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## Ernest O. Lawrence Radiation Laboratory

# THE LIPID SYNDROME IN MAMMALIAN RADIOBIOLOGY WITH EMPHASIS ON POSTIRRADIATION PROTECTION OF ANIMALS WITH LIPIDS

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# THE LIPID SYNDROME IN MAMMALIAN RADIOBIOLOGY WITH EMPHASIS ON POSTIRRADIATION PROTECTION OF ANIMALS WITH LIPIDS

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## ABSTRACT

Our studies have shown conclusively that post-irradiation olive-oil treatment approximately doubles the survival of mid-lethally irradiated male mice. Olive oil is still beneficial when administered to animals 24 hr after whole-body irradiation.

The efficacy of a number of other fatty materials against X-radiation was tested to determine whether this protective effect was peculiar to olive oil. Among these, methyl oleate, triolein, and peanut oil were equally effective as olive oil. Safflower oil fortified with antioxidant was also beneficial. Methyl stearate is considered dietarily unessential, but it too was helpful. On the other hand, methyl palmitate was ineffective.

Linoleic acid is essential in animal diets. Therefore, pure methyl linoleate and trilinolein were tested on our lethally irradiated mice. Surprisingly, the linoleates potentiated lethality of our X-irradiated animals. Experiments with antioxidants indicate that this toxicity of linoleate is due probably to the formation of lipid peroxides.

These studies have shown that oleate is the most active fatty-acid component in vegetable oils against X-radiation.

Comparative studies with mineral oil and robane (perhydro-squalene) support the chemical nature of postirradiation protection by olive oil.

A number of particulate substances have been reported to help animals recover from lethal irradiation. Protection by these agents is attributed to a defensive mechanism of the animal against infection. A typical thymic response characterized by marked decrease in thymus weight is observed in animals 3 to 4 days after particulate injection. Powdered glass and starch induced this characteristic foreign-body reaction, but olive oil did not. These studies lend further credence to the chemical nature of postirradiation protection of animals by oils.

It is well established that mice and other mammals when exposed to a single high dose of X-radiation become sterile after a period of fertility which immediately follows the irradiation. Furthermore, if permanent sterility has not been induced, these animals will regain their fertility.

Our postirradiation oil-treated mice were twice as fertile as the irradiated controls when they were mated 30 days after whole-body irradiation. The sizes of the litters from these matings were similar. Oil treatment did not alter foetal viability.

The number of circulating leukocytes in the peripheral blood of our oil-treated and untreated animals was essentially similar during the first 2 weeks after irradiation. However, oil treatment significantly shortened recovery time of the leukocyte values to the normal level. These results support the view that postirradiation oil treatment does not reverse radiation damage but facilitates the recovery processes.

Studies of blood-lipid changes in our mice have shown a significant increase in stearic acid with concomitant decrease in oleic acid as early as 6 hr after 2000-r whole-body X-irradiation. A marked increase in concentration of arachidonic acid was also noted 48 hr after irradiation. These serum fatty-acid changes appear associated with the marked serum triglyceride depression following irradiation.

Modal analysis of our oil-treated animals has unmasked a 15-day lethality peak which is markedly suppressed by olive oil treatment.

# I. INTRODUCTION

Whatever the basic mechanism of the action of ionizing radiations on biological systems may be, a principle concern, in addition to that of academic interest, is the matter of mitigating its effects on man.

The ever-increasing use of radioisotopes and nuclear devices increases ones chance of being exposed accidentally to lethal radiation. A number of workers in atomic establishments and institutions where nuclear reactors, particle accelerators, or large quantities of radioactive materials are used, have been exposed to radiation, some tragically (219, 333). However, excluding the possibility of war-prompted radiation injuries as occurred at Hiroshima and Nagasaki during World War II (87, 320) and cases like the Marshallese (1954) and Japanese fisherman (1956) who were injured when caught unwittingly in fallout radiations from nuclear tests, radiation injuries will at present most likely be confined to workers in nuclear establishments. The most recent accident occurred at Idaho Falls (1961) where three employees were lethally irradiated. But radiation hazards to the whole population cannot be ignored. One must be naively optimistic to assume that atomic weapons will not be used in some future war. Also foreseeable in the near future is space navigation with its radiation hazards to astronauts. Therefore, a definite need exists for protective and therapeutic agents against radiation injuries.

The very harmful and frequency lethal effects of ionizing radiations on living organisms have been known for over half a century. During this interim, as attested to by thousands of papers devoted to this subject, much has been done to elucidate their mechanism of actions on various systems.

The earliest reports on the deleterious effects of radiation in man appeared immediately following the discovery of X-rays by Röntgen in 1895. Leppin (273) and Stevens (339) observed that X-radiations causes epilation and inflammation of the skin. Epilation resulting from X-ray photography was reported by Daniel (103). Subsequently, many excellent articles and reviews on this subject have appeared.

In recent years, the general biochemical effects of ionizing radiations have been extensively surveyed by Ord and Stocken (318, 319), DuBois and Petersen (123), and Holmes(227). Other good reviews dealing with various aspects of radiation biochemistry have appeared (95, 145, 171, 181, 184, 212, 214, 249, 324, 390, 400). The problem of enzyme inactivation certainly cannot be excluded from this list. Errera (147) has recently published a very comprehensive review of the literature on this subject.

Of the many effects radiation has on living things, the genetic effects were among the first to be carefully studied, because such effects often produce morphological changes which are most easily observed. Many abnormalities resulting from damage to the chromosomes that were observed in these pioneering studies are cited in Duggar's classic treatise on the "Biological Effects of Radiation" (125). Recently, a number of good papers on this subject have appeared (72, 131, 220, 250, 353, 354). Publications dealing with other aspects of radiobiology, including cellular (21, 186, 310, 388, 423), histopathological (51, 174, 208, 263, 285), and physiological (53, 97, 101, 116, 128, 185, 233, 279, 316, 323, 349, 413) effects of ionizing radiations are also cited.

The many excellent books, symposia, and monographs on this subject cannot be ignored. Among others, Hollaender (220), Bacq and Alexander (26), Lea (272), Dessauer (106), Rajewsky (338), Symposium on Radiobiology (27, 314), Spear (389), Proceedings of the International Conference on the Peaceful Uses of Atomic Energy (333, 334), Progress in Radiobiology (304), Advances in Radiobiology (215), Proceedings of the International Congress of Radiation Research (366), Manhattan Project (49, 51, 426, 427), and Errera and Forssberg (148) are all excellent sources of information on the actions of ionizing radiations on biological systems.

In the early days of radiobiolgical studies, before highly reactive substances (free radicals ) and oxidants (peroxides) were established as responsible for many biological effects, there seemed little hope of modifying the actions of ionizing radiations with chemical agents.

However, it is interesting to note that as early as 1909--long before the concept of direct and indirect actions of ionizing radiation on living cells was published (272)--Schwartz (361) reported on the protective role of ischemia in cutaneous radiation. Also known were the effects on radiosensitivity of oxygen (228, 241, 311), hydration (330), and temperature (228).

# II. RADIATION PROTECTION--A REVIEW

## A. Preirradiation Protection

### 1. General Discussion

In 1929, Risse (341) first postulated that X-rays decompose water into OH and H radicals. The significance of this free-radical hypothesis was not realized until 1944 when Weiss (419) re-examined the problem of the chemical basis of indirect action of ionizing radiation in aqueous systems. In 1948, direct evidence of the existence of OH radicals in aqueous media was furnished by Dainton (102), and a year later Barron and his associates (40, 41) demonstrated that sulfhydryl (-SH) enzymes as phosphoglyceraldehyde dehydrogenase and adenosine triphosphatase *in vitro* can be protected against X-irradiation and be reactivated by adding glutathione. Subsequently, a number of papers appeared on the efficacy of various chemicals against radiations. Patt *et al.* (325, 326, 328), and Smith and his collaborators (370) demonstrated the protective effect of cysteine (-SH amino acid) and glutathione (-SH tripeptide) in rats and mice. Chapman and his co-workers (73, 74) found that glutathione gave good protection if injected in the reduced form immediately before irradiation. It is ineffective when given *per os* (73, 74, 98, 325). In 1951, Bacq, Herve and colleagues (34) first demonstrated the excellent protective action of cysteamine (β-mercaptoethylamine). This has been confirmed by a number of investigators (105, 211, 264, 286, 301, 352, 406, 422). Bacq and Herve (31) and others (35, 119, 352, 406) have shown further that cysteamine when administered intraperitoneally in equimolar quantities is over five times as effective as cysteine in attenuating the effect of radiation in mice. For example, where 1200 mg cysteine per kg body weight elevated the $LD_{50(30)}$ survival dose from 765 to 1120 r, 150 mg cysteamine per kg body weight elevated the mid-lethal dose to about 1100 r (119). Cystamine, the decarboxylated form of cystine, unlike the latter is also a very effective protector (31). It is reported to be less toxic than cysteamine when fed continuously in the diet (25, 35).

The systematic search for protective substances has resulted in the discovery of new sulfhydryl chemicals with radioprotective qualities (118, 246, 359, 363, 374, 416). The most active of these compounds are S, 2-aminoethylisothiuronium. Br·HBr (AET) and S, 3-aminopropylisothiuronium · Br · HBr (APT) which on a molar basis are reported to be three times as effective as cysteamine in protecting mice (119).

Studies of the relation between chemical structure and protective effect of the sulfhydryl compounds have shown that $-NH_2$ and the -SH groups are essential for their protective activities (8, 45, 117, 118, 266). Doherty et al. have shown further that the amine and sulfhydryl radicals should be separated by no more than three methylene groups for protective activity (117, 118). The ethyl and propyl thiourea compounds just described are effective when administered orally, intraperitoneally, or intravenously (222). The oral route provides protection for about 6 hr in mice (119).

Other sulfhydryl compounds have been found to help animals or microorganisms against radiation. Among the latter are sodium bisulfide (65), 2, 3-dimercaptopropanol (BAL) (22, 66, 225, 226, 234, 424), mercaptosuccinic acid, and mercaptopyruvic acid (66). Van Bekkum (43) has reported on the excellent protective action on mice of dithiocarbamic acid derivatives and the cysteamine derivatives 1-amino-propanethiol-2 and 2-amino-propanethiol-1 (81).

Inasmuch as there are numerous reports on the beneficial value of a large variety of miscellaneous substances and agents, we will consider them only briefly because efficacies against radiation do not measure up to the sulfhydryl-amine compounds described above. Cyanide injected before irradiation in toxic but nonlethal doses was found to help mice survive lethal irradiation (22, 33, 369), but Dowdy et al. found cyanide ineffective in rats and concluded that it will protect animals only if it decreases tissue oxygen tension (121). Anoxia induced prior to and maintained during exposure to radiation increases survival of animals (121, 260, 274, 397, 398), microorganisms (15, 223, 225, 228, 241, 311), and mammalian tumor cells (94, 98, 201).

The protective effect of hypothermia in mice (231, 259, 260, 405) and rats (11, 196, 293), ischemia of organs and tissues (70, 154, 293, 317, 361), morphine (16, 244), p-aminopropiophenone (188, 404), pitressin, serotonin, histamine, epinephrine, and other amines in mice (23, 29, 30, 31, 45, 47, 152, 187, 265, 268, 297, 396), sodium nitrite (82), the pyrogallol derivatives 4-decanoylpyrogallol and 4-laurylpyrogallol (261), and carbon monoxide (55, 253) all may be a consequence of decreased tissue oxygen tension. Beaumariage (42), however, was unable to protect chicks with epinephrine against the lethal effects of 2000-r whole-body irradiation. Also to be considered with these hypoxia-inducing agents as radiation modifiers are simple alcohols and glycols in microorganisms (225) and in mammals (32, 83, 306, 355). Massive doses of sugars are reported to help rats (31, 225, 278). Microorganisms are also aided by certain carboxylic acids (225, 394, 412), but mice are pporly protected (31). The ability of these metabolites to alleviate radiation lethality is also attributed to removal of environmental and intracellular oxygen. However, Thompson et al. (412) have shown that aeration of the pyruvate-enriched culture medium during irradiation does not alter the protective capacity of pyruvic acid. Magnesium (52), cobalt (322), glucosamine (127, 262), cholinergic agents (64, 200), homologous serum or plasma (407), colchicine (376), anesthetic agents (190), foreign proteins (183), and autolyzed yeast extracts and RNA (107, 282, 283) are reported to help organisms survive lethal exposure to ionizing radiation.

Some workers have claimed that antibacterial agents such as terramycin (93, 192)streptomycin (302), lycopene (167), properdin, zymosan,and similar agents (305, 348) are effective in reducing radiation mortality, when administered before or after irradiation, although others (20, 173, 179, 254, 384) have found them ineffective. Some of the inconsistencies in the protective value of antibacterial agents can be resolved by assuming the existence of enzootic differences among experimental animals.

There are also a number of publications amply demonstrating that dehydration ameliorates radioresistance in microorganisms, seeds, and spores (69, 73, 113, 156, 175, 209, 221, 330).

2. Modes of Action of Protective Agents

In view of the existence of a seemingly endless and diverse array of protective agents against radiation, it is small wonder that in this chaotic list of substances some orderliness in protective behavior exists. Specifically, the current belief is that radiation protection is mediated by one or more of the following basic processes: (a) radical scavenging (8, 26, 118, 119), (b) chemical-complex formation (132, 133, 195, 252), (c) anoxia induction (24, 45, 81, 187), and (d) resonance or energy-transfer effect (67, 68, 182, 289, 393), with the mechanism(s) depending on the protective material. The various mechanisms of protective and sensitizing action against ionizing radiations are lucidly discussed by Eldjarn and Pihl (133) in their recent review. Also of interest are Maisin and Doherty's (287) article on protection of erythropoietic, lymphopoietic, and other mammalian tissues with AET, cysteamine, and serotonin, as well as the reports of Kalkwarf (245) and Hollaender et al. (224) on radiation protection and therapy with chemicals and bone-marrow treatments.

## B. Postirradiation Protection

Protective drugs highly effective for short durations (few hours) against radiation are now obtainable in the form of sugar-coated pills. However, neither drug nor treatment with comparable therapeutic value against radiation injuries is available today. But bone-marrow and spleen transplantation therapy against hematopoietic syndromes appear promising, and work along these lines has progressed during the past decade to the stage of clinical experimentation.

It has been known as early as 1903 that blood-forming tissues are one of the most sensitive to ionizing radiations (205, 208). Consequently, a logical avenue of approach to study the problems of lethal effects of ionizing radiations and experimental therapy against such effects on mammals is through hematopoietic organ shielding.

In 1949, working on this premise, Jacobson et al. discovered that spleen shielding during irradiation considerably reduced the mortality of irradiated mice (239, 240). Transplantation of autologous and isologous nonirradiated spleens and intraperitoneal injection of isologous spleen cells were also effective. Lorenz and co-workers achieved impressive postirradiation protection in mice and guinea pigs through isologous bone-marrow injection (281). In the succeeding years, the therapeutic value of autologous, isologous, homologous, and heterologous bone-marrow and spleen transplants were investigated in different species by a number of workers (12, 38, 90, 91, 115, 157, 160, 218, 238, 280, 331, 347, 360, 381), with varying degrees of success. The most successful bone-marrow transplantations were achieved in animals subjected to whole-body irradiation in excess of the minimal $LD_{100}$ doses. In many instances 80 to 100% of these lethally irradiated-treated animals have survived for 30 days. Understandably, at higher doses which cause intestinal deaths, bone-marrow therapy is no longer effective.

In view of their observations that homologous and heterologous blood-forming tissues are therapeutically effective against radiation deaths, Jacobson (236) and Lorenz et al. (90, 91, 280, 281) advanced the idea of a humoral factor(s) in spleen and bone marrow capable of stimulating the regeneration of hematopoietic tissues. The work of Cole et al. (84, 85, 86) on the therapeutic value of cell-free extracts of hematopoietic tissues appeared to further substantiate this humoral hypothesis. Nevertheless, others including Barnes and Loutit (38) found this humoral hypothesis of Jacobson and Lorenz unacceptable. They found similar 30-day survival rates between homologous and isologous spleen transplanted mice, but all of the homologous spleen-treated animals died within 100 postirradiation days (38). No such

delayed mortality was observed in animals treated with isologous tissues. They logically postulated that recovery is achieved in lethally irradiated animals through hematopoietic cell repopulation by viable donor cells and advanced the cellular hypotheses (37).

The identification of donor-type blood cells (166, 276, 288, 315, 417) in host animals several months after lethal irradiation is highly convincing that hematopoietic cell elements are transplanted when bone-marrow is injected. A number of other direct and indirect evidences in support of the cellular hypothesis have subsequently appeared (36, 38, 165, 176, 238, 300, 345, 351, 364, 375, 420, 425), demonstrating that cell-free preparations of hematopoietic tissues are therapeutically ineffective and that viable blood-tissue-regenerating cells are necessary for recovery. As unequivocal as these results are, the report of Goldwasser and White (178) on the beneficial effect of noncellular hog intestinal mucosol preparations and Ellinger's (136, 139, 143) consistent findings that postirradiation treatment with cell-free spleen extracts increases survival of lethally irradiated mice and guinea pigs, lend credence to this humoral hypothesis. Also of interest is the beneficial effect of rat nucleic acid preparations (321). As these "humoral factors" appear effective only in animals irradiated with less than 100% lethal doses, it seems reasonable to assume that at sub-total-lethal doses (disregarding infections), radiation death is not due solely to aplasia of the hematopoietic tissues.

Although bone-marrow transplantation against radiation injuries is promising and has already been attempted clinically (207, 298, 340, 411), some extremely serious problems associated with secondary disease (44) must be resolved before this technique can be safely adopted for treating lethally irradiated human patients. Whether this usually fatal disease, due to immunological incompatibility between host and donor tissues (37, 39, 203, 235, 418), will ever be alleviated is presently difficult to surmise. But, as host-donor incompatibility does not seem to exist in many heterologous tumor-tissue transplants, this immunological problem does not appear unsolvable.

Van Bekkum has recently published a long treatise on the effectiveness of radiation therapy and recovery of animals following bone-marrow treatment, the feasibility of marrow storage (bone-marrow bank), optimal postirradiation tissue transplantation time, the importance of radiation dose and viable-cell titer for successful graft, and other problems pertinent to this subject (44).

Hematopoietic regeneration is vital to recovery of lethally irradiated animals. Hence, the efficacy of agents known or believed to stimulate hematopoiesis have been widely tested. In most instances, however, these substances were rather ineffective therapeutically against radiation injuries (10, 112, 295, 382, 402, 407). In fact, postirradiation hematopoietic treatment potentiated mortality in rats (337).

The effect of batyl alcohol (d,l-α-octadecylglycerol ether) in mitigating lethality of X-irradiated mice is also contradictory (129, 178). Nevertheless, this class of compounds appears to stimulate bone-marrow functions (9, 60, 61, 155, 277).

A very interesting report has recently appeared on post-irradiation protection of animals with cysteine. In a series of experiments, Künkel et al. (256, 257, 258) have shown that survival of hibernating dormice increases if they are treated with cysteine immediately upon return to room temperature 21 days after irradiation. However, in similar experiments Smith (367, 368) was unable to protect lethally irradiated ground squirrels with cysteine or AET. Chemically induced hibernation after irradiation is also claimed to be helpful (190). Other substances that have been reported to benefit animals mildly when given after whole-body irradiation are atabrin (248), ground glass, and other inert materials (373, 383), bacterial endotoxins (3, 4, 50, 378, 379, 428), physiological saline (142), vitamin K (137), chloropromazine (198, 291, 403), and the flavenoids (17, 18, 19, 79, 126, 158, 339), although others claim these latter vitamins are ineffective (99, 104, 197). The B-vitamins (30, 31, 318) and vitamin E (199) appear to potentiate radiosensitivity in mice. It has been said that folic acid administered after irradiation influences neither hematopoiesis nor survival of swine (100) and mice (177), but decreases leukopenia in

mice (312). The protection of lethally irradiated rats by postirradiation parabiosis with a healthy animal (58) is attributed to hematopoietic cell repopulation (48). Recently, Powers and Kaleta (332) have shown that hydrogen sulfide treatment following irradiation reduced lethality in dry spores by about 50%.

Hormone treatments of animals following irradiation are not uniformly effective. Both ACTH and cortisone appear to increase mortality of irradiated mice (141, 385, 410, 421), although Langendorff et al. (267) as well as others (365) have found ACTH to lower radiation mortality. In intense local irradiation, cortisone treatment was shown to suppress ulceration of these tissues (46, 62, 92, 232, 292). In these instances, since tissue lesions recur even 3 months after irradiation if treatment is discontinued, Bruce and Barclay (62) feel that cortisone suppresses the inflammatory response and not the degenerative changes occurring in the irradiated tissues. Deoxycorticosterone injection succeeding irradiation is stated to reduce mortality of animals in the lower lethal ranges (138, 140). Pretreatment with estradiol is beneficial, but posttreatment is claimed by some to aggravate mortality (271, 327, 414) and by others to help recovery (303). Rixon et al. (342) have shown parathyroid extracts to be mildly effective before or after irradiation. Male sex hormones have also been tested with little success (303, 327), although testosterone cyclopentylpropionate treatment is reported to help male mice survive lethal irradiation (391). Female mice in estrus have been shown to be less sensitive to low doses of X-ray than at other times (350), but radiosensitivity is not affected by pregnancy (387).

Fluid and electrolyte losses are believed to be responsible for the early deaths observed in superlethally irradiated animals. In accordance with this idea, Conard et al. have shown that parenteral administration of electrolyte solutions following 1300-to 1800-r total-body irradiation will double the mean survival time of treated dogs over the controls and will greatly suppress the moribund state of the animals resulting from dehydration(89).

In common with severely ill animals, lethally irradiated animals often refuse food. Mice and guinea pigs will continue feeding during the first few days after lethal irradiation, but rats do not. However, all lethally irradiated animals will invariably stop eating after a few days. Attempts to alter survival of such animals by force-feeding have not been uniformly successful (5, 89, 242, 371, 377, 380). It is reported that even fasting for a few days after irradiation does not significantly alter mortality in rats, mice, and guinea pigs (377). Nevertheless, because lethally irradiated animals will lose weight continuously, the nutritional state of the animals must have some logical bearing on their demise. Will a supply of readily available food (energy) prevent this precipitous weight loss and thus mitigate some of the injurious effects of radiation?

Sugars are an excellent source of calories but only massive doses of sugars have been reported to help lethally irradiated rats and only if they are administered before irradiation (31, 225, 278). Whether prolonged feeding of glucose will help animals maintain their weights and vigors and help them along the road to recovery has not been ascertained.

Hemorrhage, fluid and electrolyte losses, bacterial infections, and nutritional inadequacies will contribute to the demise of lethally irradiated animals. Accordingly, Sorensen et al. (386) recently reduced significantly the mortality of lethally irradiated dogs through judicious administration of whole-blood transfusions, antibiotics, parenteral fluids, and nutriments.

## III. STATEMENT OF THE PROBLEM

The accumulation of lipids in organisms following whole-body irradiation has been widely observed (114, 134, 146, 217, 346), but little is known of the effect of lipids on lethally irradiated animals. Nevertheless, in a series of experiments Cheng et al. have shown that rats receiving a daily dietary supplement of as little as 2% cottonseed oil or 10 mg of methyl linoleate were much more radioresistant than animals on a fat-free diet when these animals were subjected to weekly repeated sublethal doses of radiation (75, 76, 77, 110). Recently, Ershoff reconfirmed the effects of low-fat diets on survival of X-irradiated mice (150).

Alekseeva similarly noted that yeast cells rich in fats were much more radioresistant than those poor in fats (7). He postulated that this resistance was due to preferential oxidation of the fatty reserve to oxidation of vital cellular components.

Fat is nature's emergency fuel during periods of fasting or starvation. Hence, the administration of large amounts of fats to irradiated animals may supply the temporary energy requirement of the animals. This should prevent or decelerate the catabolic degradation of essential tissue elements, and mitigate one of the lethal effects of radiation.

Furthermore, but for the proteins, lipids are the most important building blocks of living tissues and are essential to the welfare and survival of all living things. In healthy adult animals, the dietary lipids and their lipid reserves adequately supply the need for maintenance and repair of tissues due to normal wear and tear. In irradiated animals, this lipid reserve may be inadequate or unavailable for tissue reparation. If these suppositions are true, lipid treatment should help animals recover from WBR.

Our preliminary studies on the effect of olive oil on lethally irradiated mice support this hypothesis (20). In view of these and other observations, it appeared advisable to pursue further the studies of the protective effects of lipids on lethally irradiated animals.

# IV. PROCEDURE

In radiation-protection studies the general concensus is to use a lethal or near-lethal dose for all controls (31, 54, 287) because of the great variability in mortality of animals irradiated at the mid-lethal doses (MLD). This, however, is not always a wise choice, particularly in postirradiation protection studies, because radiation syndrome varies with doses. A chemical agent which is beneficial at a given dose range may be ineffective at another level of exposure (135).

Ellinger and his associates have shown that reproducibility of lethality in whole-body X-irradiation in the mid-lethal range is possible if one rigidly adheres to certain physical and biological experimental procedures and if proper precaution is exercised in the care and handling of the animals (144).

## A. Breeding and Care of Experimental Animals

Two strains of Swiss mice were employed exclusively in the present studies. The Namru strain was bred in our laboratory. In order to obtain uniformly heterozygous litters, the breeding was carefully randomized. The Webster strain was obtained from Simonsen Laboratory in Gilroy, California. Generally, the offsprings were weaned at 28 days and caged individually in labelled glass jars (Fig. 1) from 2 to 3 weeks prior to irradiation and until the experiments were terminated. They were fed water and Simonsen Laboratory white diet ad libitum (See Table I). The jars, which were lined with sterile wood shavings, were cleaned weekly. In noncritical experiments, groups of 10 to 12 animals were kept in 14-by-8-by-6 in., sterile, stainless steel cages lined with sterile wood shavings. The cages were also cleaned weekly.

ZN-2712

Fig. 1. Mouse cages made from 1-pint wide-mouth Mason glass jars for pre- and postirradiation isolation of experimental animals.

Table I. Simonsen Laboratory White Diet

| | | |
|---|---|---|
| Crude protein | not less than . . . | 24.0% |
| Crude fat | not less than . . . | 6.75% |
| Fiber | not more than . . . | 3.0% |
| Ash | not more than . . . | 4.7% |

Contents: Ground wheat, dried skim milk, casein, iodized salt, rice bran, vegetable oil, vitamin oil, minerals (calcium carbonate, dicalcium phosphate, phosphatic clay, calcium sulphate, magnesium carbonate, manganese sulphate, iron sulphate, iron oxide, copper sulphate, sodium borate, disodium phosphate, iron phosphate, potassium iodide, cobalt carbonate, zinc sulphate, potassium anise).

## B. Selecting and Grouping of Experimental Animals

In order to have consistent uniformity, the animals were generally culled on the basis of age, weight, and weight gain. Litter offsprings were equally distributed among the experimental groups.

Unless indicated, only 6 to 7 weeks old mice weighting 26 ± 4 g (Namru) and 28 ± 4 g (Webster) and showing progressive weight gain during the week preceding the experiments were used.

## C. Irradiation and Dosimetry

The X-ray source was from a Phillips 250-kv, 25-ma deep-therapy unit operated at 200 kvp, 15 ma, with a 0.5-mm Cu and 1.0-mm Al filter. Dose rate was determined to ± 2% periodically during the experiment with four 250-r-meter Victoreen thimble chambers. The dosimeters were positioned in the lucite mouse holders as shown in Fig. 2.

In our initial comparative experiments, the animals received total-body X-irradiation in a single exposure at an air dose rate of about 9 r per minute. In subsequent studies the dose rate was adjusted to 20 r per minute. Generally, 40 animals were irradiated simultaneously. Whenever possible, during any exposure, all experimental groups were represented equally.

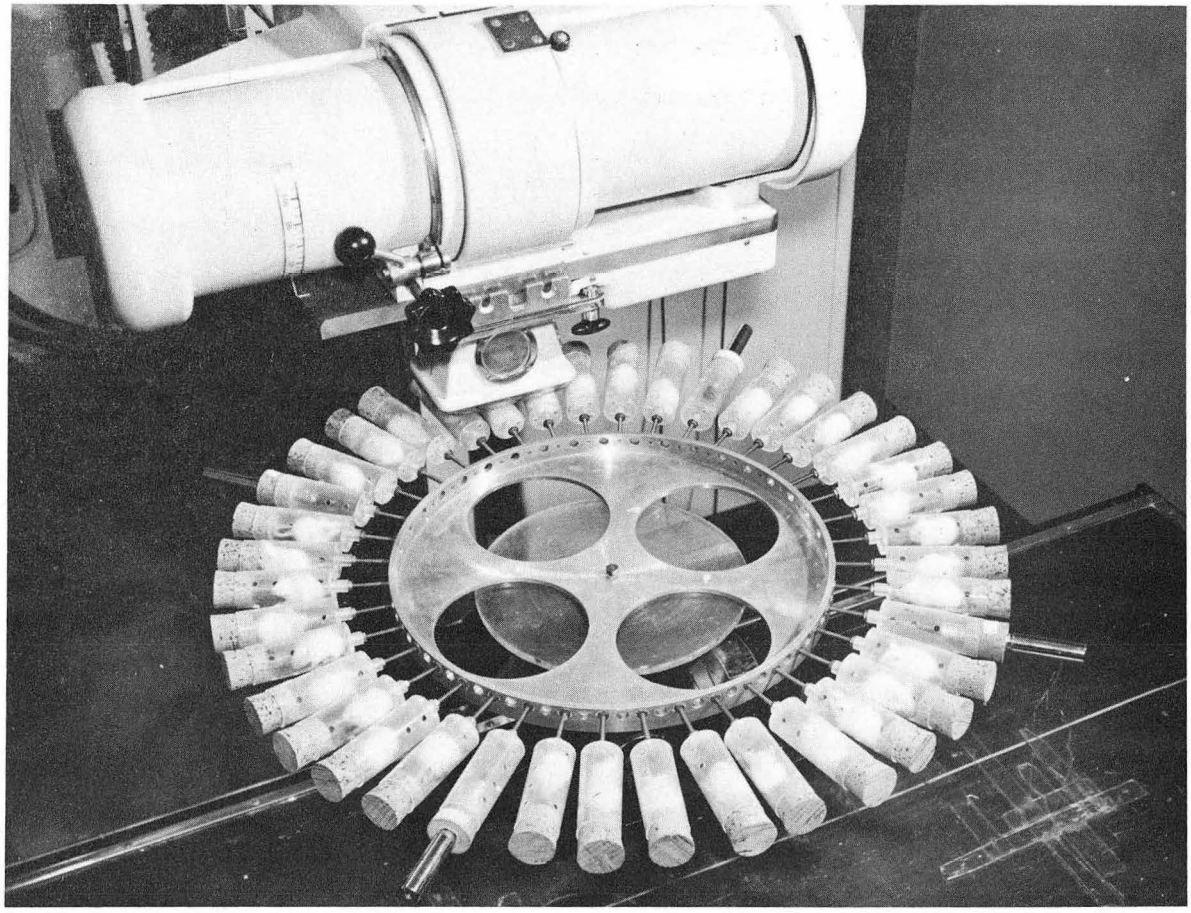

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Fig. 2. Experimental setup for simultaneously exposing mice to uniform whole-body X-radiation. The irradiation positioning wheel, lucite mouse canister, and rotator are shown.

## D. Lucite Canister, Irradiation-Positioning Wheel, and Rotator

The mouse canisters shown in Fig. 2 were made from 1 1/2-in. o.d. molded lucite tubings to the following specifications:

a. Machine bored to 1/16-in. uniform wall thickness
b. Inside diameter 1 3/8 in.
c. Over-all length---3 3/4 in.
d. Air vents---16 uniformly spaced 1/4 in. holes on the canister wall and four on the end plate.

To minimize back scattering, the canisters were separated from the irradiation positioning wheel by means of 2-in.-long aluminum spindles. In order to have an absolutely planar surface, the positioning wheel was machined from a 1 1/4-in. thick dural plate. The wheel was rotated at 3 rpm.

## E. Comparative Study of Irradiation Methodology

A study of irradiation technique was conducted to test the reproducibility of 30-day survival under our experimental conditions. For this study, two groups of Swiss Namru male mice were used. The mice in Group A (Table II) were handled according to the general procedure described above. Group B animals (Table II) were not uniformly heterozygous. On weaning at 21 to 28 days, groups of 10 to 12 animals were kept in stainless steel cages for 3 to 4 weeks. The mice were not weighed during this period. Only healthy-appearing animals weighing 25 ± 7 gm were selected. They were fed water and white diet ad libitum. The metal cages were cleaned weekly. The technique of irradiation and dosimetry was identical for both groups, but the mouse canisters used in Group B were of smaller diameter. In these holders the larger animals were unable to move freely and occasionally one would become wedged in the canister while attempting to alter its position and become asphyxiated during irradiation. After exposure the animals were returned to their respective cages for observation. A dose-survival curve of our experimental animals for whole-body irradiation was also obtained (Fig. 3).

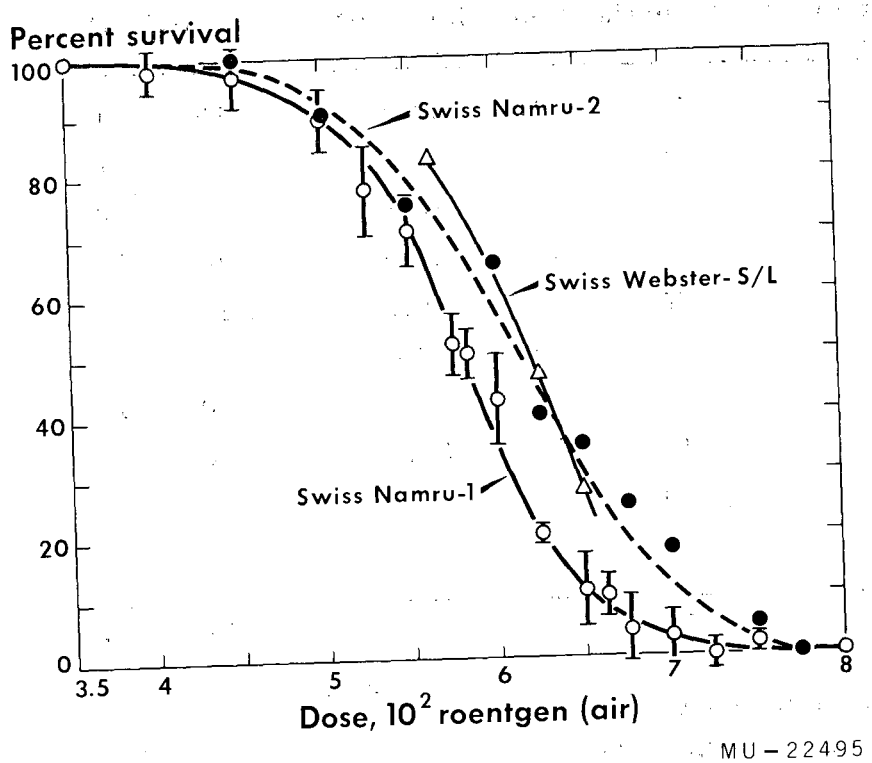


Fig. 3. Dose-survival curve of 6 to 7 weeks old male Swiss Webster white mice following whole-body X-irradiation. The animals were individually caged and fed Simonsen Laboratory white diet throughout the experiment. A standard deviation is indicated where five or more measurements were taken over a period of several months. In such instances, each point represents over 40 animals.

Table II. Effect of Methodology on the mortality of X-irradiated mice in the mid-lethal range $LD_{40(30)}$ to $LD_{60(30)}$

| | Group A Rigorous control | | | Group B Nonrigorous control | | |
|---|---|---|---|---|---|---|
| Experiment No. | Animals | Dead | Mortality (%) | Animals | Dead | Mortality (%) |
| 1 | 10 | 5 | 50.0 | 10 | 1 | 10.0 |
| 2 | 19 | 8 | 42.1 | 9 | 8 | 88.9 |
| 3 | 11 | 6 | 54.5 | 10 | 4 | 40.0 |
| 4 | 20 | 10 | 50.0 | 20 | 15 | 75.0 |
| 5 | 40 | 20 | 50.0 | 20 | 5 | 25.0 |
| 6 | 9 | 4 | 44.4 | 9 | 9 | 100.0 |
| 7 | 10 | 4 | 40.0 | 20 | 12 | 60.0 |
| 8 | 18 | 11 | 61.1 | 20 | 0 | 0.0 |
| 9 | 10 | 6 | 60.0 | | | |
| 10 | 10 | 4 | 40.0 | | | |
| Total | 157 | 78 | | 118 | 54 | |
| Average mortality | | | 49.7 ± 7.7 | | | 45.8 ± 37.2 |

± one standard deviation.

## F. Protective and Therapeutic Studies

The experimental animals generally received a single intraperitoneal injection of test material within an hour after WBR. Whenever possible, the dose controls were similarly treated. As survival frequencies of sham injected and uninjected animals were alike (Fig. 4), the oil group controls were usually uninjected.

The vegetable oils, synthetic triglycerides, and methyl esters of the fatty acids investigated for postirradiation protective properties are listed in Table III. Also indicated are a number of substances that were used to ascertain the role of lipids in WB irradiated animals. The fatty-acid compositions of the vegetable oils are given in Table IV.

## G. Fertility Tests

To study the effect of postirradiation lipid treatment on recovery of male mice from radiation-induced sterility, two-hundred 8-to9-weeks-old male mice were exposed to whole-body X-irradiation. A third unirradiated group was kept as control. One day after MLD exposure, 10 males each from the irradiated-treated and -untreated, and unirradiated groups were mated with four sexually mature (10-weeks-old) females. The mated animals were kept in separate metal cages. Three days later, the males were removed and returned to their respective jars. The females were sacrificed on the 16th post-fertilization day and their uteri examined for developing foetuses. On the sixteenth postirradiation day, 10 males each from the radiated groups and 10 from the unirradiated controls were again mated and studied as described above. Similar tests were carried out on the 30 and 60 postirradiation-day survivors.

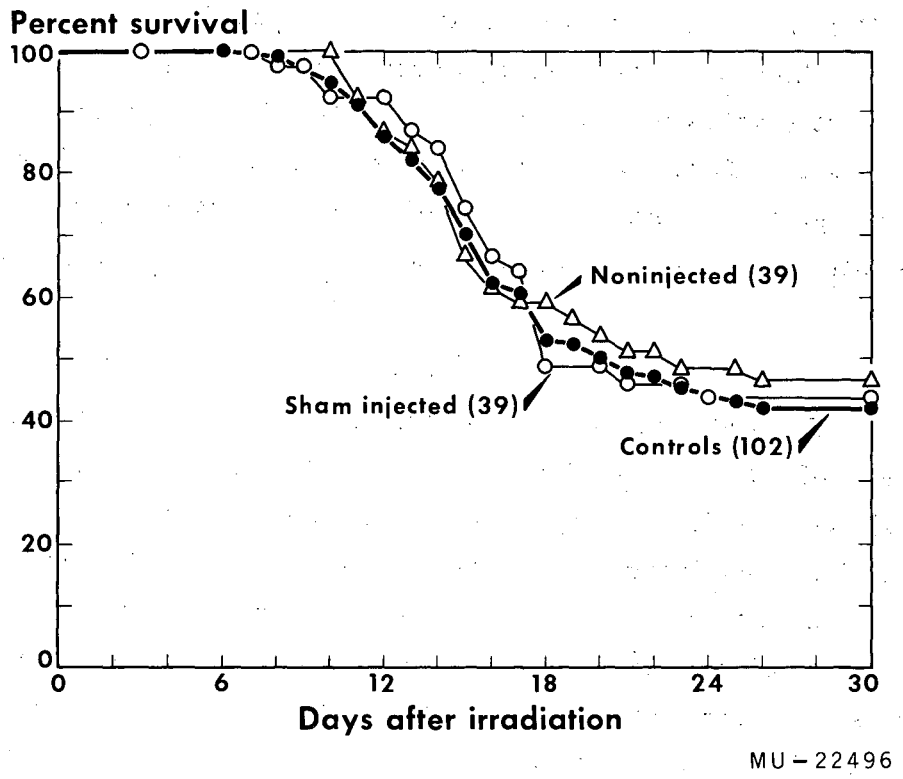


Fig. 4. Comparison of the survivals of sham injected and uninjected animals following 625-r whole-body X-irradiation. The number of animals is indicated in parentheses.

Table III. List of substances investigated, their source, and their relative effectiveness in mitigating the effects of WBR in Mice

| Material | Relative Effectiveness[a] | Source |
|---|---|---|
| Olive oil | ++++ | McKesson & Robbins; Purepac |
| Safflower oil[b] | +++ | Pacific Vegetable Oil Corp. |
| Safflower oil[c] | ++ | Pacific Vegetable Oil Corp. |
| Peanut oil | ++++ | Planters Edible Oil Co. |
| Triolein | ++++ | Hormel Foundation |
| Trilinolein | --- | Hormel Foundation |
| Methyl oleate | ++++ | Hormel Foundation |
| Methyl linoleate | -- | Hormel Foundation |
| Methyl stearate | +++ | Hormel Foundation |
| Methyl palmitate | - | Hormel Foundation |
| Mineral oil | + | E.R. Squibb & Sons |
| Normal saline | 0 | Cutter Laboratories |
| Corn starch | + | Corn Products Company |
| Powdered glass | + | Fisher Scientific Co. |
| Bovine albumin | -- | Armour Pharmaceutical Co. |
| Terramycin | 0 | Chas. Pfizer & Co., Inc. |
| Streptomycin-sulfate | 0 | E.R. Squibb & Sons |
| Lycopene | 0 | Hofmann-LaRoche |
| Oleic acid | ---- | Nutritional Biochemicals Corp. |
| Glycerine | ---- | Baker & Adamson |
| Squalene | +++ | Eastman Kodak Company |
| Robane | 0 | Robeco Chemicals, Inc. |

[a] + indicates beneficialness: mildly (+) to very beneficial (++++)
- indicates harmfulness: mildly (-) to very harmful (----)
0 indicates no effect

[b] With 0.01% propyl gallate

[c] No propyl gallate

Table IV. Percent fatty-acid composition of some vegetable oils

| Fatty acid | Dole nomen-clature | Chemical formula | Vegetable oils[a] | | |
|---|---|---|---|---|---|
| | | | Olive | Peanut | Safflower |
| Saturated: | | | | | |
| Myristic | 14:0 | $C_{14}H_{28}O_2$ | 0.1-1.1 | - | 0.1-1.5 |
| Palmitic | 16:0 | $C_{16}H_{32}O_2$ | 7-15 | 6.9 | 3-6 |
| Stearic | 18:0 | $C_{18}H_{36}O_2$ | 1-3.3 | 3-6 | 1-4 |
| Arachidic | 20:0 | $C_{20}H_{40}O_2$ | Trace | 2-4 | 0.2-0.5 |
| Behenic | 22:0 | $C_{22}H_{44}O_2$ | - | Trace-3 | - |
| Lognoceric | 24:0 | $C_{24}H_{48}O_2$ | - | 1-3 | - |
| Unsaturated: | | | | | |
| Palmitoleic | 16:1 | $C_{16}H_{30}O_2$ | - | Trace | - |
| Oleic | 18:1 | $C_{18}H_{34}O_2$ | 70-86 | 53-71 | 15-26 |
| Linoleic | 18:2 | $C_{18}H_{32}O_2$ | 4-12 | 13-27 | 51-79 |
| Linolenic | 18:3 | $C_{18}H_{30}O_2$ | - | - | 0.1-8 |

[a]Condensed from The Chemistry of Fatty Acids, Armour Industrial Chemical Company, 1959.

## H. Serum-Lipid Analysis

Blood samples for lipid analysis were obtained from mildly etherized mice by direct heart puncture. One-milliliter disposable syringes with inch-long 20-gage needles were used. Although heparinized syringes were used initially, all blood was drawn subsequently with nonheparinized syringes because tissue lipases interfered with ultracentrifugal fractionation of the serum lipids.

### 1. Ultracentrifugal Fractionation and Silicic Acid Chromatography of Serum Lipids.

After whole blood was centrifuged on the clinical centrifuge for 15 minutes, the lipids were extracted from the serum by a modification of the Sperry (392) method as adopted by Lindgren et al. (275).

Separation of serum lipoproteins into high-and low-density fractions by successive preparative ultracentrifugation on the Spinco Model-L ultracentrifuge has also been lucidly described (392).

A silicic acid chromatographic column was used to separate the ultracentrifuged lipids into cholesteryl esters, triglycerides, and phospholipids, as described by Freeman and his associates (169). The unesterified fatty acids in the albumin fraction were isolated by the alkali-extraction method of Borgstrom (56).

### 2. Gas-Liquid Chromatographic Analysis

Because methyl esters of fatty acids are used in gas chromatographic analysis, the lipid fractions were individually methylated by transesterification (401) prior to analysis on the chromatographic apparatus described by Upham et al. (415). Hormel gas-chromatographic methyl-ester mixtures and other pure methyl-ester mixtures were used in calibrating the apparatus. The chromatogram of a typical fatty-acid ester mixture is shown is Fig. 5.

### 3. The Punch-Card Technique (409)

Quantitative determination of each fatty-acid component in a gas-liquid chromatographic analysis of serum lipids by the standard procedure of area determination through planimetry and triangulation is exceedingly laborious and time-consuming. To facilitate this determination, the punch-card technique developed by Tandy and his

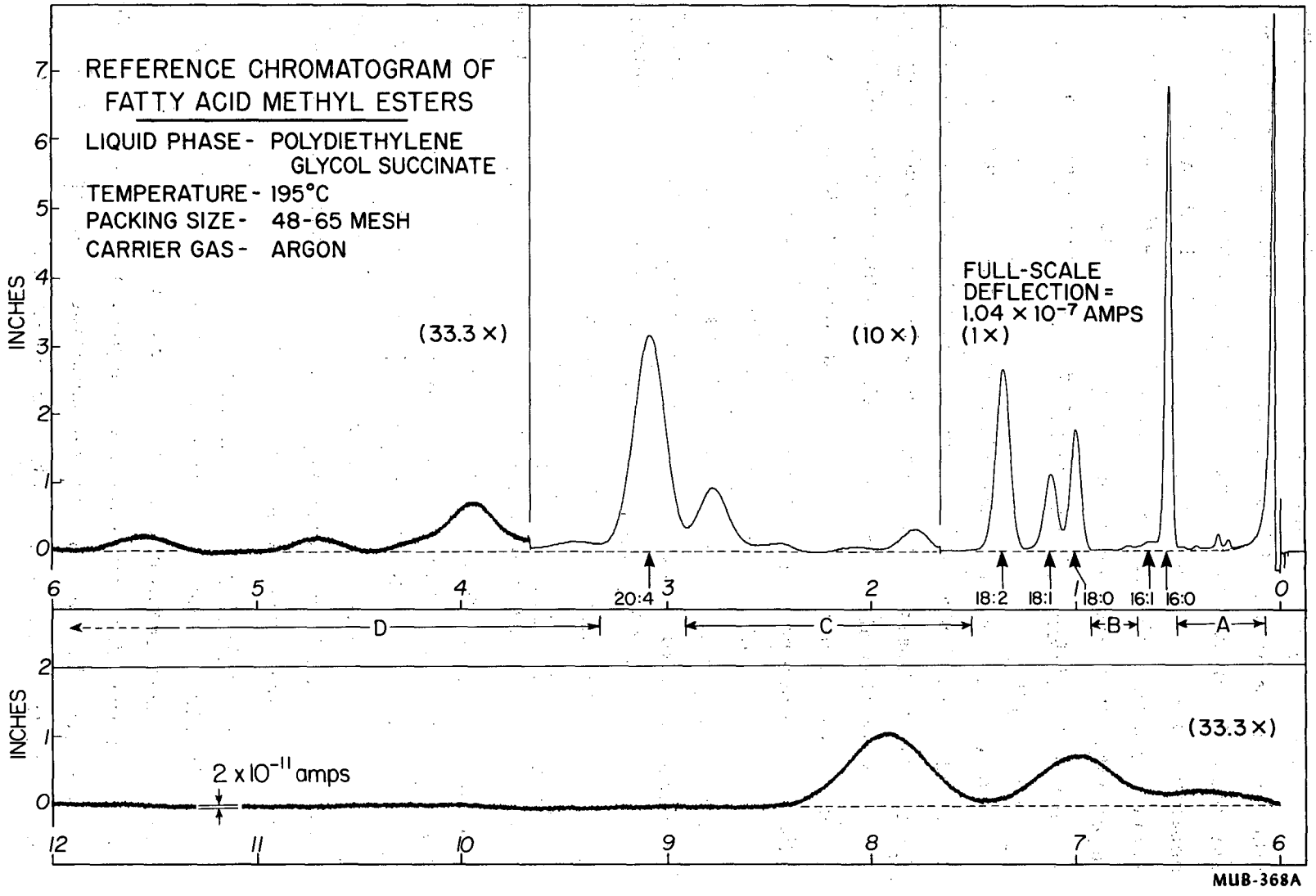


Fig. 5. Standard reference chromatogram of known fatty-acid methyl-ester mixtures for calibrating the gas-liquid chromatographic apparatus (courtesy of Tandy et al., Ref. 409).

collaborators (409) was used to obtain the present data. Briefly, for a first-order approximation, the weight of each component of the chromatogram obtained from the value of the product of its peak height and elution time is corrected by a factor that compensates for the nonlinearity of peak-height-to-mass change (Fig. 6). The weights of these fatty acid components from the first approximation are accurate to within 5 to 10%. If further accuracy is desired, a second-order correction, compensating for retention time of the components relative to methyl stearate, is applied (Fig. 7). These data are then transcribed onto standard 80-column IBM punch cards (Fig. 8) and processed in the IBM 650 electronic computer.

The fatty-acid data are reported on the basis of carbon-chain lengths and number of double bonds per molecule (see Table IV) as proposed by Dole (120). However, because there are 15 to 30 measureable components in a typical serum-lipid chromatogram, among which are a number of unidentified components, comparison of experimental data was facilitated by using certain simplifications adopted by Lindgren et al. (275). Essentially, these unidentified components have been grouped into the following four classes as indicated in Fig. 5: (a) pre-16:0, (b) 16:0-18:0, (c) 18:2-20:4, and (d) post-20:4. These four classes account for approximately 10 to 20% by weight of the total fatty-acid components in our chromatogram. The greater 80-to-90% fraction consists of identifiable methyl esters.

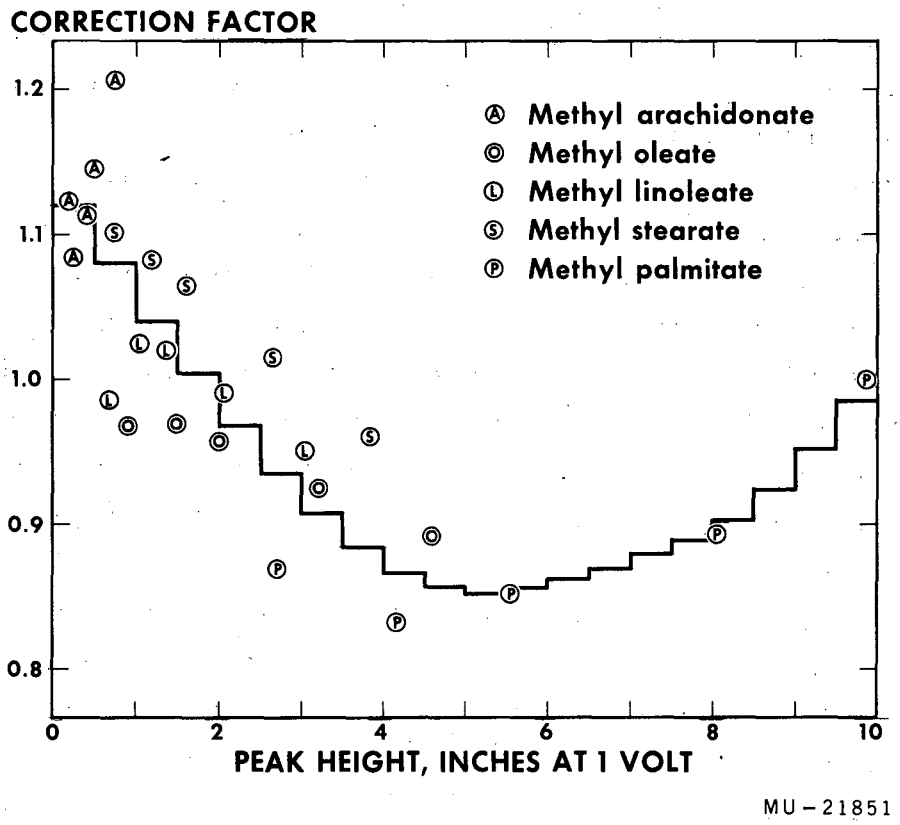


Fig. 6. First-order correction factor which is used to compensate for the nonlinearity of peak-height-to-mass change. (courtesy of Tandy et al., Ref. 409).

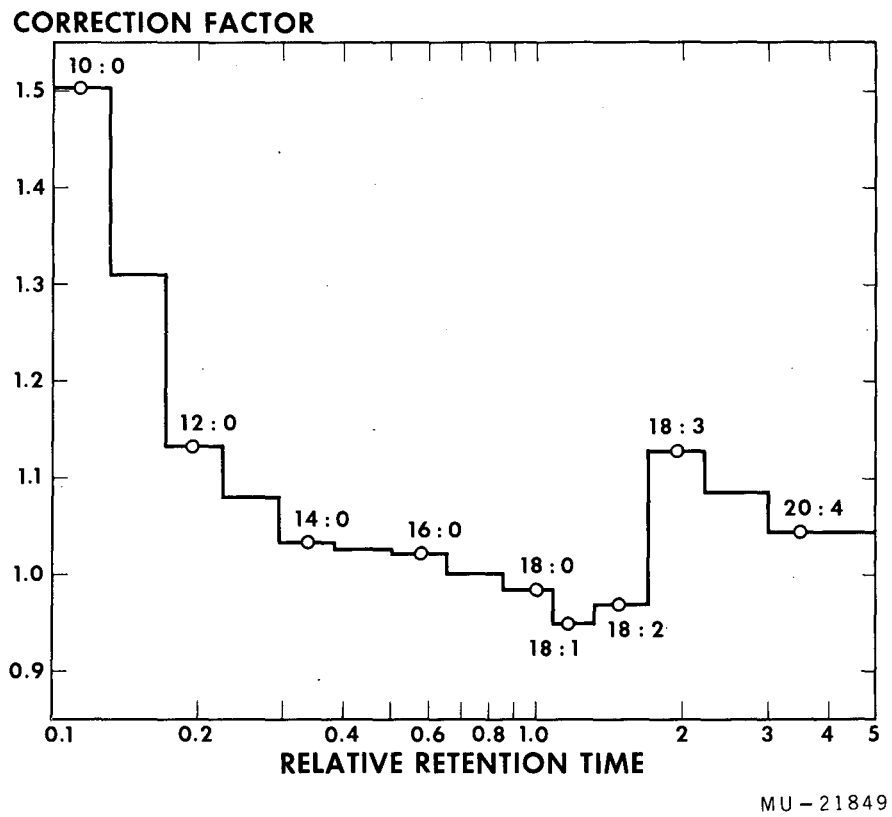


Fig. 7. Second-order correction factor which compensates for retention time of the various components relative to methyl stearate (courtesy of Tandy et al., Ref. 409).

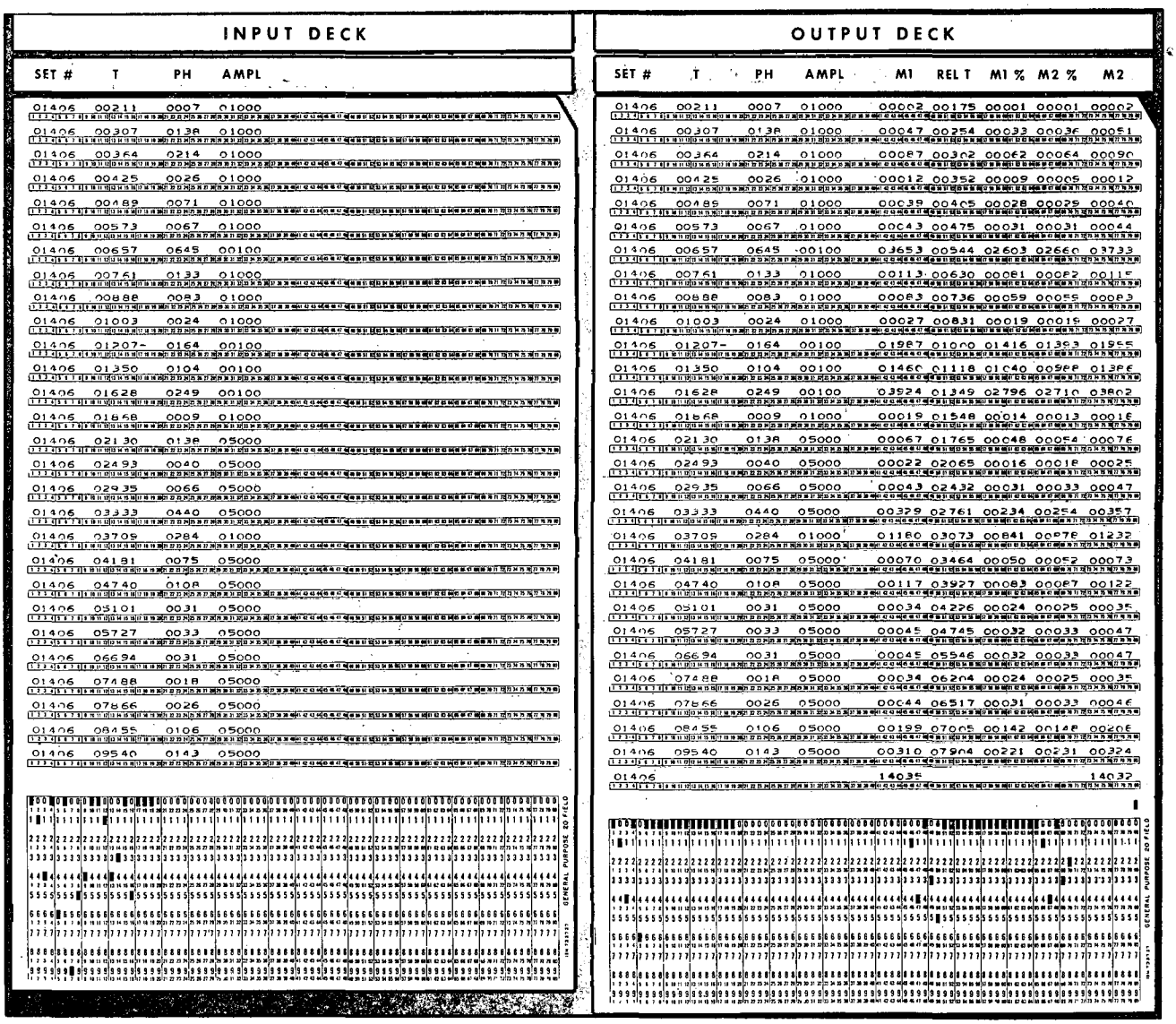


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Fig. 8. Standard 80-column IBM punch card used for processing the lipid data in the IBM 650 computer (courtesy of Tandy et al, Ref. 409).

# V. RESULTS AND DISCUSSION

## A. Comparative Study of Irradiation Methodology

The ultimate criterion for accepting a substance as protective or therapeutic is based on the difference in mortality between experimental and control animals. It is, therefore, vitally important in radiation-protection studies to be able to reproduce mortality in irradiated animals. To achieve this, one must consistently adhere to rigorous physical and biological experimental practices. The results of our comparative study listed in Table II lucidly demonstrate this requirement. The average 30-day mortality of Group-A (rigorous-control) mice in the mid-lethal range ($LD_{40}$ to $LD_{60}$) was 49.7 ± 7.7% as compared to 45.8 ± 37.2% in Group B (nonrigorous control). Group-A mortality ranged from 40.0 to 61.1% as compared to 0 to 100% in Group B.

## B. Lipid Therapy Against Whole-Body X-Irradiation

Without exception, survival of postirradiation oil-treated animals was higher than the controls. The data presented in Table V demonstrates this therapeutic value of certain vegetable oils and their fatty-acid methyl esters. As we have shown previously (20), olive oil is mildly beneficial against total-lethal doses. The summary of experiments 5 to 16 in Table V shows an average increase in survival of 37.5% in the treated over the dose controls,* for a 625-r whole-body dose. Experiments 1 to 4 were omitted from this summary because the mouse strain and X-ray dose rate used in these four experiments differed from those of experiments 5 to 16. A single intraperitoneal injection of 1 ml of olive oil an hour before or after WB irradiation was equally protective and therapeutic (Fig. 9). Recent experiments indicate that protection is even greater if olive oil is given to the animals 24 hr before than immediately before or after irradiation (Fig. 10). Olive oil is still beneficial when injected 24 to 48 hr after irradiation. However, studies now in progress indicate that olive oil

*The chi-square test was used to determine the probability: $\chi^2 \simeq 63$; $P << 0.001$.

Table V. Therapeutic value of fats on whole-body X-irradiation of 6-weeks-old male Swiss white mice

| | | | | Postirradiation oil-treated | | | Control | | |
|---|---|---|---|---|---|---|---|---|---|
| Exp. No. | Mice strain | Fat treatment | Dose r/air | Total animals | No. surv. | % surv. | Total animals | No. surv. | % surv. |
| 1 | Donner | Olive | 660 | 116 | 19 | 16.4 | 77 | 4 | 5.2 |
| 2 | Donner | Olive | 750 | 40 | 3 | 7.5 | 40 | 1 | 2.5 |
| 3 | Donner | Olive | 625 | 14 | 8 | 57.1 | 13 | 4 | 30.8 |
| 4 | Donner | Olive | 587 | 40 | 35 | 87.5 | 40 | 20 | 50.0 |
| 5 | Webster S/L | Olive | 625 | 24 | 17 | 70.8 | 24 | 11 | 45.8 |
| 6 | Webster S/L | Olive | 625 | 24 | 16 | 66.7 | 24 | 8 | 33.3 |
| 7 | Webster S/L | Olive | 625 | 20 | 18 | 90.0 | 30 | 13 | 43.3 |
| 8 | Webster S/L | Olive | 625 | 24 | 19 | 79.2 | 24 | 11 | 45.3 |
| 9 | Webster S/L | Olive | 625 | 24 | 15 | 62.5 | 24 | 9 | 37.5 |
| 10 | Webster S/L | Methyl oleate | 625 | 24 | 16 | 66.7 | 24 | 11 | 45.8 |
| 11 | Webster S/L | Peanut | 625 | 24 | 18 | 75.0 | 24 | 11 | 45.8 |
| 12 | Webster S/L | Safflower[a] | 625 | 24 | 17 | 70.8 | 24 | 11 | 45.8 |
| 13 | Webster S/L | Triolein | 625 | 24 | 19 | 79.2 | 24 | 11 | 45.8 |
| 14 | Webster S/L | Methyl oleate | 625 | 24 | 19 | 79.2 | 24 | 11 | 45.8 |
| 15 | Webster S/L | Olive + stearate | 625 | 24 | 22 | 91.7 | 24 | 11 | 45.8 |
| 16 | Webster S/L | Olive + stearate | 625 | 24 | 18 | 75.0 | 24 | 9 | 37.5 |
| Summary of Webster S/L strain (Exp. Nos. 5 to 16) | | | | | | | | | |
| 5-16 | | All oil | 625 r | 289 | 214 | 75.4 | 294 | 127 | 43.2 |

[a]0.01% propyl gallate added as antioxidant.

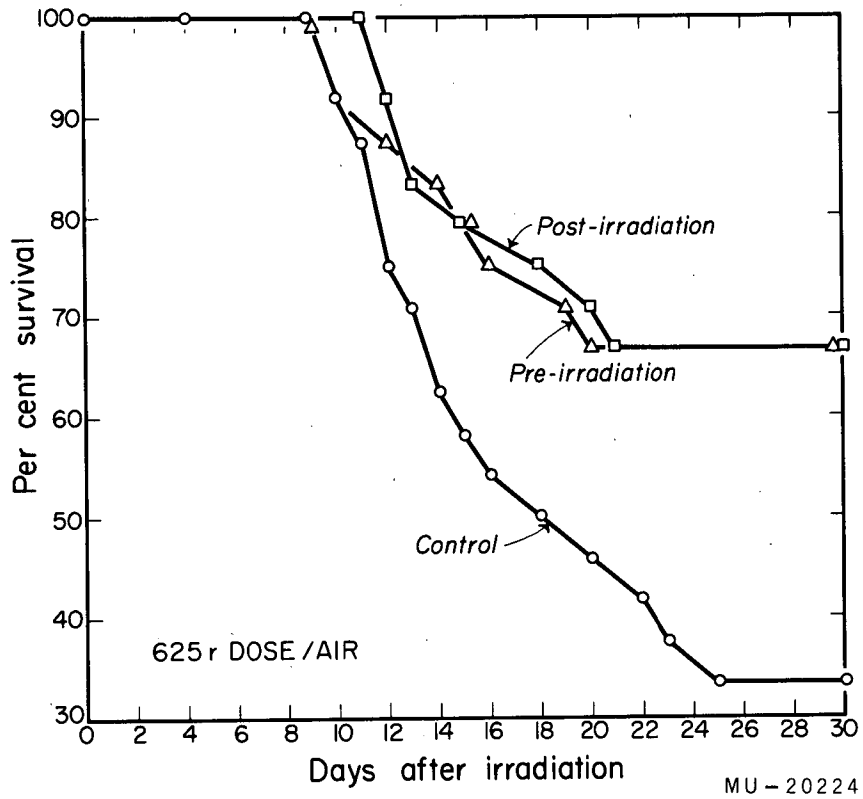


Fig. 9. Effect of 1 ml olive oil injected intraperitoneally within an hour before or after whole-body X-irradiation on survival of male Swiss white mice (48 animals per group)

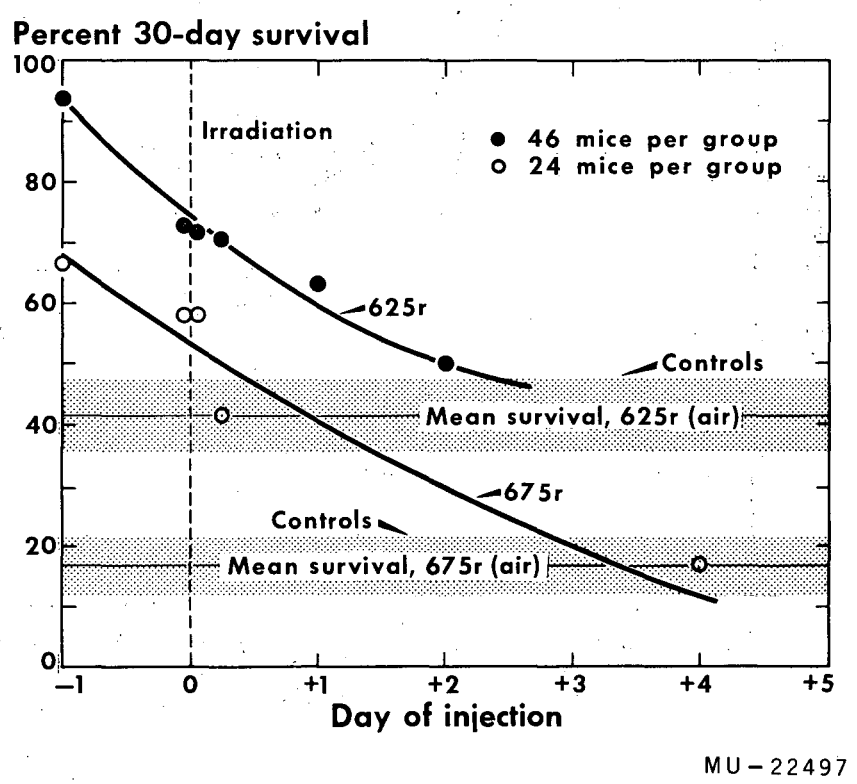


Fig. 10. Effect of time of intraperitoneal injection of one-ml olive oil on survival of X-irradiated mice. The standard deviations of survival of the 625-and 675-r controls are indicated by shadings.

is not as effective when given to animals 3 days before or after exposure to radiation. Oil treatment 6 to 9 days after WB irradiation even potentiated lethality.

The controls in these oil-therapy experiments were usually uninjected since percentage survivals of the sham-injected and uninjected animals were similar (Fig. 4). Because olive oil contains traces of nonsaponifiable fats, these were concentrated by saponification of the oil and tested on irradiated animals. The result (Fig. 11) indicates that this component is therapeutically ineffective. However, chemically pure (>99%) methyl oleate and triolein (~99%) were as effective as olive oil (Fig. 12).

To ascertain whether this therapeutic effect was peculiar to olive oil, the efficacy against X-radiation of a number of other lipid, nonlipid, and particulate materials were tested. The results are summarized in Table III. Peanut oil and safflower oil were found to be equally effective (Fig. 13). Methyl stearate, which is considered dietarily unessential, was also beneficial, while methyl palmitate was not (Fig. 14). To confirm this ineffectiveness of palmitate, a similar experiment was performed. Mineral oil was used in place of the olive oil as the solvent. As expected, the palmitate was again ineffective (Fig. 15). In fact, in both instances methyl palmitate potentiated the harmful effect of radiation. Methyl linoleate is essential in animal diet. But 1-ml intraperitoneally injected into our animals was ineffective and appeared even harmful (Fig. 16). This is consistent with recent findings of Bowen and Thick (57), who isolated from pine seed a factor similar to linoleic acid that increases the sensitivity of seeds to ionizing radiation. Trilinolein was even more toxic (Fig. 17). Since these compounds were highly purified and precaution was exercized to avoid oxidation, a lethally toxic oxidation product must form when these substances are injected into irradiated animals. This "fatty toxin" may be the lipid hydroperoxides observed by Dubouloz, Bacq, and others (28, 124, 229, 230) in irradiated animals. Normal unirradiated animals may have an adequate supply of antioxidants in their system to inhibit the formation of these toxins from their body fats.

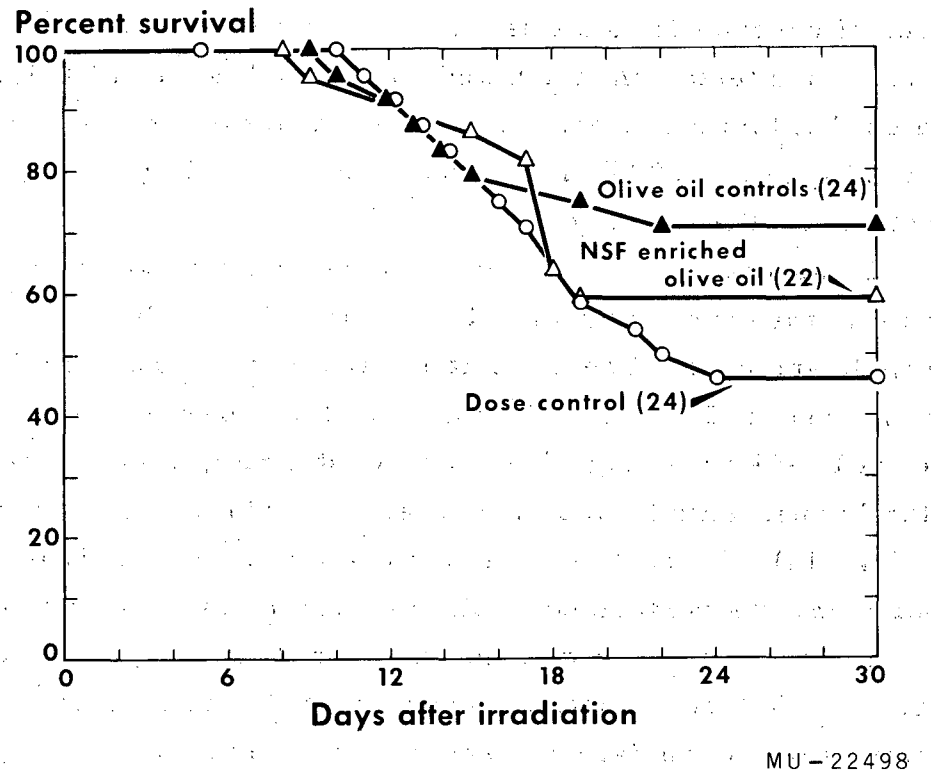


Fig. 11. Effect of nonsaponifiable fraction (NSF) of olive oil on survival of lethally irradiated mice. The NSF was extracted from olive oil after saponification, dried under nitrogen, and redissolved in pure olive oil. One-half ml of this 50x NSF concentrated oil was injected intraperitoneally 1 hr after irradiation. The number of animals is indicated in parentheses.

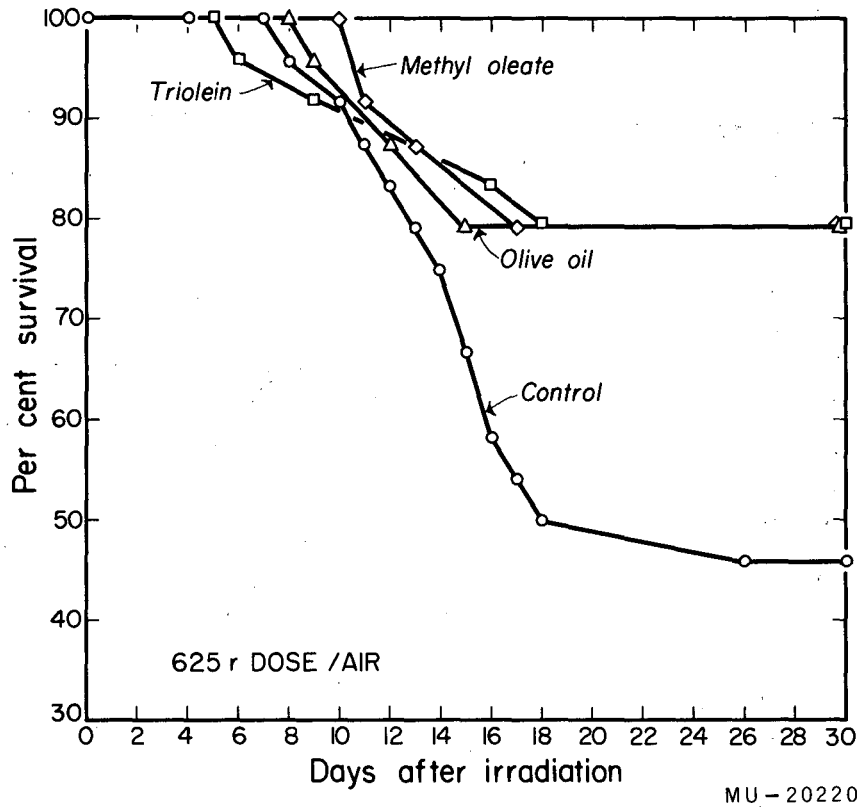


Fig. 12. Comparative therapeutic effect of 1-ml methyl oleate, triolein, and olive oil injected intraperitoneally in mice (24 animals per group) within 1 hr after whole-body X-irradiation.

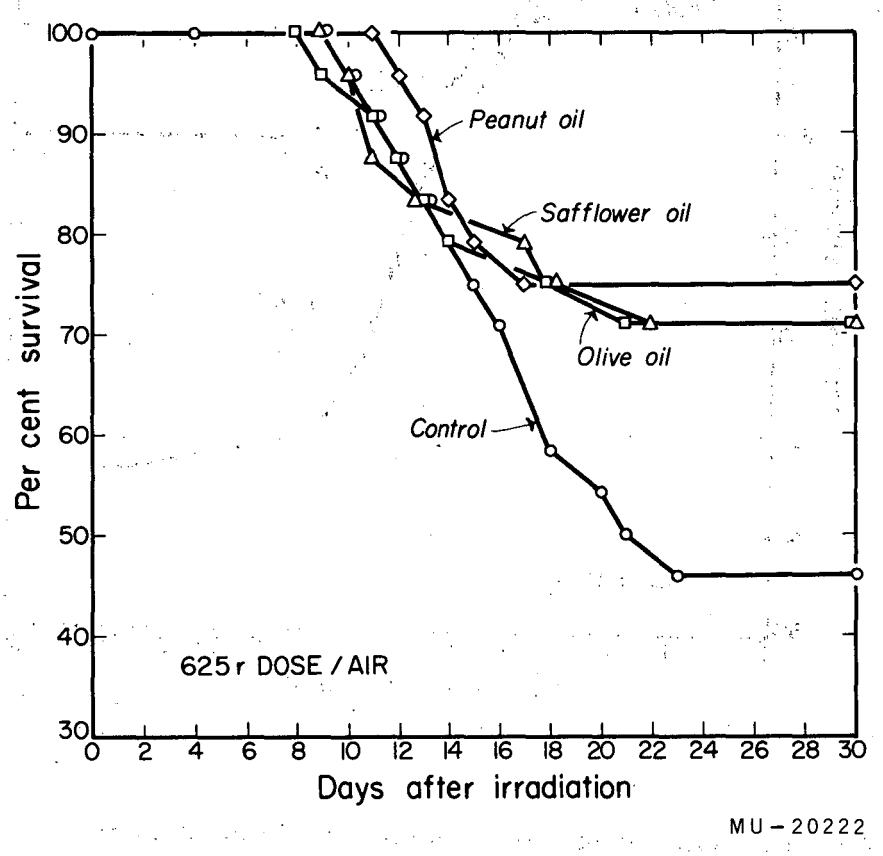


Fig. 13. Comparative effect on survival of mice of 1 ml olive oil, peanut oil, and safflower oil (0.01% propyl gallate added) injected intraperitoneally within 1 hr after whole-body lethal X-irradiation. Each group was represented by 24 animals.

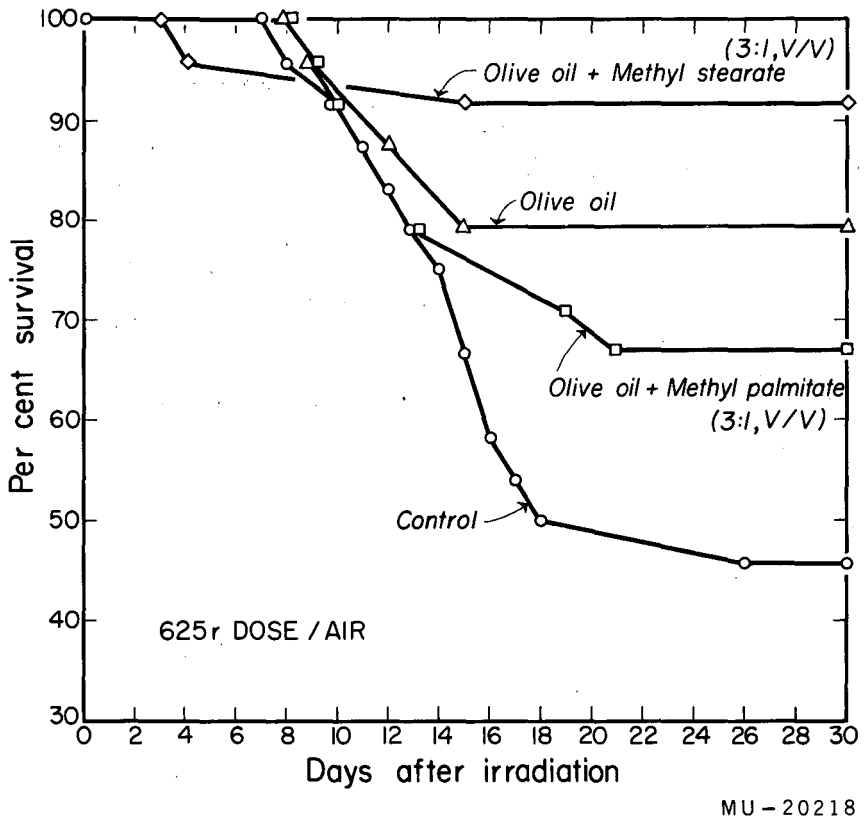


Fig. 14. Modification of the therapeutic value of olive oil on X-irradiated mice (24 animals per group) by saturated fats.

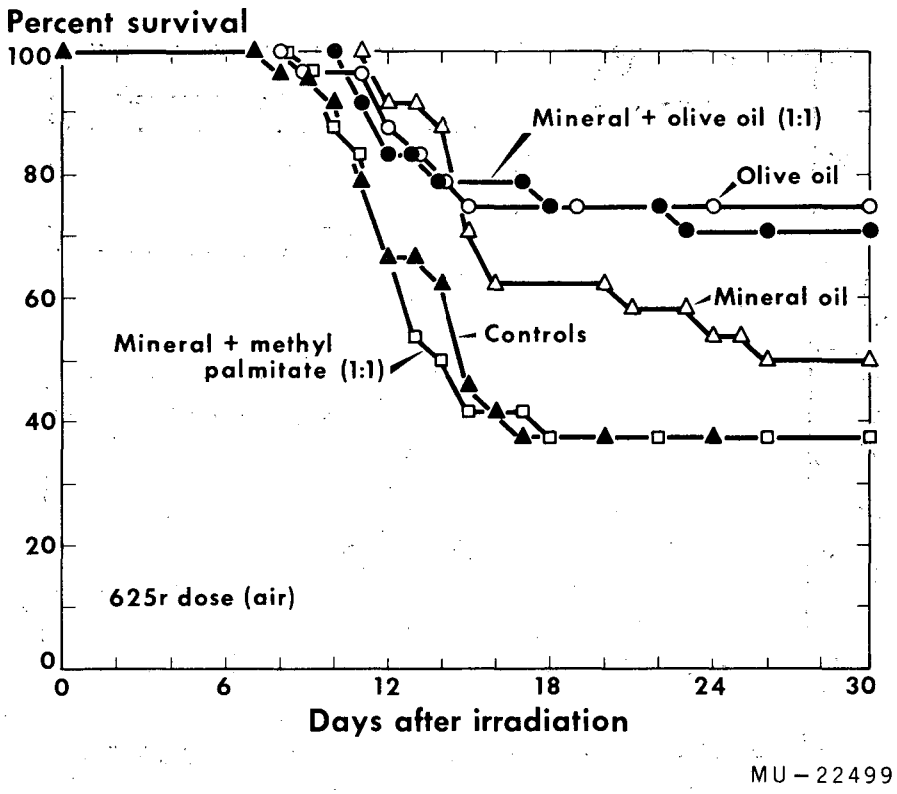


Fig. 15. The inability of methyl palmitate to mitigate lethality of X-irradiated mice (24 animals per group). One ml oil was injected within 1 hr after whole-body irradiation.

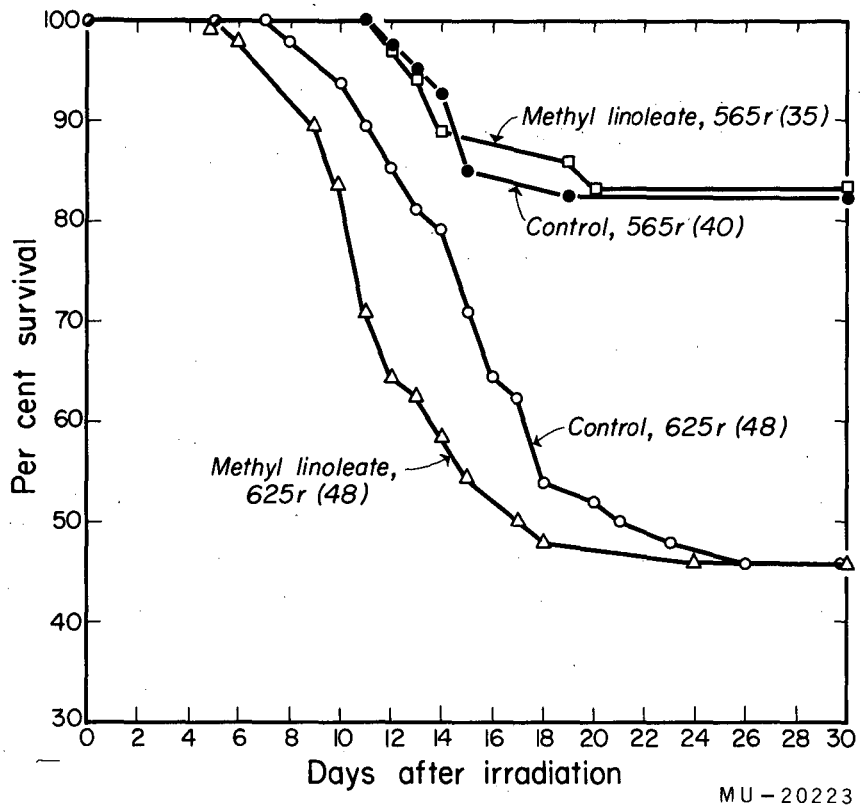


Fig. 16. Effect on survival of mice of 1 ml methyl linoleate injected intraperitoneally within an hour after whole-body X-irradiation. The number of animals is indicated in parentheses.

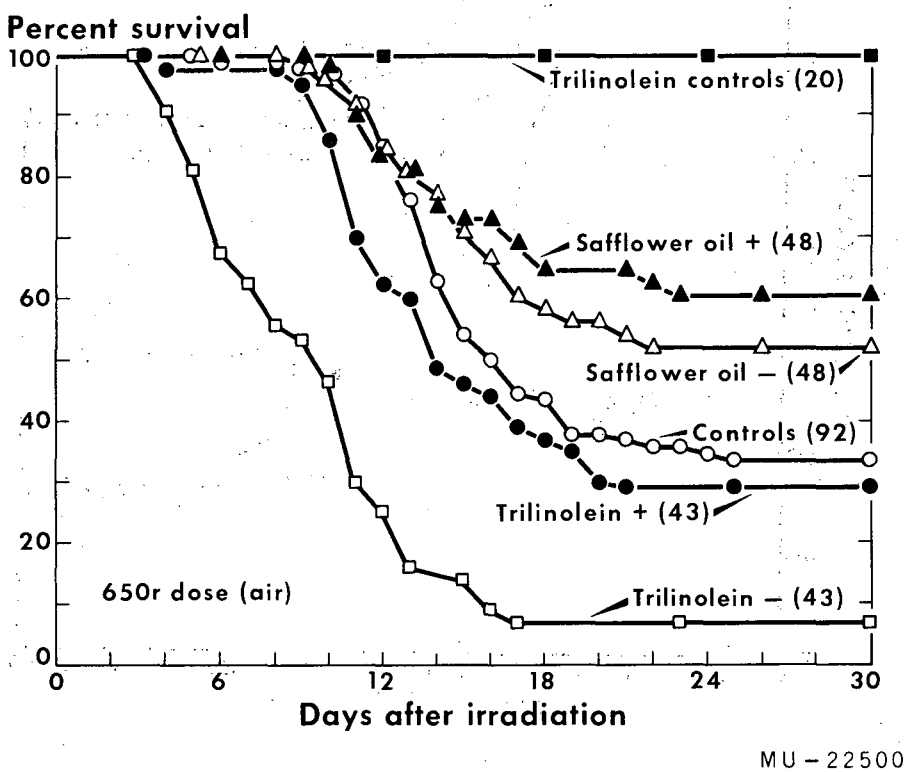


Fig. 17. The ability of d, α-tocopherol to attenuate the toxic effect of trilinolein on lethally irradiated mice. Safflower oil fortified with 0.01% propyl gallate was slightly better than the oil without the antioxidant preservative. The trilinolein control was unirradiated. The number of animals is given in parentheses. Here + indicates with antioxidant, - indicates without.

However, one ml of trilinolein injected into unirradiated mice was mildly lethal (Table VI). A lack of antioxidant in the animal's tissues capable of coping with this sudden increase in oxidizable linoleates could account for this toxicity. This would explain why antioxidant containing safflower oil (51 to 79% linoleic acid; see Table IV) was beneficial. Figure 17 also shows that α-tocopherol attenuates the toxic effect of trilinolein ($P < 0.02$). This is not due to a direct effect of α-tocopherol on the animal as evident from the result shown in Fig. 18. At least the effect of α-tocopherol is not statistically significant. Nevertheless, Ershoff and Steers (151) have shown that some antioxidants, e.g., propyl gallate, butylated hydroxy toluene, etc. will significantly prolong survival of mice exposed to multiple sub-lethal doses of X-radiation. The naturally occurring antioxidant, α-tocopherol, was not beneficial. Furth et al. have also administered α-tocopherol in oil to rats before irradiation and found it ineffective (172).

The evidence presented above proves that certain oils do help animals recover from MLD irradiation. Further, this postirradiation protective effect of oil is not due to the essential fatty acids, because both methyl linoleate and trilinolein were ineffective, while dietarily "unessential" triolein and methyl oleate were as protective as olive oil.

## Olive oil, a Substitute for Oleate

Because it contains 70 to 86% oleic acid (Table IV), olive oil was used in most of our studies on irradiated animals.

A series of experiments were conducted to ascertain the optimum dose for maximum protection. The results, tabulated in Table VII, show that intraperitoneal injection of 0.25 to 1.0 ml olive oil will protect equally animals exposed to MLD irradiation.

Table VI. Toxicity of single intraperitoneal injection of various substances in nonirradiated male mice

| Item injected | No. animals | Quantity injected | Weeks following injection: No. dead 1 | 2 | 3 | % survival 4 |
|---|---|---|---|---|---|---|
| Olive oil | 100 | 1 ml | 0 | 0 | 0 | 100 |
| Peanut oil | 24 | 1 ml | 0 | 0 | 0 | 100 |
| Safflower oil[a] | 24 | 1 ml | 0 | 0 | 0 | 100 |
| Safflower oil | 24 | 1 ml | 0 | 0 | 0 | 100 |
| Mineral oil | 44 | 1 ml | 0 | 0 | 0 | 100 |
| Robane | 24 | 1 ml | 0 | 0 | 0 | 100 |
| Methyl oleate | 40 | 1 ml | 0 | 0 | 0 | 100 |
| Methyl palmitate | 24 | 1 ml | 0 | 0 | 0 | 100 |
| Methyl stearate | 40 | 1 ml | 0 | 0 | 0 | 100 |
| Methyl linoleate[b] | 20 | 1 ml | 0 | 0 | 0 | 100 |
| Methyl linoleate | 20 | 1 ml | 0 | 0 | 0 | 100 |
| Trilinolein | 40 | 1 ml | 2 | 0 | 0 | 95 |
| Triolein | 40 | 1 ml | 0 | 0 | 0 | 100 |
| Oleic acid | 24 | 1 ml | 24 | 0 | 0 | 0 |
| Selachyl alcohol | | | | | | |
| + olive oil | 30 | 2 mg/0.5 ml | 1 | 0 | 0 | 97 |
| + olive | 90 | 3 to 6 mg/ml | 1 | 0 | 0 | 98.9 |
| + olive | 10 | 20 mg/0.5 ml | 0 | 0 | 0 | 100 |
| Glass in saline | 24 | 20 mg/ml | 0 | 0 | 0 | 100 |
| Starch in saline | 24 | 0.1 g/ml | 0 | 0 | 0 | 100 |
| Glycerine | 5 | 1 ml | 5 | 0 | 0 | 0 |

[a]With 0.01 per cent propyl gallate added

[b]With 0.5 per cent by volume d, α-tocopherol added

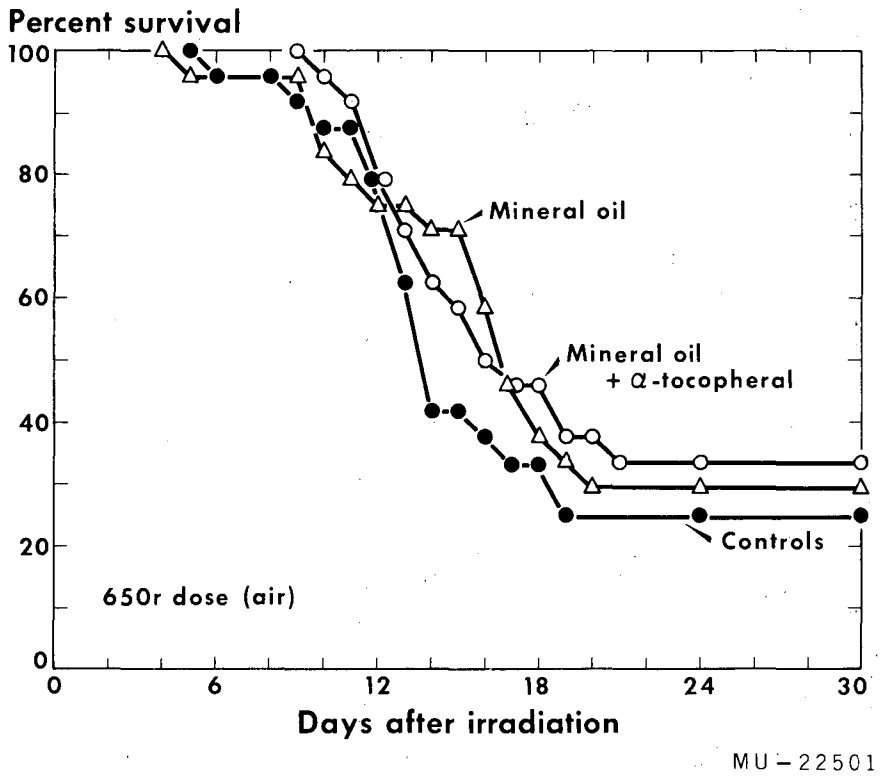


Fig. 18. Effect of d, α-tocopherol on survival of X-irradiated mice (24 animals per group). One ml mineral oil with or without 0.4% α-tocopherol (by volume) was injected into the animals within 1 hr after whole-body irradiation.

Table VII. Effect of quantity of olive oil on 30-day survival of male Swiss white mice exposed to 650-r whole-body irradiation

| Oil I.P. injected (ml) | Control | | | One-hr postirrad. | | | Six-hr postirrad. | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total animals | No. surv. | Surv. (%) | Total animals | No. surv. | Surv. (%) | Total animals | No. surv. | Surv. (%) |
| 0.10 | 40 | 11 | 27.5 | 40 | 15 | 37.5 | | | |
| 0.25 | 104 | 30 | 28.8 | 84 | 50 | 59.5 | 20 | 13 | 65.0 |
| 0.50 | 124 | 34 | 27.4 | 84 | 48 | 57.1 | 40 | 25 | 62.5 |
| 1.00 | 104 | 32 | 30.8 | 60 | 36 | 60.0 | 44 | 27 | 61.4 |
| 2.00 | 20 | 5 | 25.0 | 20 | 7 | 35.0 | | | |

The "chemical" Nature of Lipid Protection

Postirradiation protection with olive oil could have been due to physical factors alone, e.g., (a) inflammatory reaction stimulating the reticulo-endothelial system (RES) in defense against infection, and (b) emollient action of the oil on the intestines to aid peristalsis. Therefore, experiments designed to clarify the nature of this protective mechanism were conducted.

Relatively nontoxic and nonutilizable oils may have a similar physical effect on animals as olive oil. The effectiveness of mineral oil in mitigating the lethal effects of WBR was therefore investigated. Figure 19 shows that mineral oil is only one-third as effective as olive oil ($P < 0.001$). That mineral oil was not completely ineffective appears to lend some credence to the physical nature of lipid protection. However, prolonged use of mineral oil is reported to elicit a foreign-body reaction characterized by the appearance of cells of chronic inflammation (14, 180, 408). Stryker has demonstrated the presence of mineral oil in mesenteric lymph-nodes, liver and spleen of their treated animals. Our histological studies on mice 30, 60, and 90 days after treatment with mineral oil substantiate these findings(290). Unlike mineral oil, olive oil did not elicit any inflammatory reaction.

Firket and Lindhoff (159) have shown further that intraperitoneal injection of liquid paraffin (petrolatum) causes a typical caryoclastic reaction in the thymus, lymph-nodes, and spleen of mouse. Because this foreign-body reaction, although chronic, could account for the mildly beneficial action of mineral oil on our irradiated mice, another nontoxic and less irritating oil was tested for protective action.

Preliminary histopathological studies indicate that robane (perhydrosqualene) is less irritating than mineral oil (290). It is a saturated hydrocarbon of animal derivation prepared from squalene by hydrogenation (343). We found this oil to be completely ineffective against whole-body X-irradiation. On the other hand, the unsaturated, biogenic and digestible squalene was found to protect irradiated mice (Table III).

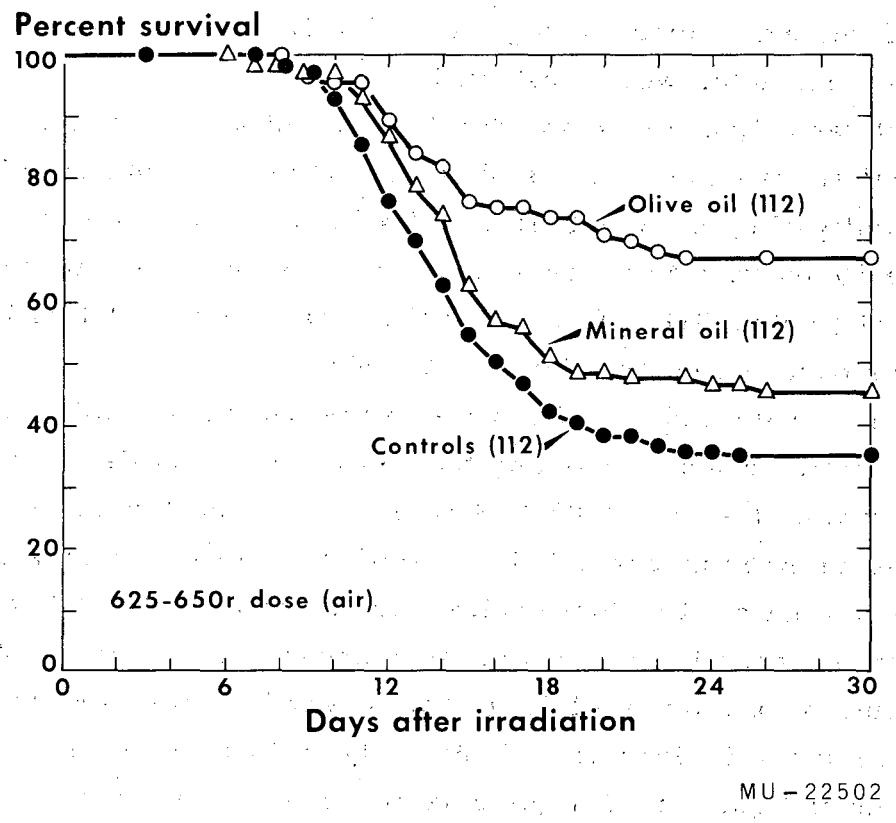


Fig. 19. Survival of X-irradiated mice following intraperitoneal injection of 1 ml olive or mineral oil (petrolatum) within 1 hr after whole-body irradiation. The number of animals is indicated in parentheses.

The thymus does not react to mineral oil and olive oil as it does to particulate substances like powdered glass and starch. In 3 days, the thymus weight of starch-and glass-injected animals decreased to almost one-third normal (Fig. 20), but its weight in saline-, mineral-oil-, and olive-oil-injected groups did not differ statistically from that of the controls.

As parenteral administration of powdered glass is reported to enhance survival of MLD irradiated animals by RES stimulation (373, 383), we repeated this experiment. Figure 21 confirms that powdered glass does help irradiated animals. We then suspended glass in olive oil and tested this mixture on our irradiated mice. Figure 22 shows a mildly additive effect of glass and oil on survival of irradiated animals. However, further experiments are necessary to verify this result.

Corn starch will also elicit a foreign-body reaction (Fig. 20). Its protective effect was therefore investigated. It appeared mildly beneficial on male mice exposed to 650-r WBR (Fig. 23), but these results are not statistically significant ($P \sim 0.3$). Females are much more resistant to WBR than males (2, 194, and Fig. 23). In females, intraperitoneal injection of starch following irradiation was significantly helpful ($P < 0.05$), (Fig. 23).

These results support our view that oil and particulate substances have different protective actions on irradiated animals.

If the beneficial effect of oils on lethally irradiated mice was due to their emollient actions (lubricating the intestine to facilitate peristaltic actions), oral or subcutaneous administration of the oil should have been ineffective. But the percent survival was approximately three times greater in orally ($P < 0.025$) and subcutaneously ($P < 0.001$) treated animals than in the irradiated controls (Fig. 24).

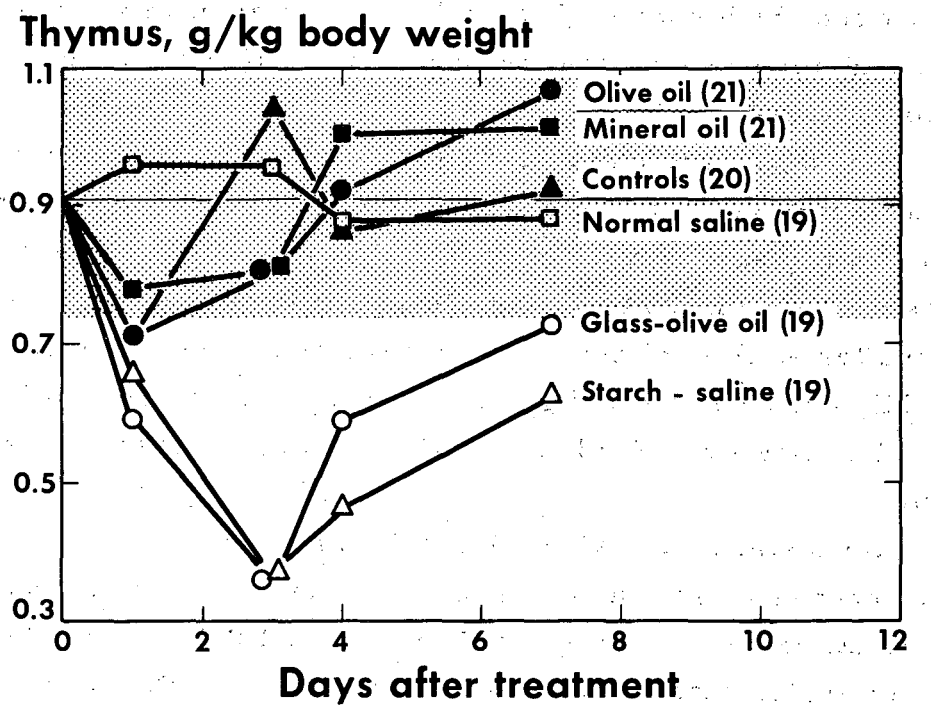


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Fig. 20. Effect of intraperitoneal injection of foreign substances on thymus weight of unirradiated male mice 8 to 10 weeks old. One ml of olive oil, saline, mineral oil, 0.2 gm starch per ml saline or 40 mg ground glass (< 40 μ ) per ml olive oil was injected into the animals. One standard deviation in thymus weight of the control animals is indicated by the shading. The number of animals is indicated in parentheses.

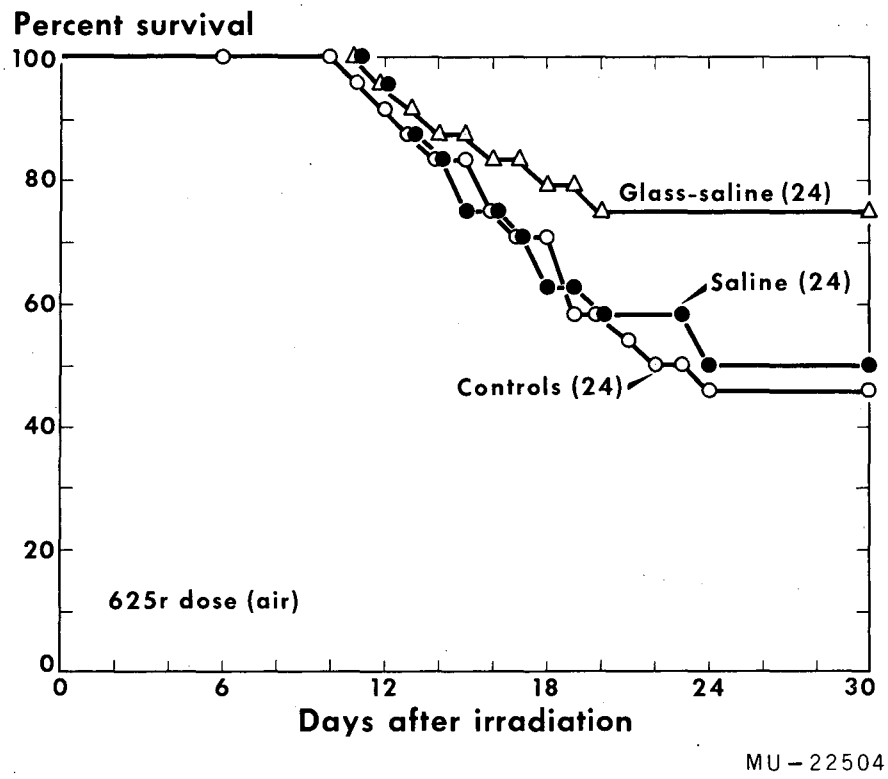


Fig. 21. Effect of glass administered intraperitoneally within an hour after whole-body irradiation on survival of mice. One group of animals received 20 mg sterile glass (~40 μ) in 1 ml of normal saline. The saline group received one ml of normal saline. The number of animals is indicated in parentheses.

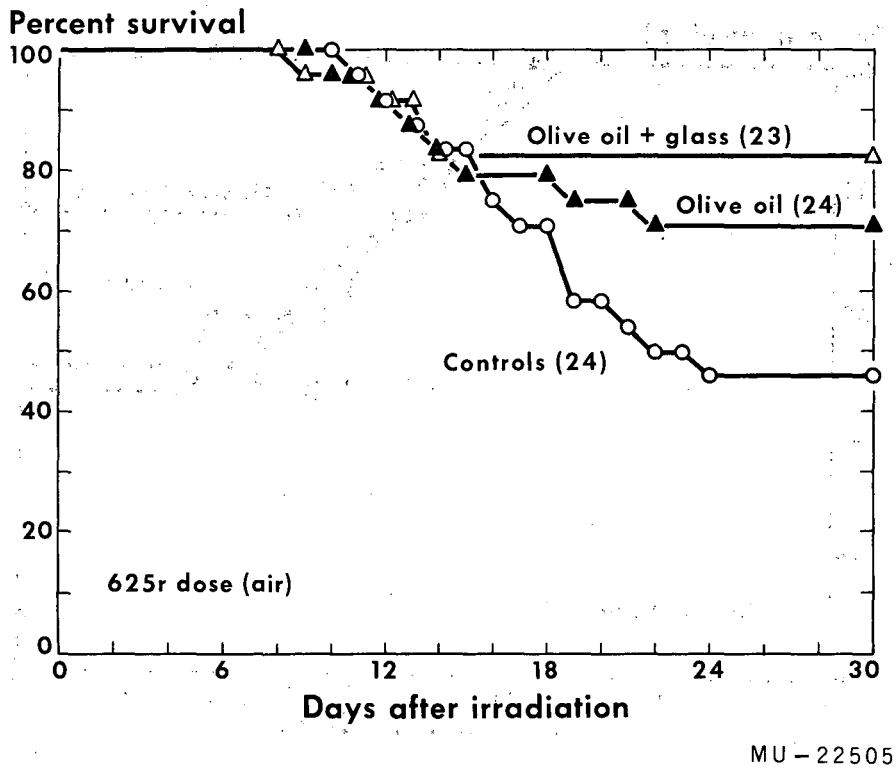


Fig. 22. Synergistic effect of glass and oil on survival of lethally irradiated mice. Experimental animals received intraperitoneally within an hour after whole-body irradiation 1 ml of olive oil containing 20 mg of sterile powdered glass (~40 μ). The number of animals is indicated in parentheses.

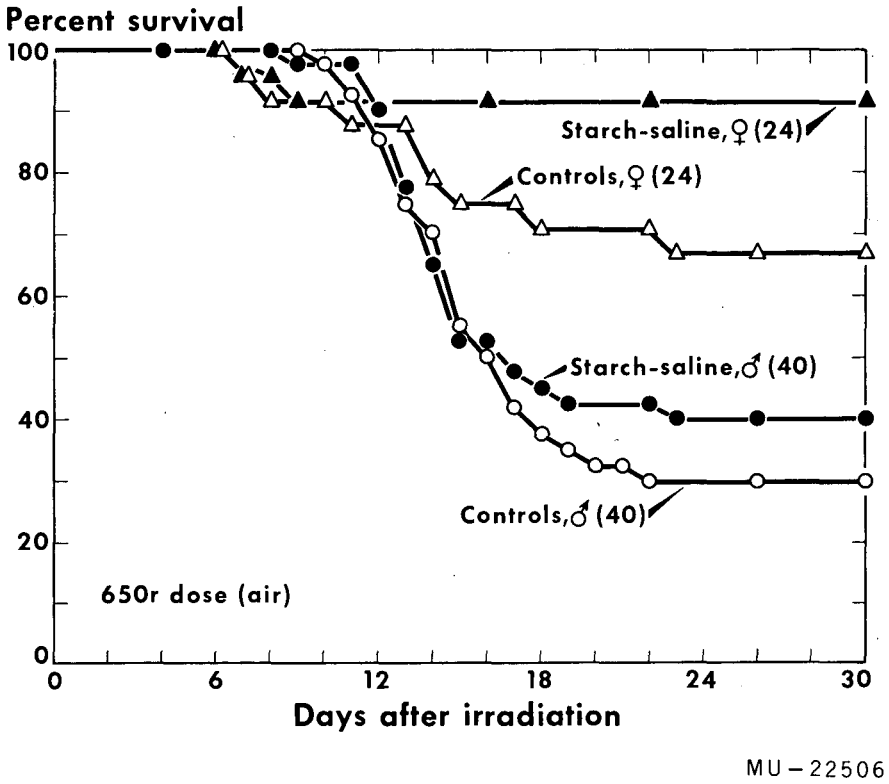


Fig. 23. Effect of starch administered intraperitoneally within 1 hr after whole-body X-irradiation on survival of 7-weeks-old male and female Swiss mice. Experimental animals received 0.1 gm of corn starch suspended in 1 ml of normal saline. The controls received 1 ml of saline after irradiation. The number of animals is given in parentheses.

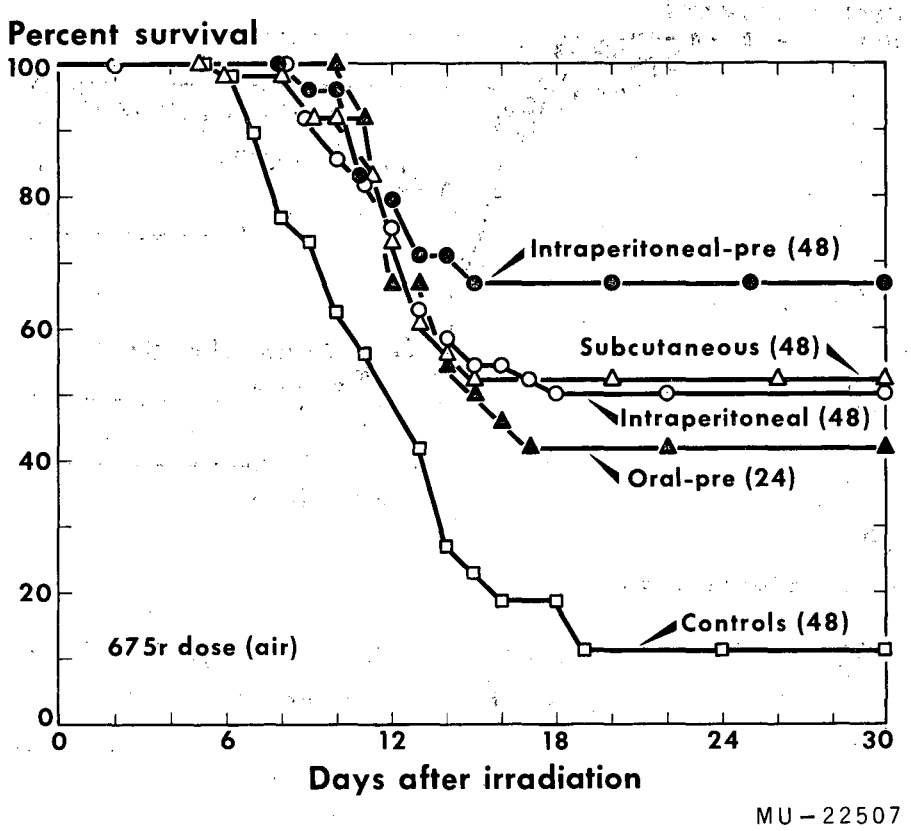


Fig. 24. Mode of olive oil administration on survival of lethally irradiated mice. The oral group given oil-concentrated pellets 24 hr before irradiation consumed 0.6 ± 0.3 gm of olive oil. The injected animals received 1 ml of oil an hour before or after irradiation. The number of animals is given in parentheses.

## C. Physiological Response to Lipid Treatment

In view of the apparent chemical nature of postirradiation protection of animals with certain oils, fertility, hematologic, and other studies were initiated to ascertain the effect of these oils on recovery of damaged tissues.

### 1. Olive Oil in Radiation-Induced Sterility.

It is well established that mice and other mammals exposed to a single high dose of X-radiation becomes sterile after a period of fertility which immediately follows irradiation. Furthermore, unless permanent sterility had been induced (at extremely high doses), in time these animals regain their fertility (59, 210, 220). With this in mind, a series of breeding experiments were conducted.

Table VIII shows olive oil-treated and untreated male animals in the 1-to 15-day postirradiation period to be equal but somewhat less fertile than the unirradiated controls. The olive oil-treated

Table VIII. Effect of olive-oil treatment on fertility[a] of male mice following exposure to 650-r whole-body X-radiation

| Experimental Groups | Time of mating after irradiation | | | | | |
|---|---|---|---|---|---|---|
| | 1 to 15 day | | 30 to 45 day | | 60 to 75 day | |
| | No. male | % fertile | No. male | % fertile | No. male | % fertile |
| Control | 20 | 85 | - | - | 100 | 98 |
| Untreated | 20 | 65 | 18 | 33 | 18 | 94 |
| Treated | 20 | 65 | 20 | 60 | 20 | 100 |

[a]Fertility is based on successful mating of irradiated males with mature unirradiated females.

animals in the 30-to 45-day postirradiation group were twice as fertile as the corresponding irradiated-untreated animals. Nevertheless, they were only 60% as fertile as the unirradiated controls. By 60 to 75 days postirradiation, both groups appeared completely recovered. The sizes of the litters from mating these irradiated males with sexually mature unirradiated females are shown in Table IX. The irradiated-oil-treated animals were much more successful than the unirradiated-untreated in the early matings (1 to 3 days). The treated animals in the 15-to 17-day group were less able to mate than the untreated animals. This probably is because animals which were predestined to die without treatment were protected by oil treatment. It is not unreasonable to assume that these animals were inherently weaker (more sensitive to radiation), hence, less able to mate than those that would have survived without treatment. But the average size of the litters in these two groups was the same.

The oil-treated animals were much more successful in late matings (30 to 45 days) than the untreated group. Even in the 60-to 75-day groups, mating was higher in treated animals.

The 15-to 17-day mating (Table IX) has shown further that oil treatment does not influence foetal viability.

Chi-square tests (Table X) show that olive oil treatment has helped irradiated males significantly to recover sooner from sterility caused by whole-body radiation.

These results tend to support the hypothesis that postirradiation oil treatment does not reverse radiation damage but facilitates recovery by stimulating the regenerative processes.

2. Hematologic Recovery Following Lipid Therapy

Spleen-and marrow-transplant studies have shown that functional blood-forming tissues are necessary for recovery from lethal irradiation (38). Studies have also shown that hematopoietic tissues are extremely sensitive to ionizing radiations (237). In view of these observations, it appeared logical to analyze hematologic recovery in our postirradiation olive-oil-treated mice.

Table IX. Litter sizes from mating of postirradiation olive-oil-treated males with unirradiated sexually mature female mice. Animals were exposed to 650-r whole body X-radiation. The number of females is given in parentheses.

| Experimental Group | Early postirradiation mating | | | | Late postirradiation mating | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 to 3 day | | 15 to 17 day[a] | | 30 to 45 day | | 60 to 75 day | |
| | Percent with litter | Average litter size | Percent with litter | Average litter size | Percent with litter | Average litter size | Percent with litter | Average litter size |
| Control | - | - | 47.5 (40) | 8.3 | 98.0 (100) | 9.8 | - | - |
| Untreated | 15.0 (40) | 5.7 | 37.5 (40) | 4.0 | 11.1 (90) | 3.1 | 73.0 (89) | 9.2 |
| Treated | 25.0 (40) | 5.4 | 17.5 (40) | 5.6 | 21.0 (100) | 2.7 | 88.7 (97) | 10.5 |

[a]Viable foetuses from the 15-to 17-day mating:

1. Control - - - 98.4%
2. Untreated - - 37%
3. Treated - - - 36%.

Table X. Chi-squared test on the significance of postirradiation olive-oil treatment in accelerating recovery from radiation-induced sterility in male mice.

| Experimental Group | Postirradiation test period (30 to 45 day) | $\chi^2$ | P |
|---|---|---|---|
| See Table IX | Treated vs control | 3.13 | < 0.10 |
| See Table IX | Untreated vs control | 10.59 | 0.001 |
| See Table IX | Treated vs untreated | 2.70 | ~ 0.10 |
| See Table X | Treated vs untreated | 3.39 | ~ 0.05 |

The change in the number of circulating leukocytes in peripheral blood of postirradiation oil-treated and untreated animals is shown in Fig. 25. Consistent with the findings of other investigators (237), our irradiated-untreated controls showed mild leukocytosis following exposure to radiation. This increase in the number of circulating white cells in peripheral blood was not apparent in our oil-treated group. Owing to this leukocytosis effect on the second postirradiation day, there was almost a three-fold difference (1500 WBC/$mm^3$ to 4000 WBC/$mm^3$) in the number of circulating WBC between the experimental groups. On the other hand, leukopenia was essentially the same in both groups during the first 2 weeks following irradiation. The time required for recovery of leukocyte value to the normal unirradiated level was, however, significantly shorter in the oil-treated group.

Heart blood was used to determine hematocrit values of experimental animals. But for a single point (Fig. 26), hematocrit was slightly higher in the oil-treated group. Nevertheless, as the result was not statistically significant, it is impossible to evaluate the effect of oil treatment on erythropoiesis without further experiments.

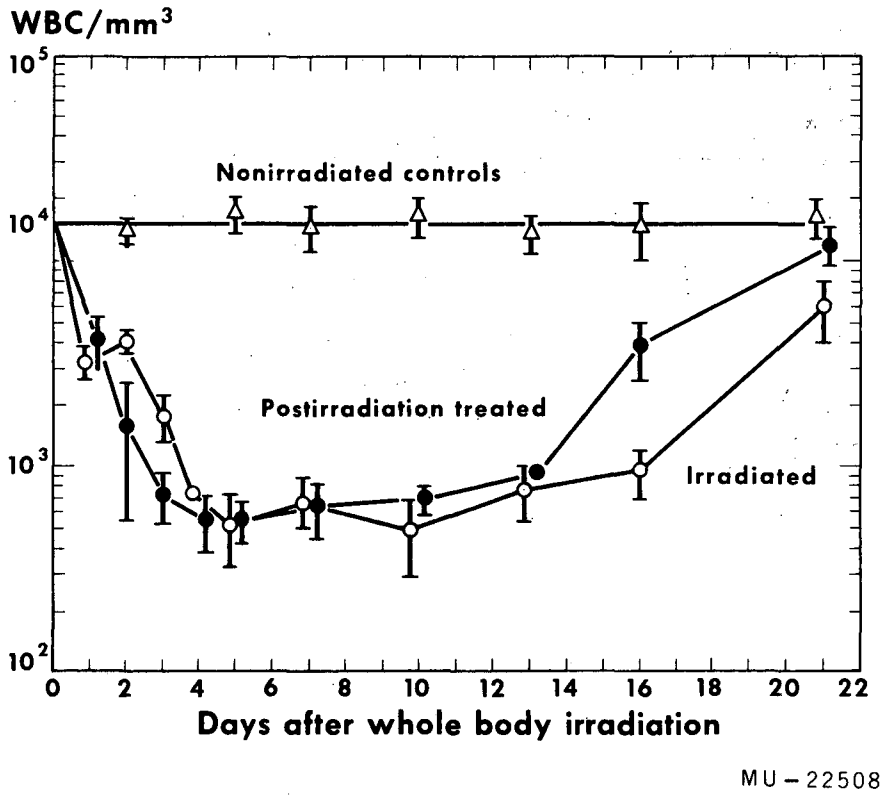


Fig. 25. Effect of intraperitoneal injection of 1 ml of olive oil an hour after whole-body irradiation on circulating leukocyte values of 6- to 7-weeks-old male mice. Eight to 10 animals were pooled for each point. The controls were uninjected. The standard deviations are indicated.

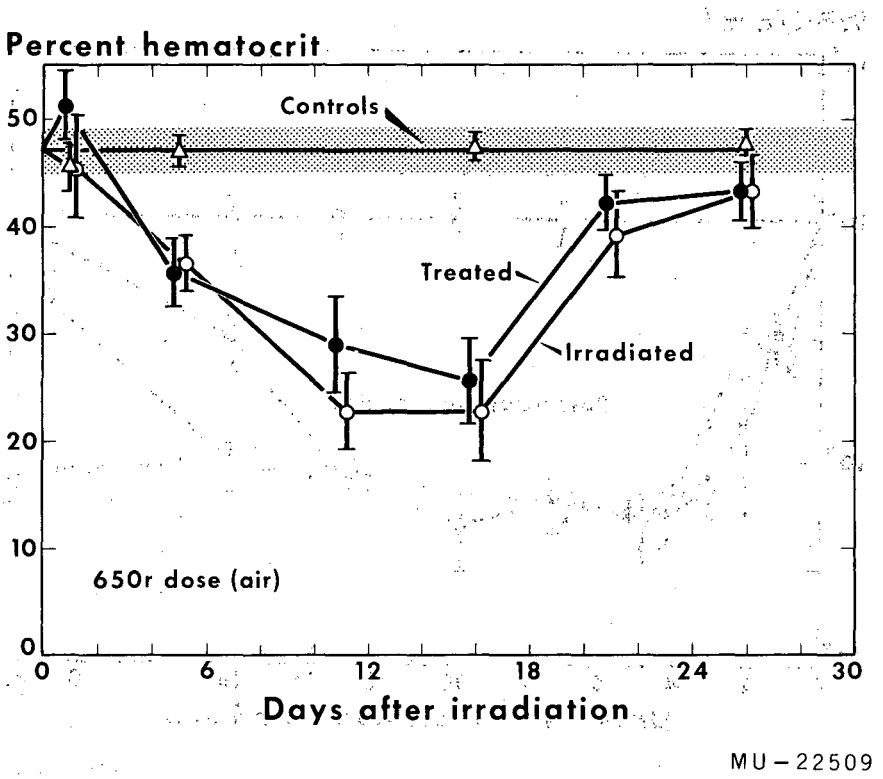


Fig. 26 Effect of olive-oil treatment on hematocrit of whole-body X-irradiated animals. Heart-blood from five to six mice was pooled to determine the hematocrit value of each point. One standard deviation is indicated. The standard deviation of the unirradiated controls is shown by shading.

3. Effect of Olive-Oil Treatment on Body Weight.

In common with any severely debilitating illness, animals invariably lose weight after lethal exposure to ionizing radiations. As postirradiation olive-oil treatment mitigates lethality, the weights of treated and untreated animals were examined following WBR. Both weight curves $LD_{60}$ (Fig. 27) and $LD_{93}$ (Fig. 28) indicate that post-irradiation oil-treated survivors fare better than the corresponding irradiated controls. In the $LD_{93}$ group, the greatest protection against weight-loss occurred on the twelfth postirradiation day. The maximum weight lost by oil-treated animals was 7% as compared to 16% in the controls (Fig. 28). The weights of treated and untreated survivors in the $LD_{60}$ group were similar up to the twelfth post-irradiation day. In the succeeding days the treated animals gained more weight than the untreated group.

D. Lipid Treatment on Effects of Fractionated Dose

Life span of animals exposed to a single or multiple doses of radiations are shortened (63, 80, 243). Even mildly irradiated animals cannot escape this aging effect of radiation. Hence, "Can medication given after an animal had been exposed to ionizing radiation reverse or at least attenuate this aging process?"

Postirradiation olive-oil treatment helps animals to recover from a single lethal irradiation. An experiment was conducted, therefore, to see what effect this oil treatment has on survival of an animal exposed to a second mildly lethal dose of X-radiation. The result of the experiment is shown in Fig. 29. After a total whole-body dose of 1130 r given in two separate doses within an interval of 30 days, 65% of the treated animals were alive at the end of 60 days as compared to 26% in the untreated group.

Unfortunately, this experiment was not extended beyond 60 days. Nevertheless, the trend of survival following oil therapy is encouraging and warrants further studies along this line.

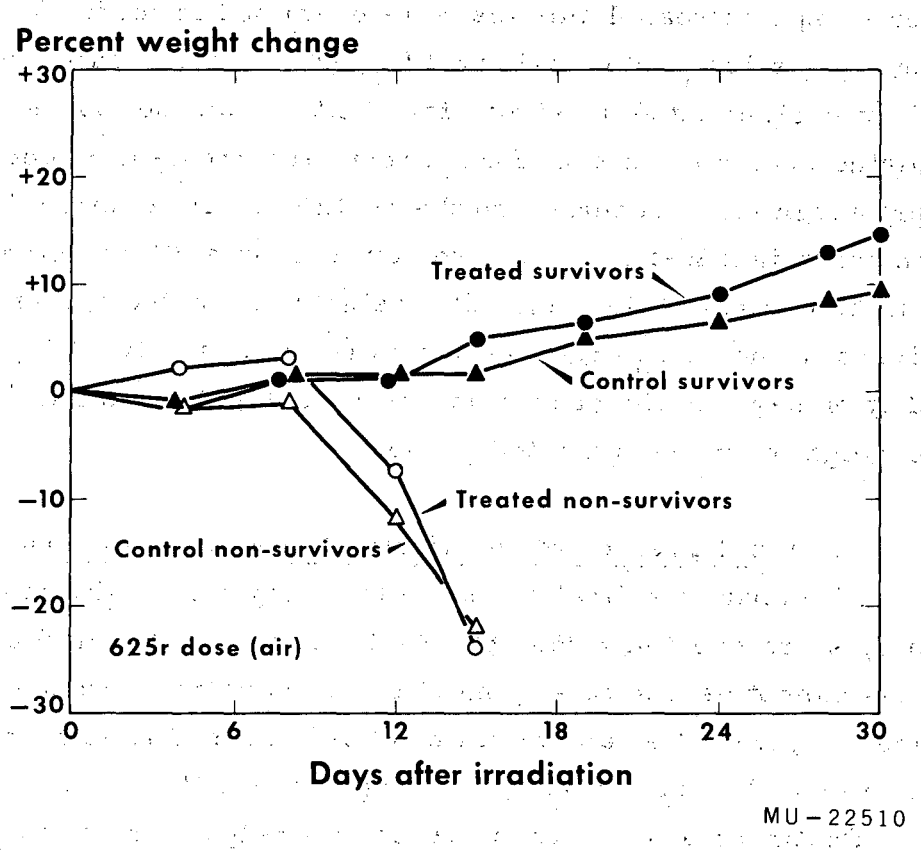


Fig. 27. Weight curve of $LD_{60(30)}$ whole-body X-irradiated male Swiss white mice. The treated animals received 1 ml olive oil intraperitoneally within an hour after exposure.

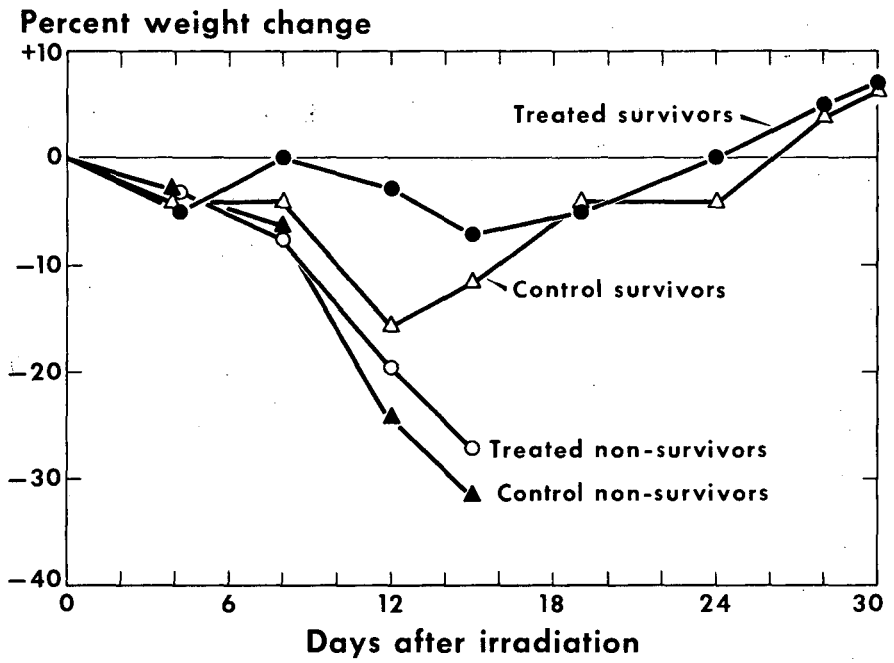


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Fig. 28. Weight curve of $LD_{93(30)}$ whole-body X-irradiated male Swiss Webster white mice. The treated animals received 1 ml olive oil within an hour after exposure.

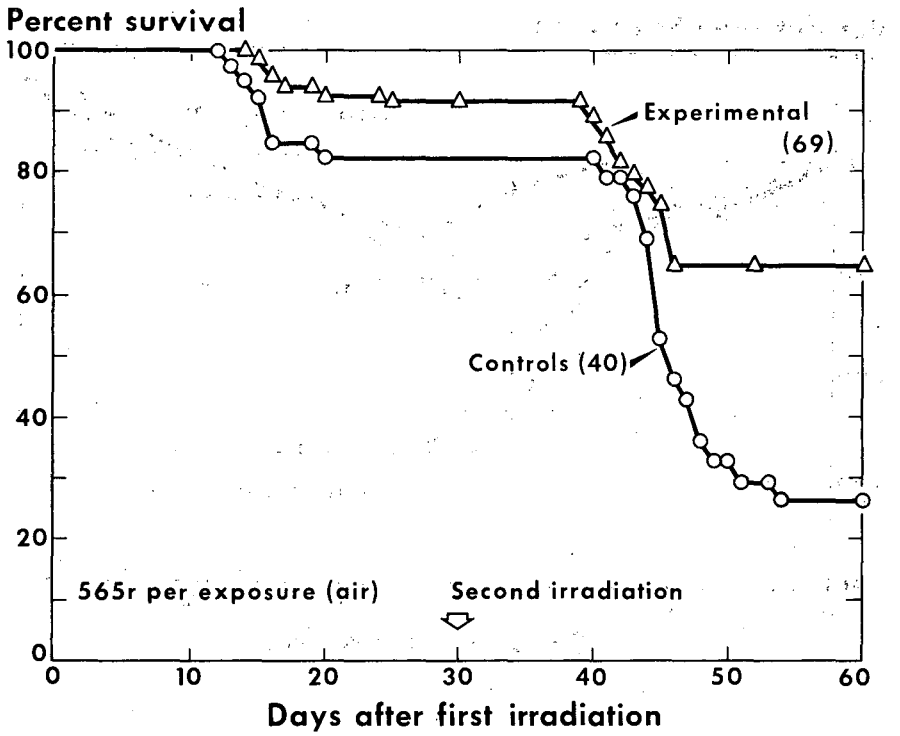


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Fig. 29. Effect of olive oil on survival of mice exposed to 1130-r whole-body X-irradiation delivered in 2 doses of 565 r each at 30-day interval. The experimental animals received 0.5 ml oil within an hour after the first and 1.0 ml oil following the second exposure. The number of animals is given in parentheses.

The ratios of percentage kill between the oil-treated and untreated animals from the two irradiations were similar, e.g., first kill, 85%: 17.5% = 0.49; second kill, 27.0% : 56.5% = 0.48. Hence, oil treatment appears to have helped those animals that would have succumbed to radiation otherwise to recover sufficiently and be physically similar (against lethal effects of radiation) to the animals that survived naturally the first exposure.

An interesting experiment would be to see how animals protected from the first irradiation with oil will be affected by a second exposure without oil therapy. An increase in survival over the irradiated-untreated controls will definitely indicate that treated animals remember less of the previous insult.

## E. Plasma Fatty-Acid Changes Following Whole-Body Irradiation

Hayes and Hewitt have noted that an extremely large increase of lipoproteins in the serum of lethally irradiated rabbits enhanced their chances for survival (204). A similar effect was observed earlier by Steadman (395). Their observations and our findings that postirradiation oil treatment helps animals survive lethal exposures to X-radiations led us to analyze lipids in our irradiated-treated and untreated mice.

### 1. Acute Lipid Response

In our preliminary studies, male mice were exposed to 1000- and 2000-r whole-body total-lethal doses of X-radiation. These high doses were selected because lipid response to radiation is likely to occur sooner at higher doses. Gas-liquid chromatographic analysis of plasma lipids showed a significant increase in stearic acid with concomitant decrease in the oleic acid fraction as early as 6 hr after irradiation (Fig. 30). A marked increase in arachidonic acid within 48 hr following exposure (Table XI)was also noted.

Of further interest was the general decrease in concentration after irradiation of other unsaturated fatty-acid components with concomitant increase in the saturated acids (Table XII). Chevallier and

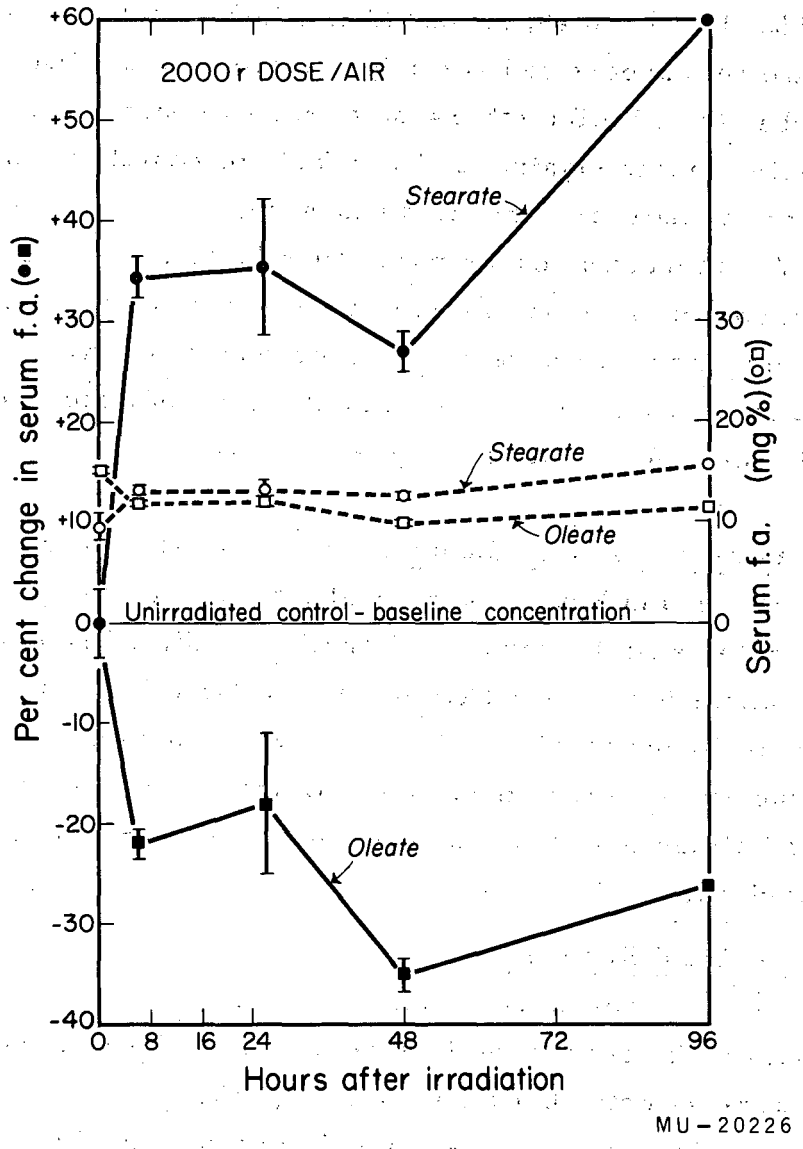


Fig. 30. Effect of whole-body X-irradiation on oleate and stearate concentrations in serum of 8- to 10-weeks-old male Swiss Webster white mice. Each point represents the fatty acid (f.a.) in serum pooled from seven to ten animals. One standard deviation is indicated.

Table XI. Percent weight changes in the serum fatty-acid fractions of 7-weeks-old male Swiss mice following exposure to 2000-r whole-body X-radiation

| Treatment | 0 r[a] Time sampled after irrad. (hr) | | Av. | 2000 r[b] Time sampled after irrad. (hr) | | | | Av. | Av. wt.% change between | Av. change after irrad. |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 24 | wt.%[c] | 6 | 24 | 48 | 96 | wt.%[c] | 0 & 2000 r[d] | (%) |
| No. animals | 12 | 10 | 22 | 11 | 8 | 9 | 9 | 37 | | |
| Fatty acid components: | | | | | | | | | | |
| Pre 16:0 | 1.76 | 1.49 | 1.64 | 2.53 | 1.94 | 1.09 | 2.38 | 2.02 | +0.38 | +23.2 |
| 16:0 | 23.55 | 21.78 | 22.75 | 25.67 | 22.73 | 20.31 | 28.01 | 24.30 | +1.55 | + 6.8 |
| 16:1 | 2.55 | 1.77 | 2.20 | 2.03 | 1.69 | 1.54 | 1.55 | 1.72 | -0.48 | -21.8 |
| 16:1-18:0 | 0.83 | 0.86 | 0.84 | 1.04 | 0.94 | 0.54 | 0.58 | 0.78 | -0.06 | - 7.1 |
| 18:0 | 11.04 | 8.75 | 10.00 | 13.24 | 13.38 | 12.50 | 15.76 | 13.70 | +3.70 | +37.0 |
| 18:1 | 14.97 | 15.28 | 15.11 | 11.82 | 12.34 | 9.76 | 11.25 | 11.29 | -3.82 | -25.3 |
| 18:2 | 33.04 | 37.98 | 35.29 | 31.70 | 34.00 | 33.63 | 28.12 | 31.79 | -3.50 | - 9.9 |
| 18:2-20:4 | 3.26 | 3.22 | 3.24 | 2.67 | 3.05 | 2.38 | 1.94 | 2.50 | -0.74 | -22.8 |
| 20:4 | 7.20 | 7.16 | 7.18 | 6.70 | 7.72 | 15.80 | 8.88 | 9.66 | +2.48 | +34.5 |
| Post 20:4 | 1.83 | 1.74 | 1.79 | 2.68 | 2.23 | 2.48 | 1.54 | 2.26 | +0.47 | +26.3 |

[a]Average volume of blood drawn from 0-r animals is 0.52 ml; average weight of 0-r animals is 27.6 gm.

[b]Average volume of blood drawn from 2000-r animals is 0.53 ml; average weight of 2000-r animals is 28.6 gm.

[c]Av. wt. % indicates the weight per 100.

[d](+) indicates an increase; (-), a decrease.

Table XII. Quantitative changes observed in the serum fatty acids of 7-to8-weeks-old male Swiss mice following 1000-and 2000-r whole-body X-irradiation.

| Treatment | A. Unirradiated | | | B. Irradiated | | | | |
|---|---|---|---|---|---|---|---|---|
| | Exp. 1 | Exp. 2 | Av. wt. % | 1000 r Exp. 1 | 2000 r Exp. 2 | Av. wt. % | Av. wt. % change between A and B | Av. change after exposure (%) |
| No. animals | 14 | 22 | 36 | 33 | 37 | 70 | | |
| Fatty-acid components | | | | | | | | |
| Pre 16:0 | 1.00 | 1.64 | 1.39 | 0.80 | 2.02 | 1.44 | +0.05 | + 3.6 |
| 16:0 | 21.92 | 22.75 | 22.43 | 22.53 | 24.30 | 23.47 | +1.04 | + 4.6 |
| 16:1 | 2.70 | 2.20 | 2.39 | 2.36 | 1.72 | 2.02 | -0.37 | -15.5 |
| 16:1-18:0 | 1.07 | 0.84 | 0.93 | 1.05 | 0.78 | 0.91 | -0.02 | - 2.2 |
| 18:0 | 9.34 | 10.00 | 9.74 | 10.22 | 13.70 | 12.06 | +2.32 | +23.8 |
| 18:1 | 15.23 | 15.11 | 15.16 | 13.26 | 11.29 | 12.22 | -2.94 | -19.4 |
| 18:2 | 30.38 | 35.24 | 33.35 | 32.81 | 31.79 | 32.27 | -1.08 | - 3.2 |
| 18:2-20:4 | 5.38 | 3.24 | 4.07 | 3.55 | 2.50 | 3.00 | -1.07 | -26.3 |
| 20:4 | 10.96 | 7.18 | 8.65 | 11.83 | 9.66 | 10.68 | +2.03 | +23.5 |
| Post 20:4 | 2.00 | 1.79 | 1.87 | 1.25 | 2.26 | 1.78 | -0.09 | - 4.8 |

Burg have shown that radiation oxidizes fatty acids according to their degree of unsaturation (78). Briefly, the order of oxidation is: linoleic (18:2) > oleic (18:1) > stearic (18:0). But for arachidonic acid, this would explain the postirradiation increase in saturated fatty acid and decrease in unsaturated fatty acid (Table XI and XII). However, the concentration of the polyunsaturated arachidonic acid was consistently higher after irradiation.

Analysis of serum from our animals showed a total lipid drop of 18.2% after whole-body irradiation (Table XIII). Ultracentrifugal studies disclosed a decrease of 69.2% in LDL, 18.0% in HDL and 12.8% in the UFA (Table XIII).

Table XIII. Total lipids in whole-serum and ultracentrifugated-serum fractions of nonfasting irradiated and unirradiated mice.

| Factor | No. animals | Total serum (mg/cc) | Fractionated LDL (mg/cc) | HDL (mg/cc) | UFA (mg/cc) | Total (mg/cc) |
|---|---|---|---|---|---|---|
| 0 r | 35 | 5.60 | 1.80 | 1.79 | 0.57 | 4.16 |
| 2000-r 20 hr postirrad. | 33 | 4.58 | 1.15 | 1.62 | 0.45 | 3.22 |
| Change (0-2000) | - | 1.02 | 0.65 | 0.17 | 0.12 | 0.94 |
| Percent of total change | - | 18.1 | 69.2 | 18.0 | 12.8 | - |

Generally, triglycerides account for over half of the lipid in LDL fractions. Therefore, the fall in total serum lipid that we observed in our animals may be caused by a drop in serum triglycerides. Chemical analysis confirmed this view as our irradiated animals showed a 66.7% decrease in serum triglyceride (Table XIV). Could this marked triglyceride depression following irradiation account for the individual serum fatty-acid changes?

Further analysis showed that 87.2% of the total serum lipids were incorporated in the LD and HD fractions (Table XIII). Therefore, a marked drop in LDL should greatly affect the serum fatty acid spectrum. Let us consider the following five principal fatty acids in our LD fraction:

Table XIV. Chemical fractionation of serum obtained by heart puncture from irradiated and unirradiated male Swiss mice.

| Fractions | 0 r[a] (mg/cc) | 2000 r[b] 20-hr Post. (mg/cc) | Change[c] (mg/cc) | Percent of total change |
|---|---|---|---|---|
| Cholesteryl ester | 1.01 | 0.91 | -0.10 | - 7.6 |
| Triglyceride | 1.87 | 0.99 | -0.88 | -66.7 |
| UFA | 0.29 | 0.18 | -0.11 | - 8.3 |
| Cholesterol | 0.17 | 0.19 | +0.02 | + 1.5 |
| Phospholipid | 1.72 | 1.47 | -0.26 | -19.7 |
| Total | 5.06 | 3.74 | 1.32 | -- |

[a]Zero-r serum pooled from 33 animals.

[b]2000 r serum pooled from 35 animals.

[c](+) indicates an increase; (-), a decrease.

palmitic (16:0), stearic (18:0), oleic (18:1), linoleic (18:2), and arachidonic (20:4). On a weight % basis, a 50% drop in LDL will markedly increase the serum concentration of stearic and arachidonic acid, since their weights are low in LD fraction and high in HD fraction (Table XV). Conversely, a drop in LD fraction will have a depressing effect on serum oleic-acid concentration. Because the weight percent concentration of palmitic and linoleic acids are comparable in LDL and HDL fractions (Table XV), the same LDL change described above will not greatly influence the total concentration of these two acids.

2. Effect of Fasting on Blood Lipids

The three principal lipids in blood are triglycerides (neutral fat), phospholipids, and cholesteryl esters. These compounds are considerably influenced by diet, fasting, pathological conditions, such as diabetes, and numerous other physiological factors. When fats are ingested, there is a marked increase in blood triglycerides followed after a time by changes in concentration of phospholipids and cholesteryl esters. In prolonged fasting or starvation, depot fat is believed to be mobilized and transported by the blood to liver and to extrahepatic tissues for oxidation (108, 168).

Reports on the effect of fasting on blood lipids are rather variable. Nevertheless, because fasting alters the blood-lipid picture, we investigated this effect on our irradiated and unirradiated animals. A marked decrease in LDL with concomitant increase in HDL was noted in our unirradiated, 24-hr-fasted mice (313). Hence, a fasting effect resulting from exposure to 2000-r whole-body irradiation would explain the postirradiation drop in plasma LDL. Because our nonfasting animals showed a 6 to 7% weight loss 24 hr after irradiation (our unirradiated fasting animals lost 15% of their weight in 24 hr), it is plausible that they were virtually fasting, unless fat absorption was selectively impaired in these animals. However, this is unlikely, as Mead et al. have shown that there is little interference with fat absorption in irradiated mice (296). Nevertheless, Conard has intimated

Table XV. Analysis of the fatty acids in ultracentrifuged serum fractions from 7 weeks old male Swiss mice. Blood was obtained by heart puncture from 33 unirradiated and 35 irradiated mice (20 hr after 2000-r whole-body X-irradiation).

| Lipid fractions | LDL (wt %) | | HDL (wt %) | | UFA (wt %) | | Corrected av. (wt %) | |
|---|---|---|---|---|---|---|---|---|
| Fatty acids | 0 r[a] | 2000 r[b] | 0 r | 2000 r | 0 r | 2000 r | 0 r | 2000 r |
| Pre 16:0 | 0.77 | 0.66 | 0.42 | 0.41 | 1.21 | 0.78 | 0.78 | 0.59 |
| 16:0 | 25.01 | 21.74 | 18.05 | 16.25 | 27.95 | 29.37 | 23.04 | 20.19 |
| 16:1 | 2.34 | 1.94 | 0.98 | 0.83 | 2.85 | 2.00 | 1.98 | 1.46 |
| 16:1-18:0 | 0.90 | 0.83 | 0.91 | 0.85 | 1.28 | 1.05 | 0.97 | 0.84 |
| 18:0 | 4.97 | 5.82 | 10.70 | 11.16 | 5.87 | 7.95 | 7.21 | 8.72 |
| 18:1 | 24.07 | 22.16 | 8.91 | 7.35 | 19.84 | 16.88 | 17.81 | 14.98 |
| 18:2 | 33.77 | 37.43 | 39.33 | 37.94 | 32.51 | 32.85 | 35.27 | 36.95 |
| 18:2-20:4 | 3.86 | 3.53 | 3.38 | 3.72 | 3.98 | 3.58 | 3.82 | 3.35 |
| 20:4 | 3.60 | 4.61 | 16.35 | 20.31 | 3.35 | 4.45 | 8.18 | 11.62 |
| Post 20:4 | 0.76 | 1.32 | 0.99 | 1.21 | 1.20 | 1.15 | 0.95 | 1.30 |

[a]Average volume of blood drawn from 0-r animals is 0.64 ml; average weight of these animals is 31.1 gm.

[b]Average volume of blood drawn from 2000-r animals is 0.72 ml; average weight of these animals is 30.8 gm.

that normal absorption of small amounts of nutriment does not necessarily indicate normal absorption of large or normal amounts (88).

Published data on HDL (phospholipid is the major component in this fraction) or the phospholipid-phosporus (PLP) fraction in mouse plasma following irradiation are varied. Entenman et al. have shown an increase in PLP concentration in plasma of mice exposed to 2250-r whole-body X-irradiation and subjected to fasting (146). Hewitt and Hayes have shown increased HDL concentration in plasma of nonfasting mice 24-hr after 800-r irradiation (216). In this study, a decrease was noted in HDL concentration in the plasma of 2000-r X-irradiated non-fasting animals (Table XIII). In view of these diverse results and since fasting alone will markedly increase the plasma phopholipid concentration (146, 313), we are currently investigating further the effect of fasting on changes in plasma phospholipid in X-irradiated mice.

3. Nutritive Value of Triglycerides

The importance of neutral fat in the diet for optimal growth is unequivocal. Forbes et al. (161, 162, 163, 164, 170) and Deuel et al. (109, 111, 112, 356, 357, 358) have demonstrated that rats on an adequate fat diet show greater capacity for work, increased resistance to starvation, greater nitrogen retention, etc. than animals on a low-fat or fat-free diet. Deuel et al. (111) have further shown that this effect is not due entirely to essential fatty acids in fat. Additional evidence of the importance of triglycerides in the diet of rats, dogs, and humans comes from Meng, who further believes that fats facilitate the efficient utilization of calories, since rats on fat-free diet showed the poorest growth inspite of having the highest caloric uptake (299).

4. Effect of Fat in Radiation-Induced Metabolic Changes and Tissue Breakdown

A very consistent effect of lethal whole-body irradiation is the similarity in death due to acute starvation. Because gross depletion of tissue proteins occurs in these animals, studies on metabolic changes following exposure to whole-body X-radiation have received wide attention. As early as 1907, Edsall and Pemberton attributed radiation

sickness as a toxic reaction to tissue degradation (130). This hypothesis has been supported by a number of subsequent investigators (202, 309, 344). Additional evidence along this line has appeared in recent years. Altman and his associates have fed $C^{14}$-labeled glycine to animals prior to irradiation and have noted a ten-fold increase in protein breakdown following whole-body irradiation (13). Increased excretion of nitrogenous material and other catabolic products have also been observed (6, 71, 191, 193, 247, 255, 270, 329).

A high-fat diet facilitates the retention of nitrogen. Hence, if this postirradiation tissue breakdown is partly due to increased caloric demand, fat treatment should help irradiated animals by alleviating their transient energy need and mitigate catabolism. But results on alterations in basal metabolic rates in animals following X-irradiation are equivocal. Kirchner et al. have found a slight increase in oxygen consumption following mild exposure (251). In acutely irradiated rats (death at 3 to 5 days), an increase of 35% in $QO_2$ was noted 24 hr after irradiation. Smith et al. have observed an increase in the metabolism of fasted rats exposed to 800 r, but were unable to confirm this increase on fed animals (372). Mole also found no immediate change in basal metabolic rate of rats exposed to X-radiation (307).

Reports on uptake of iodine by the thyroid glands of whole-body-irradiated animals are also varied (153, 308). In view of these inconsistencies on postirradiation thyroid function and on basal metabolic changes, the general concensus today is that thyroid function is not significantly altered after whole-body irradiation. Nevertheless, Mateyko and Edelmann (294) have observed significant increase in thyroid-stimulating hormone in the pituitary of whole-body-and hypophyseal-irradiated rats 6 hr after irradiation (294). If, therefore, the thyroid does become hyperactive immediately following whole-body irradiation, and since the beneficial effect of fat in hyperthyroidism has been proven by Aberlin and others (1, 149, 189), injection of fat should help irradiated animals by reducing their basal metabolism or by supplying them with sufficient calories to meet their increased energy need. Furthermore there are indications that animals are

temporarily incapable of utilizing carbohydrates after they have been exposed to radiation (213, 362), if this is true, their caloric requirement should become even greater. Metabolic studies on X-irradiated oil-treated and untreated animals should therefore yield some very interesting information.

## F. The Lipid Syndrome

Much has been written about the relationship of various factors--intensity of dose, time after irradiation, animal species used, and type of radiation used--to modes of death following lethal irradiation. These modes of death or lethality peaks have been associated with a variety of syndromes (95, 96, 269, 335, 336).

An interesting approach to the study of death modes, based on selective modification of mortality peaks with protective agents, was proposed by Luchnik (284) and Quastler and Zucker (336). The latter investigators have suggested that irradiated animals treated with specific protectors may reveal heretofore-unknown syndromes and help us to better understand already-known radiation syndromes.

Death from exposure to ionizing radiation is believed due to a number of competing factors. Changing any of these modifying factors will alter the dominance of one mechanism over the other (335). Hence, animals protected from the 3-to 5-day intestinal death by intestine-shielding or by parenteral administration of fluids and electroytes (89) will die later of bone-marrow aplasia (marrow syndrome), unless they were also protected against this syndrome.

In view of the above proposal, we investigated the modes of death of our lethally irradiated oil-treated and untreated animals, hoping to better understand these syndromes. About 1700 animals were used for this study.

Mice irradiated with whole-body MLD to TLD invariably die of marrow death with a lethality peak at around day 11 or 12 (20, 96). The mortality distributions of our mice for the dose ranges $LD_{90-100}$ and $LD_{50-75}$ are shown in Fig. 31. Only the period from day 9 to day 17 inclusive will be considered here, because postirradiation oil

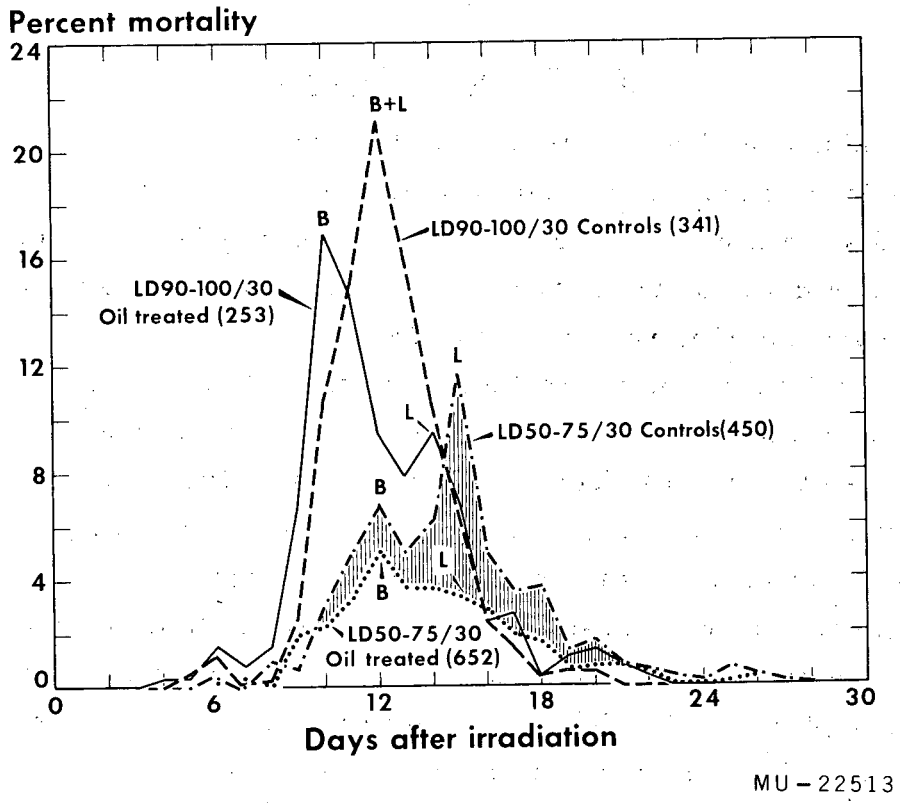


Fig. 31. X-ray mortality peaks of 6- to 7-weeks-old male Swiss Webster white mice for whole-body irradiation. Olive-oil treatment unmasked a second peak in the bone marrow (B) peak of the $LD_{90-100}$ group which corresponds to the 15-day lipid (L) peak of the $LD_{50-75}$ group. The 15-day peak was greatly suppressed by oil treatment.

treatment maximally affected survival during this period. Moreover, 75% of our MLD irradiated and 90% of our near-TLD irradiated mice died during this period. The $LD_{90-100}$ controls showed the typical single marrow peak at day 12. In the corresponding oil-treated group, the bone-marrow peak became bimodal as in the MLD control. Unmasking of the 14-day peak (corresponding to the 15-day peak in the MLD control) in the TLD oil-treated group indicates that at least two factors are responsible for marrow syndrome, one of which is highly lipid sensitive. Modal analysis of the MLD groups showed that oil treatment had markedly suppressed the 15-day peak. The 12-day (marrow) peak of the oil-treated group was also smaller than that of the control.

The statistical significance of the changes in the 12-day and 15-day peak heights were analyzed by comparing the number of animals dying between days 9 to 13 and days 13 to 17 in the oil-treated and untreated groups. In the 9-to 13-day group, 107 out of 652 treated animals died as compared to 95 dead out of 450 untreated. A chi-square test gave $\chi^2 = 3.93$, $P < 0.05$. In the 13-to 17-day group, 101 out of 652 treated animals died as compared to 143 dead out of 450 untreated. A chi-square test gave $\chi^2 = 40.97$, $P << 0.001$.

In view of these studies, there can be little doubt regarding the authenticity of the 15-day (lipid) peak. Nevertheless, it must be emphasized that we do not know the chemical mechanism(s) whereby fats help animals recover from this lipid syndrome.

## VI. SUMMARY

1. In radiation protection studies one must be able to consistently reproduce lethality. Because this is a difficult task, investigators have often used total-lethal or near total-lethal doses for such studies. This is not always wise, because chemicals that may be therapeutically ineffective at total-lethal doses, but very effective against mid-lethal doses can easily be overlooked.

Our first objective was, therefore, to achieve reproducibility by standardizing the physical and biological experimental conditions. By vigorous adherence to certain experimental practices, we were able to consistently maintain an average $LD_{50}$ mortality of 49.7 ± 7.7%. In contrast, the average $LD_{50}$ mortality of our routinely handled controls was 45.8 ± 37.2%.

2. Qualitative and quantitative changes in lipids following whole-body irradiation have been extensively investigated, but little is known of their effects on lethally irradiated animals. Nevertheless, much tangible evidence strongly suggests that fats may be actively involved in radiation syndromes. Studies on the effect of lipids on pre- and post-irradiated mice were, therefore, undertaken. Olive oil was fortuitously chosen for the preliminary studies. On the basis of total survival, the beneficial effect of olive oil was small in the near total-lethal dose irradiated animals. But there was a three-fold increase in survival of the treated (16.4% to 5.2% and 7.5% to 2.5%) over the dose controls. In the mid-lethal-dose irradiated groups, survival of the olive-oil-treated animals was approximately double the controls (75.4% to 43.2%).

3. To ascertain whether this postirradiation protective effect was peculiar to olive oil, the beneficial effect against X-radiation of nonsaponifiable fats in olive oil, safflower oil, robane, squalene, etc. was investigated. Some of these oils and esters were equally as effective as olive oil, other less effective, and some were even harmful. The linoleates <u>per se</u> were toxic. However, antioxidants were able to mitigate this toxic effect.

4. The effect on survival of time, mode, and quantity of oil injected was analyzed. Survival following intraperitoneal injection of 0.25 to 1.0 ml olive oil was essentially similar. Most effective time of injection was 24 hr before irradiation. Injecting oil immediately before or after exposure of the animals to mid-lethal dose was equally effective. Olive oil was beneficial even when given 24 hr after whole-body irradiation. Intraperitoneal injection was superior to oral or subcutaneous administration.

5. Experiments designed to clarify the nature of postirradiation protection by lipids are presented. Evidences from these experiments support a chemical mechanism.

6. In view of the apparent chemical nature of protection by oil, fertility, hematologic, and other studies were conducted to ascertain the effect of oil on recovery of damaged tissues. These studies indicate that postirradiation oil treatment does not reverse radiation damage but facilitates the recovery process. The 30- to 45-day postirradiation olive-oil-treated animals were twice as fertile as the corresponding untreated group, but by 60 to 75 days postirradiation, both groups appeared completely recovered. The 15-to 17-day postirradiation oil-treated animals were less able to mate than the untreated animals, but by 30 to 45 days after irradiation the oil-treated animals were better able to mate than the corresponding untreated group.

The number of circulating leukocytes in the peripheral blood of treated and untreated animals were similar during the first 2 weeks following whole-body irradiation, but the time required for recovery of the leukocyte value to the normal level was significantly shorter in the oil-treated animals.

7. Concomitantly, blood-lipid changes in our experimental animals were investigated on the gas-liquid chromatographic apparatus.

A significant stearic acid increase with corresponding decrease in oleic acid concentration was observed in the plasma of our mice as early as 6 hr after 2000-r whole-body X-irradiation. Marked increase in concentration of arachidonic acid was also noted 48 hr after

exposure. But in general, there was a decrease in concentration of unsaturated fatty acids with concomitant increase in saturated fatty acids in the plasma. The marked serum triglyceride depression following irradiation appeared to cause these plasma fatty-acid changes. A slight decrease in the concentration of high-density lipids in plasma was also noted after irradiation. Fasting can account for the low-density-lipid (triglyceride) and high-density-lipid (phospholipid) changes in plasma.

8. The possible effect of fats in mitigating radiation-induced metabolic changes and tissue breakdown are also discussed.

9. Mice irradiated with whole-body mid-lethal to total-lethal doses predominantly die of bone-marrow aplasia. Modal analysis shows a lethality peak at around day 11 or 12. Our total-lethal dose irradiated animals showed the characteristic bone-marrow peak on the twelfth postirradiation day, but our mid-lethally irradiated mice showed two distinct mortality peaks, one at day 12 and another at day 15.

Modal analysis of our oil-treated animals, furthermore, unmasked a 15-day peak in the total-lethal dose group. In the mid-lethal dose group, oil treatment markedly suppressed this 15-day peak.

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## APPENDIX. ABBREVIATIONS

The following abbreviations have been used in the text and are listed alphabetically.

ACTH - adrenocorticotropic hormone
AET - S, 2-aminoethylisothiuronium · Br · HBr
APT - S, 3-aminopropylisothiuronium · Br · HBr
BAL - 2, 3-dimercaptopropanol
f. a. - fatty acid
HDL - high-density lipid
kvp - kilovolt peak
$LD_{50}$ - 50% lethal dose at 30 days
LDL - low-density lipid
MLD - mid-lethal dose
NSF - nonsaponifiable fraction
PLP - phospholipid-phosphorus
RES - reticulo-endothelial system
RNA - ribonucleic acid
TLD - total-lethal dose
UFA - unesterified fatty acid
WB - whole-body
WBC - white blood cell
WBR - whole-body radiation

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