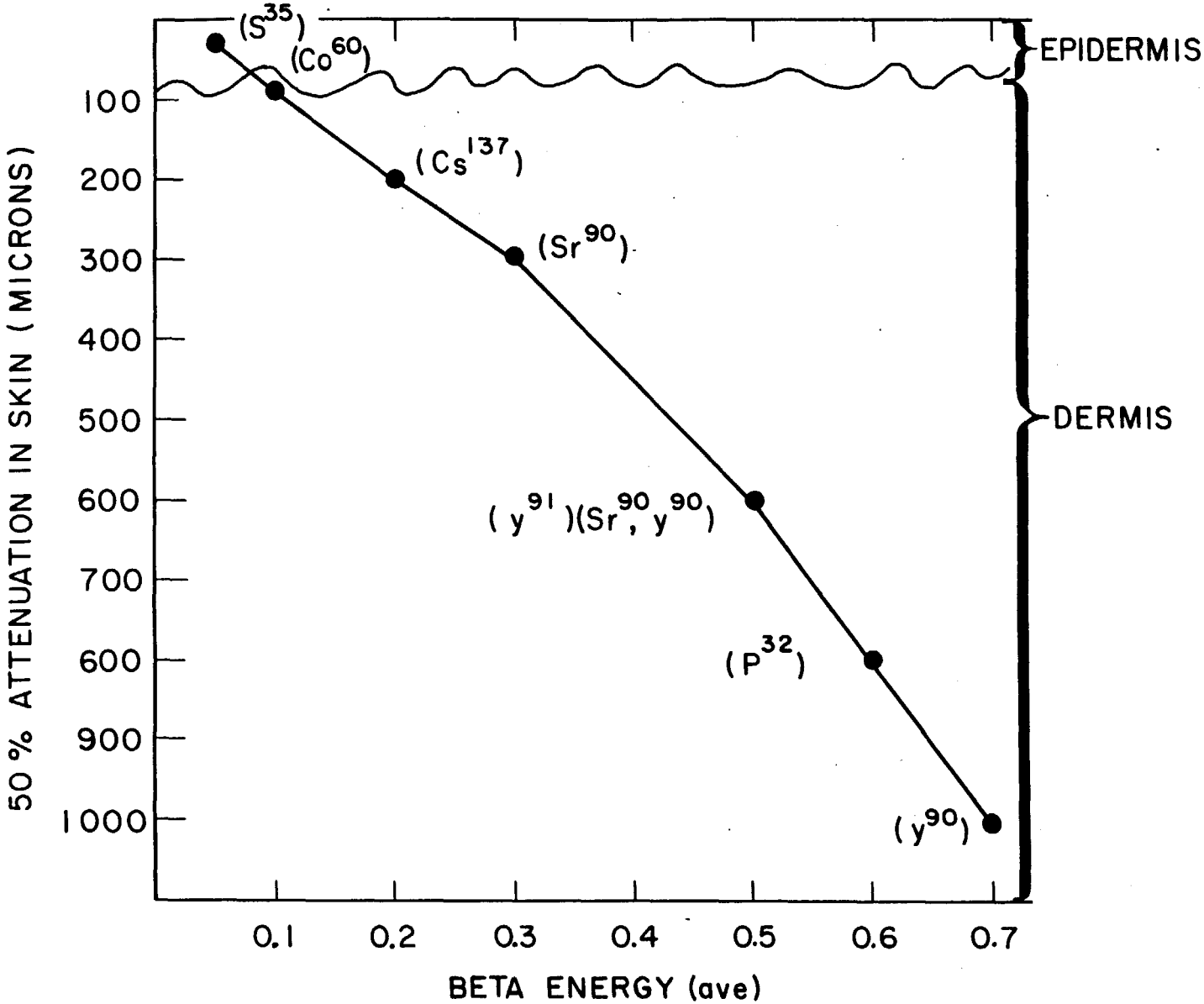

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the damage is spotty in character with areas of damage surrounded by relatively normal tissue.

The histopathological changes induced in the skin by fallout in the Marshallese lesions were studied in section of a number of biopsies taken during the first 7 weeks, at 6 months and at 2 years. Details of these changes can be found elsewhere (Conard et al.). Some of the major changes seen are summarized below. During the early, acute period of the lesions, the epidermis showed marked damage characterized by atrophy and flattening of the rete pegs with disorganization of malpigian and basal layers and marked cellular changes (pleomorphic nuclei, pyknosis and cytoplasmic halos). Additional features were atrophy or absence of the stratum granulosum, imperfect keratinization, and loose fibrillation and hyperkeratosis of the stratum corneum. Cells laden with pigment were frequently present throughout the epidermis. In the dermis the changes were largely confined to the upper part with edema, telangiectasis of vessels with perivascular infiltration of lymphocytes. Chromatophores filled with melanin were prominent. Fig. 10 shows some of these changes in a pigmented lesion biopsied 3 weeks after exposure.

By six months there was considerable improvement in the histological appearance of the lesions. The following changes were found to persist in varying degrees: focal atrophy of the stratum granulosum, slight focal pigmentary disturbances in cells of the basal layer, and slight disturbances in polarity of the epithelial cells in basal papiliary projections. In the dermis, telangiectasis of slight to moderate degree persisted.

At two years, biopsies at sites of persistent gross abnormalities revealed that none of the lesions were neoplastic or showed alterations suggestive of a precancerous condition. In some sections, acanthosis, absence

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THE HEMATOLOGY OF IONIZING RADIATION

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E.P. Cronkite, V.P. Bond and R.A. Conard

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THE HEMATOLOGY OF IONIZING RADIATION

B.P. Cronkite, V.P. Bond, and R.A. Conard

8.1 Scope and Status.

The advent of the atomic era has been a great stimulus to research in the field of hematology. This is quite understandable because changes in the blood and blood-forming organs, imperfect indices though they may be, still remain the most sensitive biological evidences for excessive exposure to penetrating ionizing radiations. With this chapter will be considered the more common changes that are induced within blood and blood-forming organs by acute and chronic exposure to ionizing radiations.

8.1.1. Early Reports. These changes have been studied extensively since the early part of this century. Despite this, a diverse mass of data exists in the literature, arising primarily from the inability of the early investigators to describe and measure adequately the dosage of ionizing radiation; accordingly, there are many conflicting reports. However, the original reports of Heinecke, 1903-5, remain qualitatively correct as does the excellent report on blood changes in patients undergoing therapeutic irradiation (Minot and Spurling). An excellent analytic review up to 1942 is that of Dunlap in Warren's general review. Since then there have been various general dissertations on the relation of hematopoiesis to the effects of ionizing radiation (Lawrence, et al., and Osgood).

8.2 Cause of Discrepancies in Data.

In addition to the discrepancies in dosage measurements, the differences in species sensitivity and response were not appreciated until the last two decades. Of particular importance is the fact that many investigators were not aware of the difference between the pictures produced by uniform total-body exposure, unequal total-body exposure, and that produced by partial-body exposure. Complete or

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partial shielding of a portion of the body will greatly increase the amount of radiation that can be tolerated. Many of the phenomena that have been described for irradiation of portions of the body can be produced only by amounts of radiation that are greatly in excess of the amount of radiation that will kill one hundred per cent of the animals. For example, many of the characteristic histologic lesions of the gastrointestinal tract produced by local irradiation do not develop with amounts of radiation that produce a 100% mortality when the entire body is uniformly and simultaneously irradiated. The response of the peripheral blood is particularly altered. In a general sense, 300 r in a single dose to the entire body will give the same hematologic response as more than 600 r to the entire skeletal areas when the abdomen is shielded. These preliminary remarks express the opinion of the authors in emphasizing the futility of comparing hematologic responses unless the dosage factors, location and amount of tissue injured are accurately known. Total absorption of radiation energy as measured by the gram roentgen is not satisfactory either, because the distribution of the absorbed energy throughout the body, in part, determines the response to the total energy absorbed (see chapter by Bond et al.). Therefore, the remarks in this chapter will be largely limited to the effects on the blood produced by evenly distributed, penetrating, ionizing radiations of the same type to the whole body of animals. This type of experiment can be readily duplicated. However, it must be appreciated that these conditions may not approximate the conditions of radiation during an atomic bomb explosion. For example, there may be considerable shielding of various portions of the body by concrete and structural steel after detonation of an atomic bomb over an urban area. Regardless of that fact, this type of laboratory study affords a starting point for study of radiation phenomena of the whole animal that will serve as a point from which one can begin to extrapolate to man. This discussion further will be generally limited to the sublethal and zero to 100 per cent lethal range.

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Since one purpose of presenting this material is to provide a more complete background by which one might better understand and prophesy from animal data what changes may be anticipated in the blood of man after an atomic bomb explosion, it would be desirable if the radiation from atomic bombs were uniform and monochromatic. Unfortunately, diverse rays of various energies and unequal shielding by buildings, heavy machinery and miscellaneous intervening objects in an urban area will produce a shadowing effect and unequal depth doses in the body of man and give, in many instances, unequal total-body exposure to the spectrum of ionizing radiation produced by an atomic explosion. In addition, the energy of the scattered radiation will be a function of the scattering medium.

8.3 Mechanism of Injury.

The mechanism by which the cellular changes take place has been the source of considerable research. Changes in the hematopoietic system are obviously a response to the basic effects of ionizing radiation upon protoplasm in general. These effects are considered in separate chapters (see Chapters VI and VII). The problem of radiosensitivity of blood cells in the peripheral blood in contrast to cells in the hematopoietic organs, particularly the stem cells, has been investigated at length. At the present time there is no good evidence that the mature cells in the peripheral blood are significantly affected by amounts of radiation in the sublethal and 0-100 per cent lethal range (roughly 0-1000 r will cover all mammalian species), with the probable exception of lymphocytes. All the evidence indicates that changes in the peripheral blood are the direct and indirect results of injury to the formative cells in the hematopoietic organs. In the higher dose ranges, hematopoiesis is stopped, at least temporarily. From about the LD_{50} (that dose which kills 50 per cent within a given time limit) down, hematopoiesis is impaired for a variable time.

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8.3.1 Direct and Abscopal Effects. The problem of direct versus indirect (abscopal) injury of the hematopoietic organs has interested many workers and as yet has not been satisfactorily answered. Kornblum, Haerner and Henderson state that partial body radiation, as in therapy, has both a direct and an indirect effect upon the peripheral blood and organs of hematopoiesis. The indirect effect upon non-irradiated parts is presumably mediated through circulating toxic products. Similar indirect effects have been alluded to by many other workers. Osgood, by virtue of a bone marrow culture technique, concluded that there were no indirect effects. Barnes and Furth, using parabiotic animals, concluded that there was a slight but definite indirect effect on the non-irradiated rat of the parabiotic pair. Lawrence and associates, in a complete analysis of the problem, reviewed the existing literature and presented evidence, based on cross-circulation experiments, that led them to believe that there is no good evidence for the presence of circulating toxins that significantly affect the peripheral blood. It is the opinion of these writers that the subject is not settled but the weight of the evidence today strongly suggests that there is no circulating "leukotoxin" that acts in a destructive manner on the blood and organs of hematopoiesis or other tissues. The use of the term "indirect" by biologists has been questioned by Mole since chemists have priority on its use in a manner distinctly different from the way in which it has been used by biologists. Chemists use it to describe the effects of radiation mediated by the products of irradiation of water (the chemical effects of free radicals, peroxides, etc.). Accordingly, Mole has coined the term "abscopal" to describe effects taking place remotely from the site of irradiation. The problem of abscopal effects has been investigated by Raventos and Bond et al. The latter group concluded that abscopal effects, such as spleen, thymus and adrenal weight changes, develop only if and when the irradiation given imposed a severe stress on the animal as indicated by gross illness. Under such conditions, changes in spleen, thymus and adrenal weights are characteristic of the stress syndrome.

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Edelman et al. have reported evidence for the existence of a radiotoxin in irradiated animals. Similar experiments were repeated by Campo et al. and no evidence was found for existence of a toxic effect in serum from irradiated animals as measured by mortality or splenic thymic weight decrease in animals transfused with serum obtained from irradiated animals. These experiments do not support the concept but negative experiments do not eliminate the possibility of a radiotoxin.

3.4 Rate of Change in Peripheral Counts.

The rate of change of various elements in the peripheral blood is related to the usual life span of the blood cell. Hence, the rate of change in the level of the particular cells in the peripheral blood following radiation injury, when production is impaired, or ceases, is the result of the balance between the rate of utilization and rate of production. In the case of the red blood cell of man, which has a life span of about 125 days--a much longer life span than all of the other formed elements--changes in the red blood cell level take place at a much slower rate than white cells or platelets. In man, if all red-cell formation were to cease, there would be a daily deficit of about 0.83 per cent of the total red-cell mass (Wintrobe). The turnover of platelets, granulocytes and lymphocytes is not known with certainty. Platelets are reported to have a life span of perhaps 4 to 5 days (Lawrence and Valentine). Granulocytes reputedly have a life span of 3 to 5 days (Adams, Saunders and Lawrence). Lymphocytes are reported to be extremely short lived, with a life measured in hours (Lawrence, Ervin and Wetrich). Hamilton and Osgood, however, report a life span for some lymphatic cells of the order of 100 days which is not widely accepted. Except in the high-dose ranges, where all hematopoietic activity stops, the rate of disappearance or decrease in the number of white cells will be slower than the theoretic rate of utilization. This latter will be true only if the rate of utilization is normal after irradiation in the lethal range. Irradiation in the

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lethal range may either directly or indirectly increase the rate of utilization. For example, the animals become susceptible to infection, and the development of infections will definitely increase the rate of utilization. Thus the rates of utilization that are measured in an irradiated animal may at times give values that are greater than the normal utilization. In the case of platelets, this does not seem to be the case.

8.5 Sensitivity Factor.

There is considerable difference in the radiosensitivity of the stem cells. Precursors of erythrocytes (Bloom and Bloom) and lymphocytes (Warren) are extremely sensitive to ionizing radiation. The precursors of the granulocytic series are apparently less radiosensitive. Megakaryocytes appear relatively undiminished in number in the bone marrow of dogs exposed to lethal amounts of radiation for a period of 3 to 4 days after irradiation. In fact, megakaryocytes are still seen on the third day in the bone marrow of dogs exposed to 3000 r of 2.0 mev total body x-ray, an amount of radiation that is about seven times the hundred per cent lethal dose for dogs. In general, the immature and proliferating blood cells are more sensitive to irradiation than the adult blood cells. However, the reticuloendothelial cell, the common ancestor for all blood cells, is remarkably radioresistant. In other words, radiosensitivity of the blood-forming cell seems to go through a maximum in the course of maturation (fig. 1). Under normal conditions, the actively proliferating cells are the more radiosensitive. This last statement apparently does not hold for all conditions. Investigations by Jacobson et al. have shown that extremely hyperplastic erythroid tissue is markedly radioresistant. In addition, Tullis has presented histologic evidence that there are exceptions to the law of Bergonié and Tribondeau. It seems that the radioresistance of the reticuloendothelial cell and of hyperplastic erythroid tissue challenges in part the classical law of Bergonié and Tribondeau. This law states,

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"The biological action of roentgen rays is greater the higher the reproductive activity of the cell, the longer the period of its mitosis, and the less the degree of differentiation of the cell in respect to its morphology and function."

Recovery of the stem cells, their reproductive rate, the release from the marrow and the rate of destruction determine the reappearance rate of the peripheral elements. It may take many months for the number of cells in the peripheral blood to return to pre-irradiation levels (figs. 2 and 3). Why the peripheral level of leukocytes is sometimes set at a lower level for a long period is not known. Perhaps the release mechanism is altered. In this respect, Brecher et al. have shown that the level of blood cells in the peripheral blood of the mouse recovering from radiation injury is not a good index of the activity of the hematopoietic organs. For example, there may be extremely active hematopoiesis with persistent low levels of leukocytes in the peripheral blood. Residual injury of the formative cells may be manifested by the late appearance of blood dyscrasias. Similar delay in recovery was seen in the Marshallese (see section 8.6.5).

8.6 Variations in Number and Morphology of Blood Cells.

Specific changes in the morphology and number of cells in the peripheal blood have been extensively studied. Particular attention has been paid to the relationship of dosage to the magnitude and rate of changes in the blood. The changes that take place after a single exposure to ionizing radiation will be considered first. Jacobson and associates have studied extensively the effect of single doses of different magnitude upon the blood of rabbits. All mammals seem to follow the same general pattern, except for some differences in the rate of change.

LeRoy has described the hematologic changes that were observed in the Japanese casualties at Hirochima and Nagasaki. These changes will not be discussed in detail because the dosage factors and the general health of the Japanese are unknown factors. However, the general responses of the Japanese in respect to blood are

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comparable to that in laboratory animals in most respects, with the exception that the temporal relationships appear different. It seems that it took a longer time for the Japanese casualties to reach the minimum neutrophile and platelet levels than it does in laboratory animals. The reader is referred to the study of the hematology of atomic bomb casualties by LeRoy, and to the report of the hematological findings in the Marshallese exposed to fallout radiation (Bond et al.).

8.6.1 Lymphocytes. Lymphocytes are particularly sensitive to radiation. In vitro studies by Schrek show that there is an increased rate of destruction of normal lymphocytes after exposure to as little as 50 r. One of five suspensions of lymphocytic leukemic cells was relatively insensitive to x-ray. Schrek, in further studies, decided that, "x-rays accelerate a normal metabolic process in lymphocytes. The degeneration of irradiated and non-irradiated cells results from the development of single or multiple focal intranuclear areas of hydration."

The lymphocyte levels in the blood begin to decrease immediately after exposure. The magnitude and the rate of change are closely related to the amount of radiation received, particularly in the sub-lethal dose range. In the higher dose ranges the rate of disappearance of lymphocytes probably approaches the rate of utilization because production has been completely stopped; or disappearance may exceed the normal rate of utilization because the diffuse cellular injury may increase the demand for lymphocytes and their metabolic end productions. Thus it is easy to understand why changes in the lymphocyte levels can only be used in estimating sub-lethal exposure. Once all hematopoietic activity is stopped, changes become in part a function of normal utilization except when the dosage is so great that the cells are destroyed directly in the peripheral circulation. In rabbits (Jacobson et al.) a maximum decrease of about 25% in the lymphocyte count is detected 24 hours after exposure to 25 r. Recovery appears within two days. The greater the dosage, the greater the depression in the lymphocytes. At 800 r, a depression of 90% occurs in the first 24 hours. At a dosage of 800 r ($LD_{50/30}$)

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(that dose which kills 50 per cent of the animals within 30 days), recovery in the rabbit takes about 50 days from the time of the exposure. Between the 3rd and the 5th days after exposure, there is a temporary tendency for the lymphocytes to increase in number. This is followed by a decrease to almost the maximum depression that was present 24 to 72 hours after exposure (fig. 2). This type of recovery followed by a wave of destruction, is, in general, characteristic of all blood cells and tissues (Jacobson et al., Bloom). Similar changes were observed in swine exposed to 1000 kvp x-ray in various dosages, and in dogs after 2000 kvp x-ray (Cronkite et al.).

8.6.2 Granulocytes. In vitro studies on granulocytes have demonstrated that both the normal granulocytes and myelogenous leukemic cells are resistant to x-ray after doses of 1000 r (Schrek).

Changes in the number of granulocytes in the peripheral blood follow a different course (fig. 3). In general, all animals respond with a period of granulocytosis predominately neutrophilic or heterophilic (rabbits) during the first 24 to 48 hours after exposure to amounts of radiation in the sub-lethal and lethal range. This granulocytosis appears as two peaks in the rabbit at about 12 and 18 hours after exposure. The first peak may represent mobilization of granulocytes throughout the body. The second peak may be due to accelerated liberation of cells from the bone marrow. The granulocytosis usually does not last for more than 24 hours but may last longer in some species and under certain conditions. A definite granulocytosis, however, appears during the first 24 hours in the dog but the biphasic response of the rabbit was not observed. Generally, the maximum depression of the granulocytes is attained by 72 to 96 hours after exposure. Recovery of the granulocyte levels begins by 10 to 15 days after exposure, or sooner with small doses. In general, if granulocyte levels do not increase or remain constant, even though at a low level, by the 15th day, death usually ensues (Cronkite). As a rule, there are one or more abortive rises in the granulocytes that appear between the third and 12th days after exposure, depending on the animal species and the dose of radiation.

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This abortive rise is fairly consistent and apparently has little prognostic value. It may last for only 24 hours. The cause of this abortive rise in leukocytes is not well understood. It may be comparable to the waves of regeneration and destruction that have been described for other organs (Bloom). It has not been seen above LD_{50} in dogs and swine. Various explanations have been offered. Somatic mutations of precursors that result in abnormal progeny have been considered (Bloom) and Jacobson). These progeny or their precursors may have shorter life spans. There is no satisfactory explanation to date for this phenomenon.

8.6.3 Erythrocytes. Changes in the level of the red blood cells are much less striking in the early period after irradiation in the mid-lethal dose range. There is little increase during the first few days. In animals that survive radiation in the 0 to 100% lethal range there is a definite decrease in the levels of the red cell count, hematocrit readings and hemoglobins between the 10th and 30th days after exposure. The maximum degree of anemia is usually reached around the 15th to 20th days in the survivors. In the animals which do not survive, there is usually a marked decrease in the red cell levels a day or so before death. The decrease in the red cells are due to three factors: (1) decrease or cessation of production of red cells; (2) increased destruction; (3) hemorrhage (Jacobson et al.; Cronkite, Schwarz et al.; Davis et al.). The occasional macrocytosis that is seen in swine and other animals about 10 to 20 days after exposure to a low lethal dose is due to a concomitant reticulocytosis occuring as a result of regeneration of the bone marrow with release of large numbers of reticulocytes in the peripheral blood (Cronkite).

An increase in the number of the red cells is uncommon except in the high dose range, as was seen at Bikini during the atomic bomb test. There were some animals that developed a marked hemoconcentration within a few days of the exposure (fig. 4). The hematocrit of one goat attained a value of almost 80%. This hemoconcentration is due to dehydration resulting from anorexia, diarrhea, etc.

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Nucleated red blood cells appeared in large numbers in the goats and swine about 13 to 17 days after exposure to the atomic bomb radiation at Bikini (Cronkite). Comparable observations have been made on other animals (Warren; Jacobson et al.; Kromeke).

Reticulocyte disappearance is a very sensitive index of a single intense exposure to radiation in the lethal range (fig. 5). In view of the observations of Bloom of the great radiosensitivity of erythroblasts, one might logically expect the reticulocytes to disappear promptly. This they do within a period of about 48 hours following a single intense exposure to radiation in the lethal range (Jacobson et al; Cronkite). However, the disappearance of reticulocytes, at least in the rabbit, does not occur at as low a dose as does the reduction in the number of lymphocytes. In swine (fig. 5) and in the Japanese exposed to the atomic bomb explosion at Hiroshima and Nagasaki, a return of the reticulocytes was a good prognostic sign for recovery but did not invariably indicate a favorable outcome (LeRoy, Cronkite, Tullis and Tessmer).

Most recently Stohlman, Brecher, Schneiderman, and Cronkite demonstrated that ionizing radiations produce intravascular red cell damage and shorten red cell life span. This injury is indirect as well as progressive, i.e., it is more pronounced the longer the red cells remain in the irradiated animal although they need not be present at the time of radiation. The red cell injury is slight and in the earliest stages can only be detected by superimposing a second minimal insult such as tagging of cells with chromium which in itself does not shorten red cell life span. It is of considerable academic and practical interest that the widely-used chromium label for determination of red cell life span is not necessarily innocuous, and after irradiation either the more heavily tagged cells or the label itself is lost at an accelerated rate. The effect is probably due to the chromium metal and not to its radioactivity. During the thrombocytopenic phase of radiation injury when many red cells are extravasated and return to the general circulation via the lymphatics, this passage through an extravascular cycle adds further damage to the red cell resulting in readily measurable shortening of red cell life span.

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8.6.4 Platelets. Platelets decreased at a rate between that of the red cells and the granular leukocytes. Perhaps platelets are as sensitive an index to exposure to acute irradiation as the granulocytes in the rabbit (Jacobson et al.). In swine, goats and dogs, the decrease in platelets is definitely less rapid than that of the granular leukocytes (Cronkite). Frequently the platelets trend upwards for 4-5 days after irradiation following which there is a decrease until platelets disappear or become constant at a lower level. Above doses of radiation that produce a 90% mortality, the response of the platelets is maximal with platelets disappearing from the circulation by the 11th day. With lesser doses of radiation, the platelets do not completely disappear but become constant at a lower level. This level is apparently a function of the dose of radiation received. This new, relatively constant level may be maintained for 2-3 weeks.

The relative response of granulocytes and platelets at different per cent mortalities is illustrated in figures 6 and 7. With a 10% mortality the platelets approach zero but are maintained constant at about 5% of the normal range. At this dose the granulocytopenia is only moderate and infections were not prominent clinically. In contrast to this at 80% and 100% mortality, the platelets and the granulocytes reach zero and infections and hemorrhage are obviously present before death.

The foregoing statements cover the general picture of what occurs to the peripheral blood elements after a single intense exposure to ionizing radiation. However, this does not give a sufficiently complete picture of various facts and observations about the response of the blood to total body or to rather large segmental exposure as seen in therapeutic irradiation of some malignancies, or to what might be anticipated following exposure to mixed radiations of different penetrabilities.

8.6.5 Hematological Findings in the Marshallese Exposed to Fallout Radiations. In March 1954, groups of Marshallese and Americans were accidentally exposed to fallout gamma and beta radiations from a megaton device. The groups were observed

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carefully after the exposure, and details of clinical and laboratory findings have been published (Cronkite, Bond and Dunham). The most heavily exposed group was composed of 64 Marshallese located on Rongelap atoll at the time of the accident, and the findings in this group will be dealt with most extensively here. None of those exposed died as a result of the irradiation. The Rongelap people received an estimated dose of 175 r of gamma radiation (air dose), sufficient beta radiation dose from adherent material to result in lesions in some exposed areas of skin (chapter by Conard et al.), and minimal internal contamination with radionuclides (chapter by Robertson and Cohn). Considerable uncertainty exists in the magnitude of doses received; however, the Rongelap group can be considered to represent the high sublethal exposure range. Hematological depression was considered to have resulted from the gamma exposure with little or no contribution from the surface beta or internal emitters.

Serial hematological determinations including total white count, differential, platelet count and hematocrit were made on each exposed individual over the initial observation period of 72 days, and repeat determinations have been made at 6 months, and then at yearly intervals following the exposure (Conard et al.). Details of methods and initial findings have been reported (Bond et al.). Unexposed groups for comparison were observed initially and at the times of follow-up studies; however, variations in findings in control groups have presented difficulties in precise interpretation, as in the Japanese exposed at Hiroshima and Nagasaki.

The average leukocyte and platelet counts are shown graphically in figures 8, 9 and 10. The first counts on the Rongelap group were done on post-exposure day 3, at which time a drop in total white count was evident (the exposed Americans showed a rise in total white count in the first 48 hours, as has been reported previously). The count then fluctuated, perhaps as a result of the beta lesions, with no severe depression over the first four weeks. A marked depression then occurred, reaching minimum levels at 6 weeks. The counts approached the levels of

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the unexposed populations by 2 years. The time course of neutrophil count changes followed closely that of the total white count. Lymphocyte depression was early and profound (fig. 9) with gradual return toward normal. The counts remained below that of the unexposed groups at 3 years. The platelet count reached a low at approximately 4 weeks (fig. 10) with fairly rapid initial recovery followed by a secondary depression and slow return towards normal. At three years the mean platelet counts were still slightly below the mean of the unexposed population. The hematocrits at no time were remarkably different from the unexposed levels.

At the times of peak depression, some individuals had neutrophil counts below 1000/mm^3 and platelet counts below 75,000/mm^3. No infections attributable to the neutropenia were observed, however, and an epidemic of upper respiratory infection at approximately the time of maximum neutrophil depression was equally severe in the heavily and mildly exposed groups. No hemorrhagic phenomena could be attributed to the platelet depression. All individuals were ambulatory throughout, and no therapy (other than for the skin lesions) beyond that routinely required for any large groups of individuals was necessary or administered because of the radiation exposure.

The findings allow accurate documentation of the response of the human being to total-body gamma exposure in the high <u>sublethal</u> range, not possible in the Japanese exposed at Hiroshima and Nagasaki. The time course differs in important aspects from that seen in most laboratory animals. The total white count shows an early rise, with only minimal lowering until maximum depression occurs at approximately 6 weeks. A similar trend is seen with the neutrophil count. The drop in lymphocytes is early and severe. The platelet count falls in a regular fashion, reaching a low at approximately 30 days. The rate of recovery is considerably slower than would be anticipated from laboratory animal data and is incomplete at 3 years. These findings are consistent with the incomplete data available on the

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Japanese exposed at Hiroshima and Nagasaki, and with the findings on the human beings exposed in reactor accidents (see Dond et al.). They are also consistent with later findings in patients exposed therapeutically either to total-body x-radiation (Miller, Fletcher and Gerstner; Nickson and Dane), or to internally-administered radionuclides (Wolins).

8.6.6 Splenic, Thymic Weight Decrease. Carter et al. had previously demonstrated a very close correlation between the dose of radiation and the decrease in the splenic and thymic weights on the 5th day after exposure to radiation. These observations made it possible to use the decrease in splenic thymic weight for mammalian dosimetry and in studying the effects of substances that may primarily neutralize the effect of radiation. This type of study has been extended by Kallman and Kohn. In their studies the time of minimum weight and dose response did not follow a simple relationship. The data behave as if there are two independent cell populations with different sensitivities. However, thymic weight 5 days after irradiation was a linear function of the logarithm of the radiation dose, as shown by Carter et al. earlier. In their hands the system was very useful as a biological dosimeter. Another careful mathematical analysis of the weight loss of the thymus and spleen was that of Stroud et al. who are essentially in agreement with Carter, Kallman and Kohn on the basic relationship and the usefulness of the procedures.

8.6.7 Miscellaneous Studies. Warren has emphasized the great instability of the bone marrow in some people who have been exposed to small amounts of radiation (less than 50 r). Henshaw, Goodfellow and Warren have all remarked upon the great differences in strain, species, and individual in response to approximately the same dose. Lorenz has demonstrated the greater sensitivity and the more uniform response of the inbred animals to chronic exposure to radiation. Goodfellow has shown that humans under treatment for cancer with radium, in such a manner that a large volume of tissue is exposed, respond with an initial leukocytosis. His

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graphs demonstrate the phenomenon called "coasting" in which the white blood count continues to recede after therapy is discontinued. Maynecord has shown that repeated small exposures to x-ray may cause more complete and long-lasting damage to the bone marrow than a single exposure.

The changes induced by chronic low intensity exposure to ionizing radiation will be considered in the section on the detection of exposure to ionizing radiation.

8.6.3 Morphology of Blood Cells. Morphologic changes in the leukocytes are varied. Degenerating lymphocytes are seen in the circulation. Lymphocytic nuclei may be fragmented, pyknotic, clover-shaped or only the usual nuclear pattern may be altered. Nucleoli may become very prominent, presenting the picture of "owl's eye nucleoli" (Warren). Large phagocytic mononuclear cells may be seen containing nuclear masses and occasional red cells. The cytoplasm of the mononuclears may be excessively basophilic. Vacuoles may appear. Immature cells may be present. Degenerating granulocytes may be seen in the peripheral blood. Toxic granulation, vacuoles and basophilia may be observed. Platelets show some changes along with a reduction in number. Giant hyperchromatic platelets are usually present. Megakaryocytes have been reported as appearing in the blood, but were not seen in the blood smears of the Bikini animals. Supravital stains with Janus green and neutral red are reported as demonstrating alterations in the mitochondria and neutral red bodies. Dickie and Hempelmann have shown that there is an increase in the number of refractile neutral red bodies of the lymphocytes of persons acutely and chronically exposed to ionizing radiation. These bodies are seen only in supravital preparation, are not specific for radiation, and were also seen in the lymphocytes of persons working with toxic chemicals. Bilobed lymphocytes have been reported in the blood of human beings chronically exposed to radiation and of human beings working around cyclotrons (Ingram). Hypersegmented neutrophils have also been seen.

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8.7 Late Effects - Leukemia.

The prolonged and late effects of exposure to ionizing radiation are of great and practical importance. Some men and animals who have had a single exposure or have been chronically exposed to ionizing radiation develop a persistent leukopenia. However, this does not, at least in some cases, prevent the organism from responding to infections and stresses with a marked, transitory leukocytosis, following which the individuals may return to their previous leukopenic level (Cronkite). Bloom and Jacobson described an apparent hyperplasis of the bone marrow in some rabbits that recovered from an $LD_{50/30}$ exposure. This "over compensation" was seen about two months after exposure. This type of response leads one to speculate about the possible development of leukemia, following a single acute exposure to ionizing radiation. That leukemia will develop in animals, and probably in man, particularly lymphatic leukemia, following chronic or repeated exposure seems well established from a statistical standpoint.

8.7.1 Development of Leukemias after Chronic Exposure. Krebs et al. found that the incidence of leukemia in irradiated mice was 3.5 per thousand mice as compared to 0.6 per thousand in the control mice. Hueper demonstrated a 74% incidence of leukemia in mice that had received 400 r over a period of six weeks. The spontaneous incidence in control animals was not stated. Furth and Furth used a single and repeated doses of 200-400 r in mice and reported an eight-fold increase in myelosis and a seven-fold increase in lymphomatosis. Weitz described the development of a case of myeloid leukemia in an x-ray technician that culminated in death. The blood was normal before exposure. Lymphocytosis, eosinophilia and monocytosis preceded the positive diagnosis of leukemia. Henshaw and Hawkins reported in 1944 that the incidence of leukemia in physicians was 1.7 times as great as in the male population. March statistically analyzed the incidence of leukemia in radiologists and found it to be ten-fold greater in radiologists than non-radiologists. Henshaw, in a long series of experiments in mice, demonstrated an increased incidence of leukemia in mice that were chronically exposed to small doses of radiation. Lorenz

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and associates have shown that over 0.11 r per day will, in general, increase the incidence of malignancies in mice, including leukemic processes. The foregoing data on the statistical relationship of leukemia to chronic exposure to ionizing radiation are not conclusive proof that leukemia can be caused by ionizing radiation in man, but there is such a strong correlation that it would be foolhardy indeed to ignore the probable relationship and not to take advantage of every conceivable means to reduce the exposure of all humans to a minimum, and in addition, actively support and operate protective and investigative projects to prevent excessive exposure to ionizing radiation.

8.7.2 Leukemia after Single or a Few Repeated Doses of Radiation. Heretofore, with the exception of the relationship of chronic exposure to leukemia induction discussed in the previous section, there had been little work on the influence of single or repeated doses of radiation on leukemogenesis. However, survivors from the atomic bombs at Hiroshima and Nagasaki who were close enough to the hypocenter to have received radiation in the potentially lethal range show a significantly greater incidence of leukemia than did survivors in the group outside the range of gamma radiation (Moloney). Those who had severe, acute radiation illness have shown the highest incidence of leukemia. The leukemia has been predominantly myeloid and, to a lesser extent, monocytic. This is in contrast to radiation-induced leukemia of animals, which usually has been lymphoid. In the preclinical state of human leukemia, a low alkaline phosphatase of separated leucocytes was found along with a neutrophilic leukocytosis and the presence of increased numbers of basophiles. Moloney and associates suggest that radiation-induced chronic myelogenis leukemia is attributable to a loss of growth-regulating factors. In addition to the appearance of leukemia in the atom bomb survivors, leukemia has now been shown to occur following radioiodine treatment of thyroid carcinoma (Dlom et al.). Furthermore, Court-Brown has observed a significant increase in leukemia in human beings who have been treated for arthritis of the spine with x-ray.

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The pathogenesis of leukemia induction by radiation has been extensively studied. It has been ably reviewed by Furth and Upton. All types of ionizing radiation are leukemogenic. Single and repeated exposures can produce leukemia. Repeated properly spaced exposures result in a more rapid induction and a higher incidence. The induction rate increases with the dose. Physiologic and genetic factors markedly influence the induction of leukemia in mice. Androgens and cortisone inhibit, and estrogens enhance, the induction of lymphoid leukemia. Corticone, however, does not inhibit the production of myeloid leukemia. Shielding of the normal spleen, which contains all types of hematopoietic tissue in the mouse, protects against lymphoma induction in some strains of mice as do injections of bone marrow suspensions (Lorenz, Congdon, Kaplan and Brown, reviewed by Cronkite and Bond).

Kaplan has carried on an extensive series of studies on lymphoma induction in mice. These classical studies have shown that a particular fractionation increases the induction of lymphoma. Local thymic irradiation is ineffective in producing the tumors. Removal of the thymus prevents the lymphoma induction. Subsequently they showed that thigh shielding and injections of marrow suspensions accelerates the regeneration of thymic tissue and concomitantly thymic lymphoid tumors are inhibited. Recent studies have shown that lymphoid tumors develop in non-irradiated thymic tissue grafted into thymectomized irradiated mice. This observation would appear to establish the development of a cancer in a tissue not exposed to the carcinogenic agent. However, a cocarcinogenic effect of trauma and necrosis in the graft may have a contributory effect, and cell migration to the transplanted tissue cannot be ruled out absolutely. Recently Kaplan and associates have shown a definite time dependence for protection against induction of leukemia in mice by injections of homologous bone marrow. Lymphoid tumor induction is maximally inhibited when injections are made one and one-half hours after the last x-ray dose. After 16 days, the ability to inhibit the induction of tumors

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was lost. This group studied ribonucleic acid (RNA) and desoxyribonucleic acid (DNA) in thymic cells of thigh shielded and nonshielded irradiated mice. It was found that the DNA levels per thymic cell do not vary with age or treatment group and that RNA remains constant with time in the control group, but RNA increases 1 to 5 days after irradiation with a prompt return to normal in the thigh shielded group. The RNA per cell and RNA/DNA ratio remain markedly elevated over the entire course of treatment in the unshielded irradiated group. These authors suggest that the sustained elevation of RNA may be related to tumor induction, since shielding prevents induction and results in a rapid return of RNA to normal.

It is quite evident that leukemogenesis by ionizing radiation and the interactions between normal and irradiated hemopoietic tissues and endocrines, which are proved to influence induction, are most intricate. On the basis of the reports to date, it is not possible to determine whether the non-irradiated hemopoietic tissues supply a cellular or humoral factor that inhibits the induction. There is evidence for both views. It is also conceivable that the normal tissues may be capable of neutralizing a factor liberated from the irradiated tissues. The nature of the interactions between irradiated and normal tissues and the influence of endocrines on irradiated tissues remain obscure, but the existence of these physiological interactions that influence leukemogenesis is unquestioned.

The unquestioned, harmful late effects of ionizing radiation on hematopoiesis logically leads to a discussion on the value of a study of the blood in protecting against excessive exposure to ionizing radiation.

8.3 Factors Influencing the Effect of Ionizing Radiation.

Protective factors are discussed in detail in Chapter 10, section Although preprotective agents may protect all cellular systems into which the chemical substances can penetrate, the most striking effects are seen in the blood-producing organs.

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8.9 The Detection of Radiation Injury by Hematologic Procedures.

The detection of radiation injury logically falls into two categories; the detection of the brief, intense exposure and the detection of cumulative small exposures. By hematologic standards, the detection of the brief, intense exposure is fairly satisfactory in animals. However, the early hematologic changes in man after single intense total-body exposure to various dosages are not well known. It is regrettable that few blood studies were performed on the Japanese casualties during the first week after the atomic bomb explosions. Therefore, it is necessary at this time to attempt, for the most part, to extrapolate to man from animal data. However, the Marshallese data help considerably.

8.9.1 Acute Exposure. Beginning shortly after the acute exposure, one can anticipate a prompt decrease in the total lymphocyte count. The decrease will roughly be proportionate to the dosage in the sub-lethal range (fig. 2). The maximum depression will appear within 24 to 72 hours. The greater part of the fall takes place within 24 hours. Concomitant with a lymphopenia, a neutrophilic leukocytosis (fig. 3) can be expected. The number of refractile neutral red bodies in the lymphocytes will probably increase. From a practical standpoint, the following conclusions can be drawn:

1. If there is no significant decrease in the total lymphocyte count during the first 24 hours, the exposure has probably been less than 25 r of total-body ionizing radiation.
2. If a lymphopenia of minor degree appears with very mild or with no symptoms, the exposure is probably less than 100 r.
3. If the depression in lymphocytes approximates 50% or more of the usual lymphocyte count of man, and symptoms are present during the first 24 hours, one can conclude that the exposure has been quite heavy, in excess of 100 r.

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Needless to say, the detection of minor degrees of lymphopenia necessitates a knowledge of normal lymphocyte levels of the person concerned. Under conditions of an atomic catastrophe, this information will probably not be available, nor will it be feasible with present techniques to perform intensive blood studies. Other means of detecting exposure to ionizing radiation are:

a. the symptomatology

b. personnel radiation dosimeters and

c. the distance from the exploding bomb

These will be discussed in Chapter on Diagnosis and Therapy.

The satisfactory development of good electronic blood-counting devices greatly simplifies the logistics of performing enormous numbers of blood counts in a catastrophe.

8.9.2 Repeated Small Exposure. The detection of repeated small cumulative exposures by hematologic studies poses an entirely different problem and logically becomes part of a broad health protection program. Observations on the blood of man chronically exposed to radiation are legion. Leukocytosis, lymphocytosis, leukemoid reactions, leukocytic leukemias, erythrocytosis, reticulocytosis, leukopenia, thrombopenic purpura, aplastic anemia, leukopenic leukemia, refractive neutral red bodies in the lymphocytes and changes in the blood coagulation have been described as occurring after chronic exposure to ionizing radiations. From a review of the literature, the following hematologic observations can be considered as presumptive criteria of excessive exposure to ionizing radiation or other toxic agent:

1. Persistent leukopenia (WBC below 4000/c.mm.).
2. Persistent leukocytosis with an absolute lymphocytosis (WBC above 15,000).
3. A macrocytosis (mean corpuscular volume increased, a shift to the right in the Price-Jones curve, or an increased mean corpuscular diameter).

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4. Reticulocytosis (reticulocytes above 2 per cent).

5. Erythrocytosis (RBC over 5.6 million per c.mm. or hemoglobin over 18.0 gm./100 cc. blood).

Williams has analyzed the value of blood studies and protection against radiation injury and has concluded that numerous routine counts are unnecessary where good control of all circumstances is maintained. However, in radiation areas, more highly controlled hematologic studies are needed in order to obtain more information on the threshold and permissable values. Heide and Wahlberg have analyzed the lowering of the leukocyte count in human beings produced by minute amounts of whole-body radiation. They have utilized a statistical analysis. Although the mean leukocyte count is unchanged, the dispersion around the mean is considerably decreased by low exposure to irradiation, thus making it possible to use this statistical parameter as an indication of irradiation exposure.

A complicating observation is that of Wald et al. who has observed in the control population in Japan that was not exposed to radiation of the atomic bombs that there has been a progressive decrease in the leukocyte count over a period of the last ten years. The reasons for this change are obscure but obviously complicate the analysis of chronically exposed populations.

8.10 Evaluation of Blood Changes.

The above criteria result from either a depression of or an increased lability of hematopoiesis. The establishment of the presence of these criteria can be greatly assisted by performing parallel studies on comparable groups of human beings who are known not to be exposed to radiation or any other toxic agent. Statistical comparison of the potentially exposed control group will help to determine if a significant change has taken place. In a similar manner the pre-exposure counts of the suspected group or individual can be compared to the post-exposure counts. If there is a significant change in the latter, one can state with some certainty that there has been excessive exposure to some toxic agent. A good

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criterion of excessive exposure of a group to radiation is a significant decrease in the group average leukocyte count below the pre-exposure level or below the average of the control group. As soon as any of the above criteria have been demonstrated, the individuals must be removed from any possible contact with radiation and the following studies should be performed in order to determine if radiation injury is the cause of the abnormality. In principle, the use of a group as its own pre-exposure control sounds secure, but admittedly the observations of Wald et al. indicate the potential unreliability of this approach. Accordingly, whenever possible, a comparable population of unexposed people should also be followed.

1. Endeavor to eliminate all other causes of temporary hematologic abnormalities, such as infectious mononucleosis, infectious lymphocytosis, infectious hepatitis, virus diseases, benzol and heavy metal poisoning.
2. Study the excreta and expired air for the possible presence of ionizing radiation to help determine the type and degree of internal exposure to radioactive isotopes.
3. Study the blood at weekly intervals to detect further changes and to search for the presence of refractive, neutral red bodies in the lymphocytes.

In this discussion of the role of hematology in the detection of chronic radiation injury, it is appropriate to state the changes discussed appear generally after the damage has been sustained. The main protection against ionizing radiation injury must be an accurate physical control of the radiation intensities to which personnel are exposed.

In concluding this section, the reader is referred to the work of Knowlton and Carter in which a group of ten individuals were carefully followed over a long

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period of time while they were being chronically exposed to radiation. The hematologic studies suggest that definite changes were induced. The article demonstrates the difficulties and the potentialities of this type of analysis.

8.11 The Hemorrhagic Syndrome of Radiation Illness.

In previous editions of this book, a long detailed discussion of the various facets believed to contribute to hemorrhage were discussed. Much of the controversy has been resolved. Historically (Fernau, Schramek and Zarzychi; Fabricius-Moller; Lacassagne, Lattes and Lavedan; Shouse; Warren and Whipple) observed hemorrhage. The most critical observations on pathogenesis were made by Fabricius-Moller who correlated platelet levels with bleeding and noted that lead shielding of a leg during irradiation prevented later bleeding and the thrombopenia was much less marked. (See Chapter 10 for detailed discussion of shielding.) Allen and associates claimed that heparinemia was a major cause of bleeding in addition to the thrombopenia in irradiated dogs, and that the thrombopenia actually sensitizes to heparin. Of the latter there is little doubt. The concept of increased amounts of circulating heparin was readily accepted, probably because positive treatment by antiheparin could, in large part, control the bleeding. Such has not proved to be the case and the heparinemia concept has, in general, been refuted (Jackson et al.). The pros and cons are discussed in previous editions of this book and in a review by Cronkite and Brecher.

The following defects in hemostasis that lead to bleeding seem to be well documented. A progressive thrombopenia develops that is time- and dose-dependent. The thrombopenia leads to a quantitative deficiency in clot retraction, prothrombin utilization and capillary integrity. Lastly, at very low platelet levels with virtually no prothrombin conversion, the whole blood-clotting time becomes remarkably prolonged. Ulcerations, trauma and infections increase the bleeding tendency (Cronkite; Cronkite and Brecher, Jackson et al., and LeRoy).

The most direct evidence on the role of the platelet has been the proof that platelet transfusions will prevent bleeding or stop bleeding that has already

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commenced (Cronkite et al., Woods et al., and Allen). The control of the bleeding did not increase the survival rate at the LD_{50} level or above.

The platelet level at which bleeding may occur spontaneously was studied by Lamerton et al. in rats. At platelet levels above 40,000/mm^3, bleeding and anemia did not occur. Similarly in human beings exposed to fallout with platelet counts as low as 35,000/mm^3, bleeding was not observed (see section 8.6.6). Lastly, there is a real species difference in the rate of fall of platelets in man and other mammals (see section 8.6.6).

8.12 Value of Hematologic Studies in Prognosis of Acute Radiation Injury.

From the serial studies of the blood that have been discussed, it becomes apparent that there are certain hematologic signs that can be used as prognostic guides. None of these prognostic guides is absolute. The value of hematologic studies in radiation injury may be summarized as follows:

a. A favorable prognosis is suggested by an early reticulocytosis, a return of platelets, a granulocyte count greater than 1500 per cubic mm. and an early return of the lymphocyte.

b. An unfavorable prognosis is suggested by a complete disappearance of the lymphocytes, granulocytes and platelets, and an increase in the clotting time with the development of purpura and particularly when accompanied by fever. In animals, at least, if the favorable prognostic signs listed above do not appear by the 15th to 20th day after exposure, death is usual. The experiences of the Japanese physicians parallel the above observations, except that recovery occurred more slowly. Poor nutrition may have altered the natural course of the disease in the Japanese. Unfortunately, exceptions occur and it is impossible to prognosticate accurately the outcome of radiation illness on the basis of hematologic signs.

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8.13 Relationship of the Hematopoietic System to Survival in Radiation Injury.

This subject is extensively discussed in Chapter 10, section 10. Suffice it to say here that all post-radiation protective measures studied in animals appear to either accelerate the regeneration of hematopoietic tissues or to increase the survival time (antibiotics) by control of infection to give more time for the spontaneous regenration of the injured hemopoietic tissues.

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Fig. 8. Serial Mean Total Leukocyte and Neutrophile Counts in the Rongelap People Exposed to Fallout Radiations

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16LL005

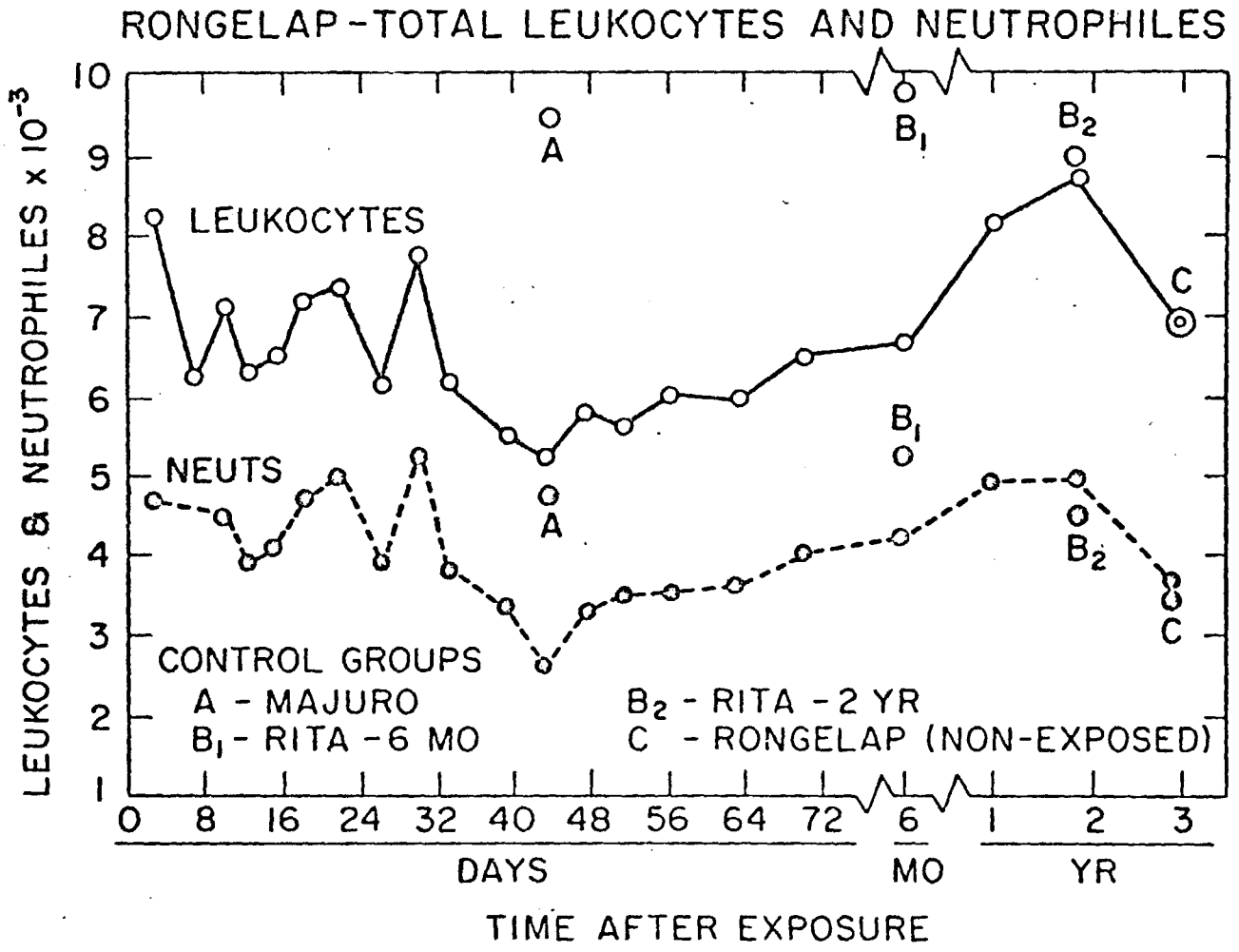
RONGELAP - TOTAL LEUKOCYTES AND NEUTROPHILES
LEUKOCYTES & NEUTROPHILES x 10^{-3}
LEUKOCYTES
NEUTS
A
B_1
B_2
C
CONTROL GROUPS
A - MAJURO
B_1 - RITA - 6 MO
B_2 - RITA - 2 YR
C - RONGELAP (NON-EXPOSED)
DAYS
MO
YR
TIME AFTER EXPOSURE

Fig. 9. Serial Mean Lymphocyte Counts in the Rongelap People Exposed to Fallout Radiations.

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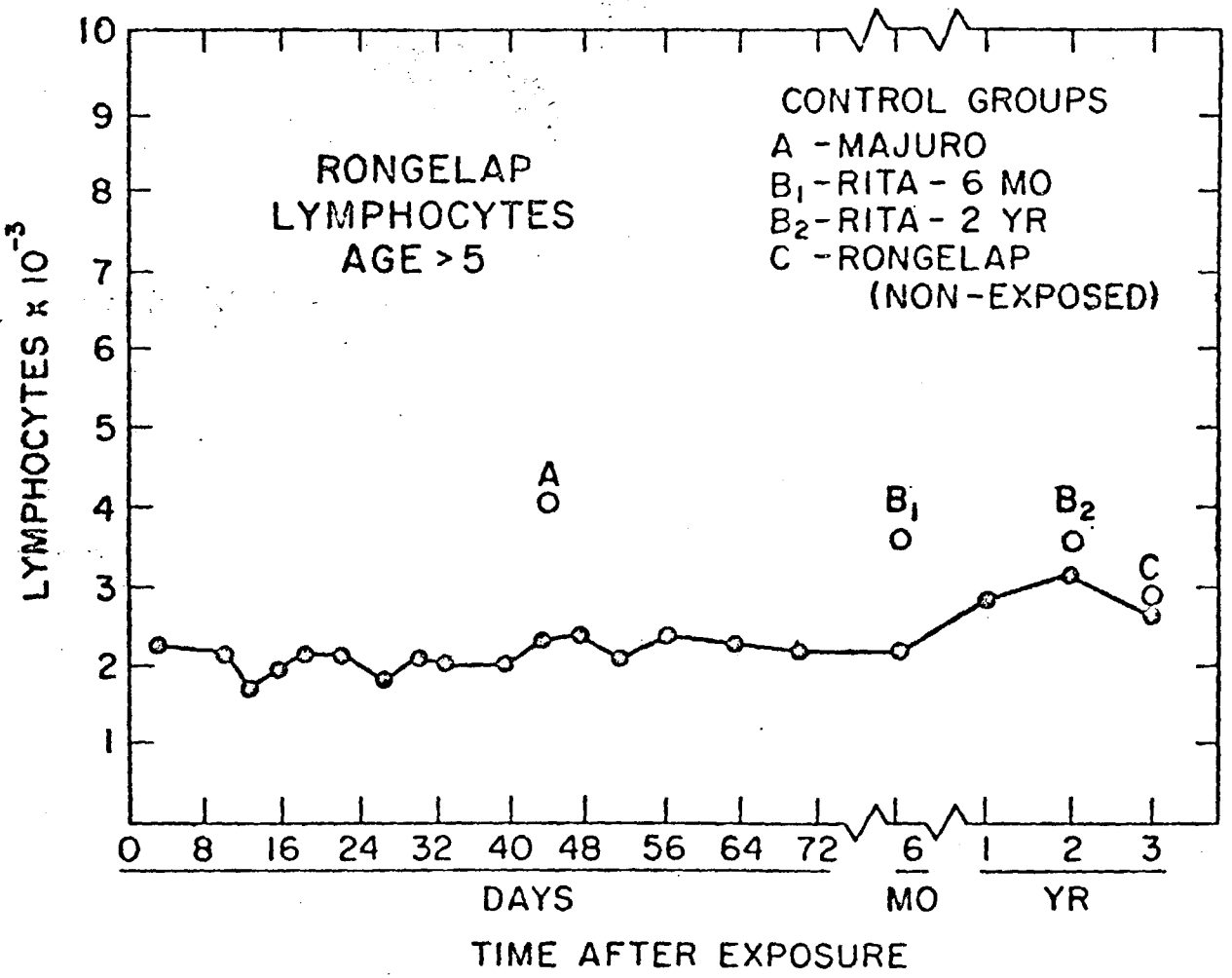
RONGELAP
LYMPHOCYTES
AGE > 5
CONTROL GROUPS
A - MAJURO
B1 - RITA - 6 MO
B2 - RITA - 2 YR
C - RONGELAP
(NON-EXPOSED)
LYMPHOCYTES x 10^-3
10
9
8
7
6
5
4
3
2
1
A
B1
B2
C
0
8
16
24
32
40
48
56
64
72
6
1
2
3
DAYS
MO
YR
TIME AFTER EXPOSURE

5007793

Fig. 10. Serial Mean Platelet Counts in the Rongelap People Exposed to Fallout Radiations.

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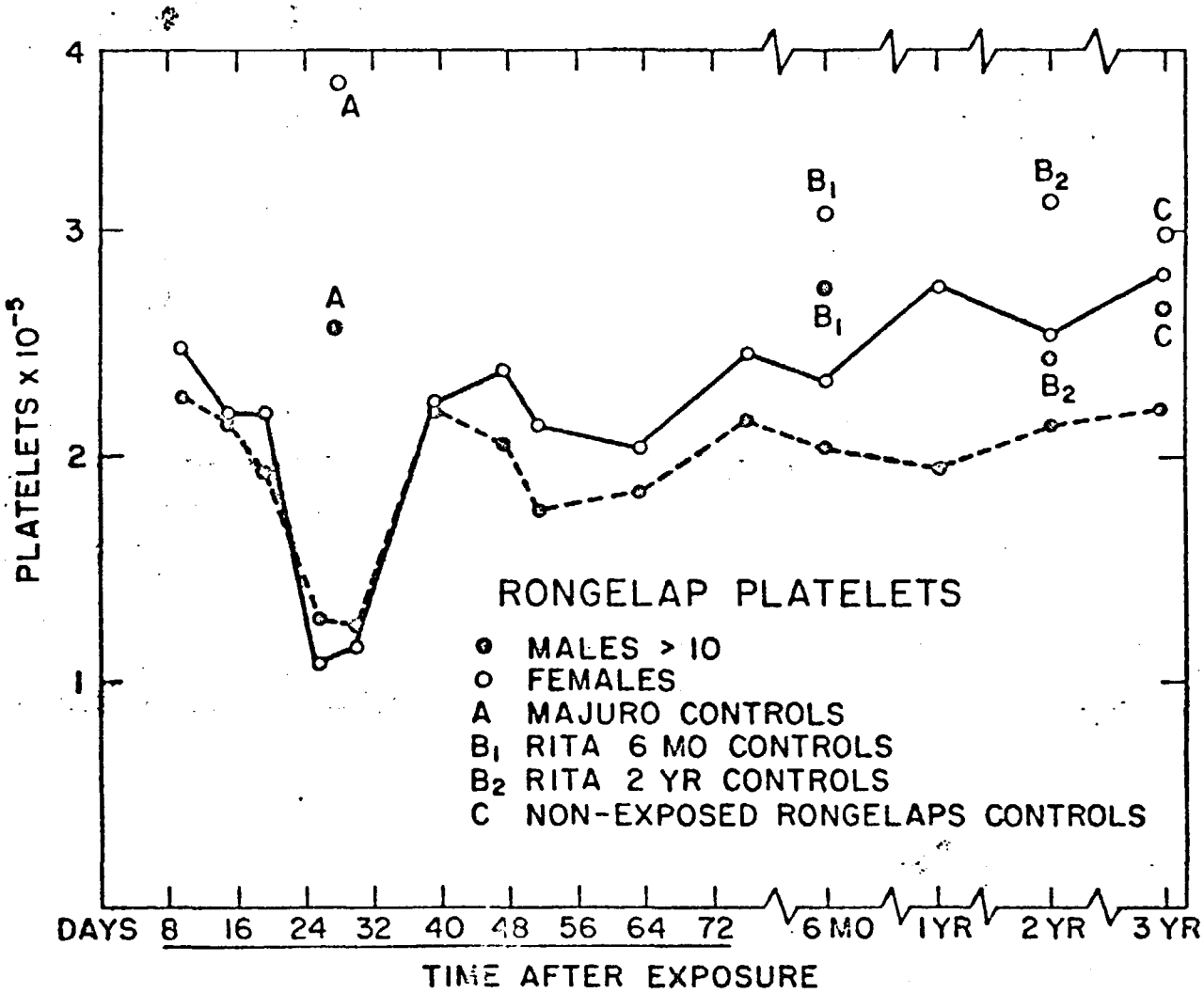
SD11005


PLATELETS x 10^{-5}
4
3
2
1
A
A
B_1
B_1
B_2
B_2
C
C
C
RONGELAP PLATELETS
MALES > 10
FEMALES
A MAJURO CONTROLS
B_1 RITA 6 MO CONTROLS
B_2 RITA 2 YR CONTROLS
C NON-EXPOSED RONGELAPS CONTROLS
DAYS 8 16 24 32 40 48 56 64 72 6 MO 1 YR 2 YR 3 YR
TIME AFTER EXPOSURE