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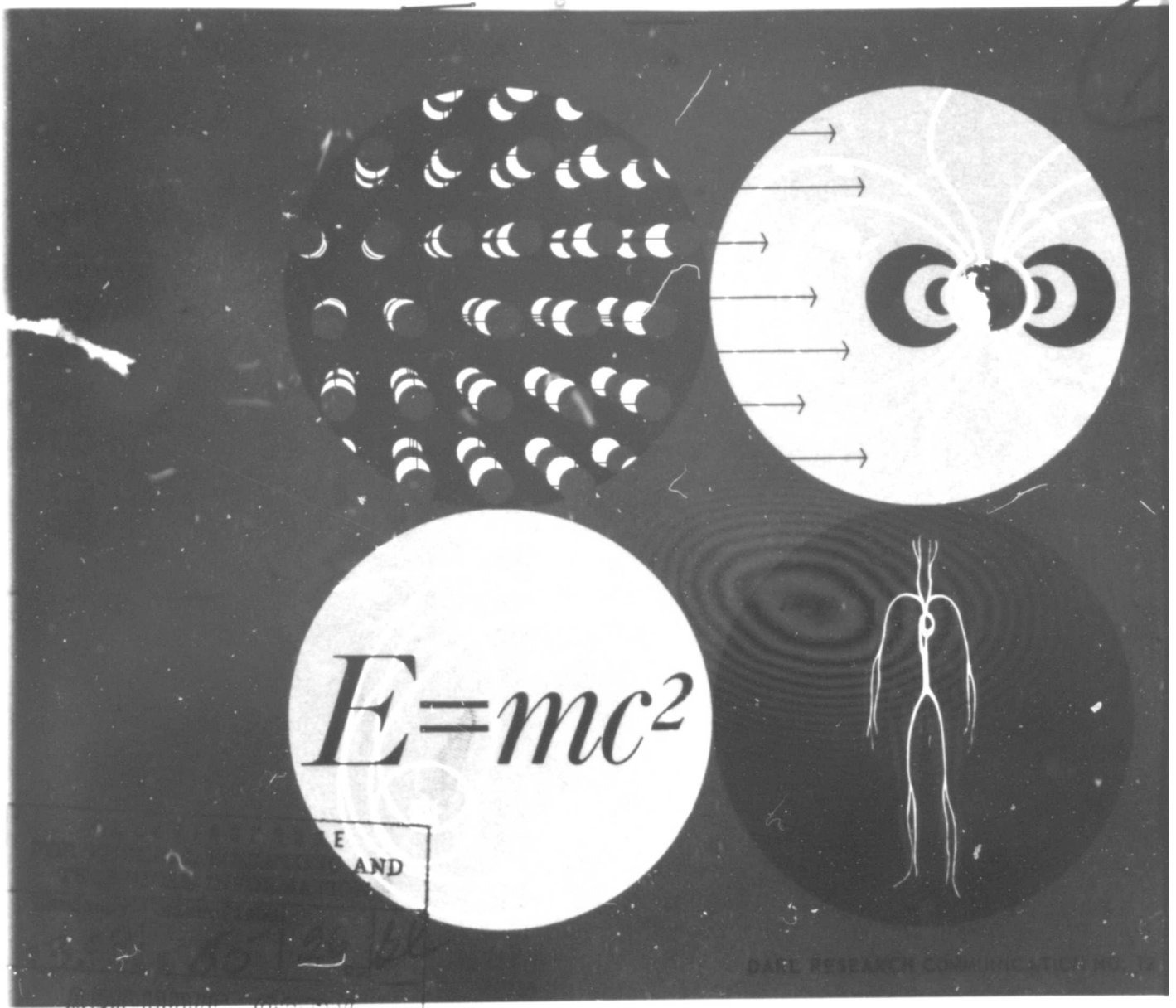




# RADIATION PROTECTION BY AUXIN ANALOGUES AND ANTIVIRAL AGENTS



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C. W. STEERS

JUNE 1966

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JUNE 1966

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## ABSTRACT

Although plant growth modifiers were found to be totally devoid of radiation-protective activity, their structural analogues were found to protect male Webster white Swiss mice against lethal doses of $^{60}Co$ $\gamma$-radiation. A broad-spectrum antiviral agent, statolon, which alone exhibited no activity, was found to synergize the protective action of certain growth modifying analogs. The possibility of latent virus involvement in radiation damage in a manner similar to bacterial lysogeny is also discussed.

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## Section 1

## BACKGROUND OF THE STUDY

This study, to determine whether auxin analogues of plant growth modifiers would influence the rate or magnitude of the response of mice to ionizing radiation, was suggested by earlier investigations by the authors which demonstrated the ability of the auxin analogue β-2,4,5-trichlorophenoxyethanol to protect mice against lethal doses of $^{60}$Co γ-radiation. Experiments were accordingly conducted to test the ability of auxin analogues and antiviral agents to delay or prevent the death of male Webster white mice subjected to normally lethal doses of $^{60}$Co γ-radiation. Certain auxin analogues were found to afford a significant degree of protection from radiation; others did not demonstrate this activity.

## Section 2

## DISCUSSION

Figure 1 shows the structures of some of these plant growth modifiers and their radiation-protective analogues. (Abbreviations are defined in the glossary at the end of this paper.) The first, 2,4,5-T -- 2,4,5-trichlorophenoxyacetic acid (Figure 1, line 1) -- is a well-known auxin-type selective herbicide (i.e., a weed killer). At low concentrations, 2,4,5-T stimulates plant cell elongation in the same manner as the natural plant growth hormone (auxin) IAA -- indolyl-3-acetic acid (line 2). Although neither of these compounds shows radiation-protective activity in mice (Table 1), their carbinol analogues, 2,4,5-TOH and IOH, protected 40 and 70 percent, respectively, of groups of mice against 1000 r $^{60}$Co $\gamma$-radiation, a dose that killed 97 percent of the untreated controls.[1] Ioxyl -- 4-hydroxy-3, 5-diiodobenzoic acid (line 3) -- is also a selective herbicide, possibly of the auxin type.[2] Ioxyl itself does not reduce radiation mortality in mice, but IoxBu(n), its n-butyl ester, does. IoxBu(n) has been reported to inhibit the growth of influenza virus in de-embryonated eggs and in tissue culture.[3] TIBA -- 2,3,5-triiodobenzoic acid (line 4) -- is a synthetic plant growth modifier, which shows auxin, auxin-synergist, or auxin-antagonist activity, depending upon concentration and type of plant tissue.[4] This plant growth modifier does not protect mice against radiation either, but its structural analogue, PIBA (p-iodobenzoic acid), does. Isatin (line 5), an indole oxidation product occurring naturally in plants and animals, has recently been shown by Galston and Chen[5] to

| | GROWTH MODIFIER | | STRUCTURAL ANALOGUE | |
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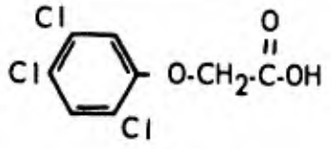
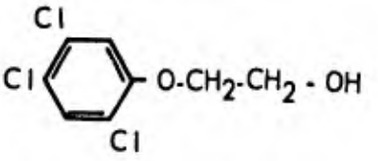
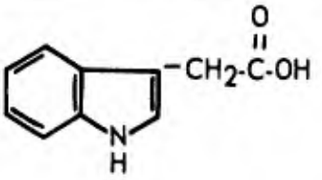
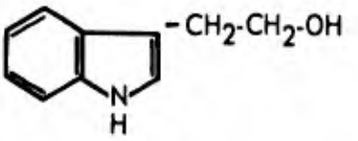
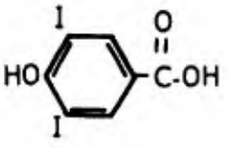
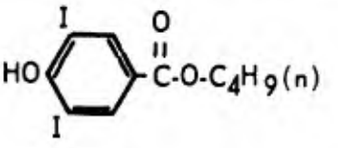
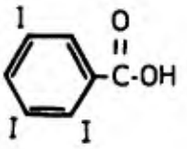
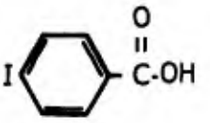
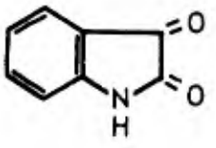
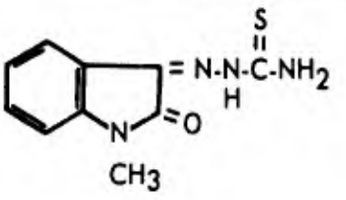
| 1 |  2, 4, 5-T | 0 |  2, 4, 5-TOH | + |
| 2 |  IAA | 0 |  IOH | + |
| 3 |  Ioxyl | 0 |  IoxBu(n) | + |
| 4 |  TIBA | 0 |  PIBA | + |
| 5 |  Isatin | 0 |  MIBT | + |
| 0 = INACTIVE | | + = ACTIVE | | |

Figure 1. Radiation-protective activity of some plant growth modifiers and structural analogues in mature male Webster white Swiss mice

Table 1

RADIATION MORTALITY OF MALE WEBSTER WHITE SWISS MICE TREATED WITH VARIOUS INACTIVE COMPOUNDS RELATED TO RADIATION-PROTECTIVE AUXIN ANALOGUES

| Compound | Concentration (mg/gm) | 1000 r Mortality | No. of Mice |
|---|---|---|---|
| 2,4,5-T | 0.2 | 100/14* | 20 |
| Ioxyl | 0.3 | 100/13 | 15 |
| | 0.4 | 100/13 | 15 |
| TIBA | 0.2 | 100/20 | 10 |
| | 0.3 | 80/29 | 10 |
| Isatin | 0.5 | 92/13 | 12 |
| IAA | 0.5 | 100/12 | 12 |
| Benzoic acid | 0.25 | 100/13 | 5 |
| | 1.0 | 100/13 | 16 |
| PABA | 0.25 | 100/27 | 20 |
| PCBA | 0.5 | 80/25 | 15 |
| 4-HBPr(n) | 0.25 | 100/12 | 20 |
| | 0.5 | 100/19 | 20 |
| IoxBu(sec) | 0.1 | 80/19 | 20 |
| Statolon | 0.2 | 100/12 | 5 |
| | 0.5 | 100/12 | 5 |

*The first number is the percentage of treated mice that died within 90 days post-irradiation; the second number is the day post-irradiation after which no deaths occurred within the 90 days.

stimulate plant growth in the same manner as IAA. In preliminary tests, isatin appears to have no radiation-protective activity in mice; however, one of its structural analogues, MIBT, N-methyl isatin-β-thiosemicarbazone, does. MIBT (also known as methisazone, Marboran, and Compound 33T55) has recently received much publicity as an antiviral agent whose activity in vitro and in vivo seems limited to the pox group of viruses.[6]

Each of our test compounds (except IOH, which was dissolved in dimethylsulfoxide) was suspended with an equal weight of gum arabic in physiological saline in a concentration that permitted the desired drug dose to be administered in a volume of 0.5 ml/20 gm of animal body weight. Mature male Webster white Swiss mice, weighing 25 to 30 grams, were injected intraperitoneally with the compounds five minutes before irradiation. Non-injected and vehicle-injected mice were irradiated as controls. A ventilated Lucite radiation chamber, one inch high and 8 inches in diameter, was used to restrain the mice within the geometrical limits of a homogeneous 9-inch field of γ-ray flux emanating from one hundred $^{60}Co$ point sources arrayed above and below the radiation cavity. Measurements of the integrated radiation dose were made in triplicate by Landsverk L-128 radiation chambers in conjunction with a Landsverk L-64 roentgen meter. Equal numbers of drug-treated and control mice were placed in the Lucite chamber and irradiated simultaneously, at 95 to 100 r/min, for 10 to 11 minutes.

The 2,4,5-TOH and IOH were obtained from Cyclo Chemical Corporation, Los Angeles; IoxBu(n) and PIBA from K and K Laboratories, New York; and MIBT from Nutritional Biochemicals Corporation, Cleveland, Ohio. The mice were obtained from Berkeley Pacific Laboratories.

Prior to these tests, all our mice were screened for Pseudomonas aeruginosa according to the methods of Flynn[7] and Wensinck, et al.,[8] in which glycerol broth is used as the bacterial growth medium. We eliminated all mice from cages in which an active P. aeruginosa infection was detected. In addition, we took heart blood samples from all animals that died after radiation and streaked them onto Pseudomonas agar P plates (Difco Laboratories). A 9-percent incidence of active P. aeruginosa was thus found post-irradiation in both drug-treated and control groups. Subcultures made from the growth on these plates showed the following incidence of gram-negative bacteria:

| | |
|---|---|
| Escherichia | 50% |
| Alcaligenes | 3% |
| Salmonella | 8% |
| Shigella | 10% |
| Proteus | 10% |

It is evident, therefore, that our radiation-protection experiments were carried out with mice that harboured a variety of potentially pathogenic bacteria. Despite this latent infection in our animal colony, 2,4,5-TOH, IoxBu(n), PIBA, MIBT, and IOH provided absolute protection for about 40 to 70 percent of the mice exposed to 1000 r $^{60}$Co $\gamma$-radiation. (In Figures 2 and 3, each curve represents at least two experiments and at least 30 mice.)

The radiation-protective effects of PIBA and of IoxBu(n) are synergized by the broad-spectrum antiviral agent statolon, an inducer of interferon.[9] The structure and properties of statolon, an anionic polysaccharide, are not well defined; one of our two lots of statolon did not synergize the auxin analogues. The synergistic lot, in powder form, consisted

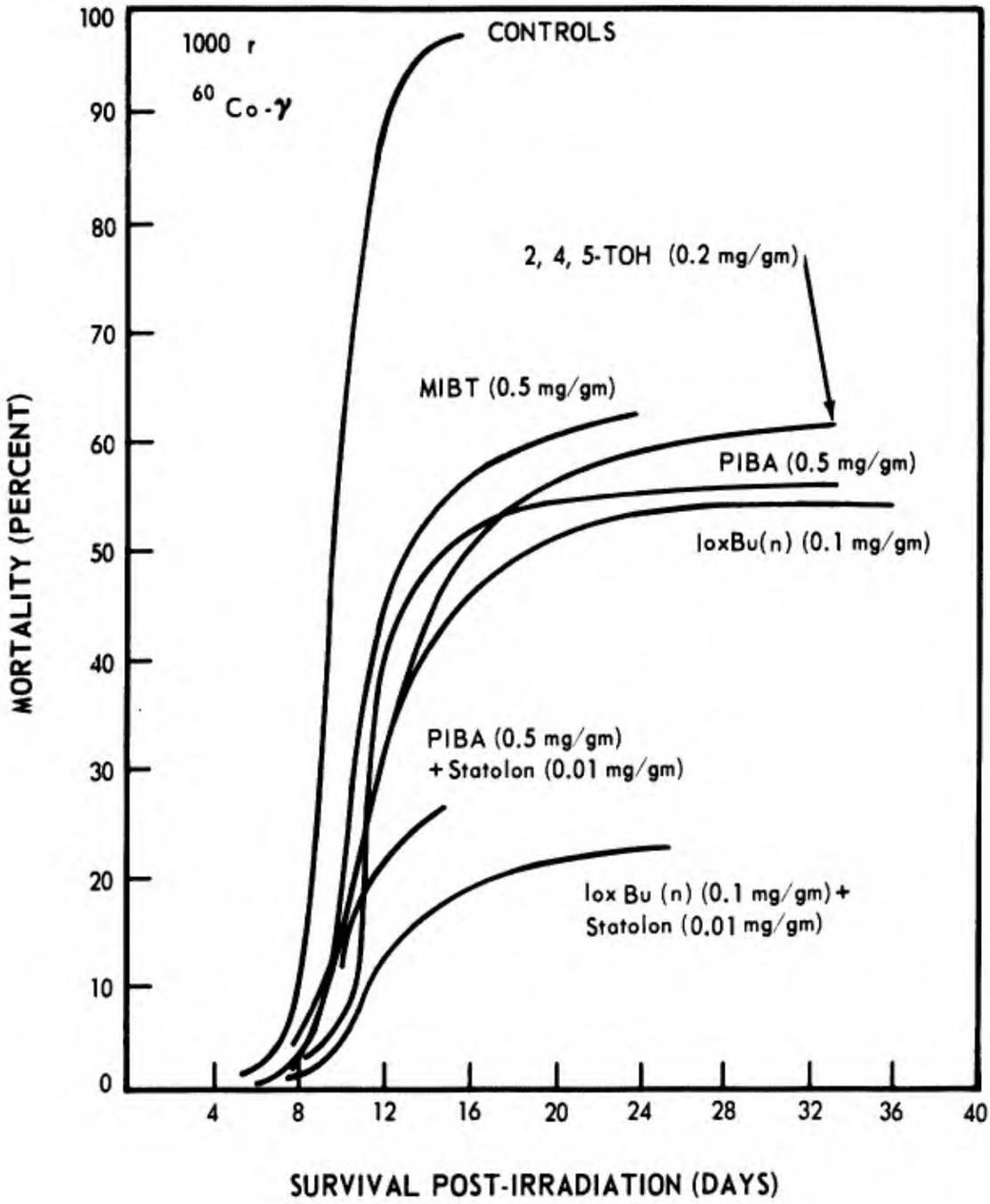



Figure 2. Effect of intraperitoneal injections of some auxin analogues and antiviral agents in reducing the mortality of mature male Webster white Swiss mice exposed to a 1000 r dose of $^{60}Co$ $\gamma$-radiation

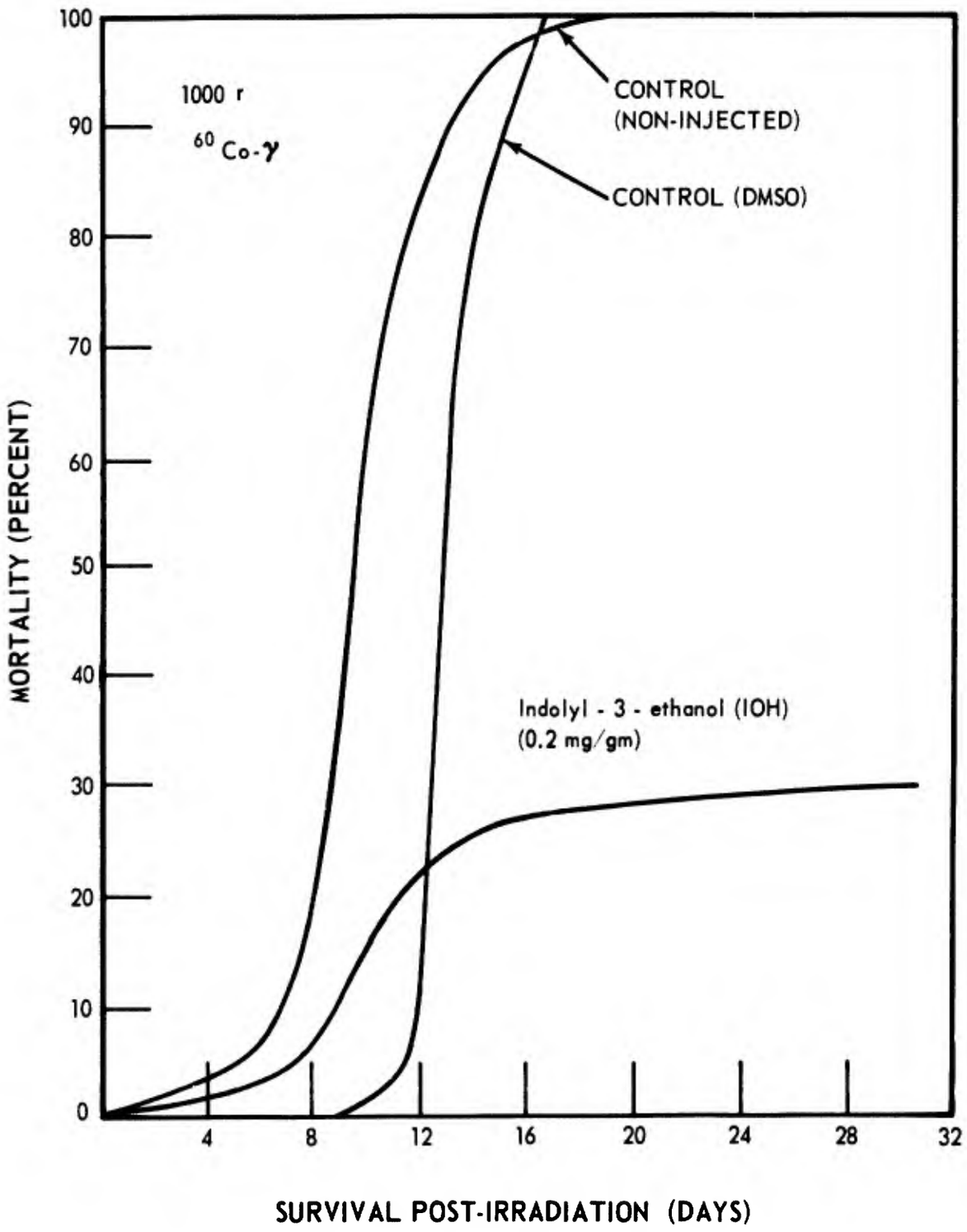



Figure 3. Effect of an intraperitoneal injection of indolyl-3-ethanol in reducing the mortality of mature male Webster white Swiss mice exposed to a 1000 r dose of $^{60}Co$ γ-radiation

of 10 percent statolon; a mixture of $NaHCO_3$ plus glucose made up the remaining 90 percent. The ineffective lot, also in powder form, consisted of 14 percent statolon; a mixture of $(NH_4)_2CO_3$ plus glucose made up the remaining 86 percent. There was also a difference in the physical appearance of the statolon-IoxBu(n) triturated preparations from the two lots. Statolon by itself provided no radiation protection in preliminary tests (Table 1).

To learn if any tissues are permanently injured by protective doses of these auxin analogues, we examined representative tissues from drug-treated mice. Irradiated mice and their non-irradiated controls (4 to 18 mice per test condition) were sacrificed 60 or 90 days after drug administration or irradiation, this period being considered sufficient for most tissue repair processes. Following incisions to expose the viscera and major cavities to fixative, the bodies were totally immersed in 10-percent formalin long enough for tissue fixation. Samples were then taken and embedded in paraffin for sectioning, and these sections were stained with hematoxylin and eosin. The tissues included mesenteric lymph node, femoral bone marrow, mesentery, omentum, genital omentum, pancreas, spleen, liver, heart, lung, thyroid, thymus, stomach, large and small intestines, kidney, adrenal, and both testes.

Microscopic examination of the tissues from drug-treated, non-irradiated mice failed to reveal any detectable histopathologic change. Of the tissues examined from drug-treated, irradiated mice exposed to 1000 r, only the testicular sections showed even slight histopathologic change. This change consisted of sporadic arrest of spermatogenesis and/or replacement of spermatogonia by Sertoli cells.

The drug-concentration range over which these compounds are radiation-protective is very narrow: a 30-percent increase from the optimum radiation-protective dose can markedly sensitize the animal to radiation, although it gives no evidence of being toxic. For example, IoxBu(n) at 0.1 mg/gm is optimal for radiation protection, but a dose of 0.15 mg/gm can sensitize to radiation. In most instances, the protective dose is approximately 1/2 $LD_{50}$. Table 2, which gives toxicity data for auxin analogues in the absence of radiation, shows the relatively narrow therapeutic index of these drugs.

Our data on structure-activity relationships for these radiation-protective compounds are limited. Substitution of an amino group (PABA) or a chlorine atom (PCBA) for the iodine atom in PIBA reduces its effectiveness against $\gamma$-radiation. Similarly, the secondary butyl ester analogue of IoxBu(n) is essentially without protective activity (Table 1).

Radiation-protective doses of both 2,4,5-TOH and IOH act as hypnotic agents in mice for periods up to an hour. The other auxin analogues do not produce this effect; IoxBu(n) and PIBA produce only a slight temporary depression.

Knowing that hypnotic and anaesthetic agents decrease oxygen uptake, we checked for a correlation between this decrease and the radiation protection afforded by 2,4,5-TOH (Table 3). This compound reduces the oxygen uptake of the animal to a little less than that during normal sleep. However, a dose of sodium pentobarbital that reduced oxygen uptake by a similar amount afforded no protection against 1000 r $^{60}Co$ $\gamma$-radiation. This finding suggests that general (but not necessarily localized) hypoxia may not be the mechanism of radiation protection by 2,4,5-TOH.

Table 2

TOXICITY DATA FOR RADIATION-PROTECTIVE AUXIN ANALOGUES

| Compound | Dose (mg/gm) | Vehicle* | Mortality (%) |
|---|---|---|---|
| IoxBu(n) | 0.25 | GA + S | 0 |
| | 0.35 | | 60 |
| | 0.40 | | >99 |
| IOH | 0.3 | PD + S | 0 |
| | 0.4 | | 40 |
| | 0.5 | | >99 |
| 2,4,5-TOH | 0.3 | PD + S | 0 |
| | 0.35 | | 20 |
| | 0.4 | | >99 |
| PIBA | 0.5 | GA + S | 0 |
| | 1.0 | | >99 |
| MIBT | 1.0 | GA + S | 0 |
| | 1.5 | | 50 |
| | 2.0 | | >99 |
| Statolon | 2.0 | GA + S | 0 |
| IoxBu(n) + Statolon | 0.1 | GA + S | |
| | 0.15 | | 0 |

*GA = gum arabic
S = saline
PD = propanediol

Table 3

EFFECT OF 2,4,5-TOH ON OXYGEN UPTAKE BY WEBSTER WHITE SWISS MICE

| Treatment* | Oxygen Uptake, ml $O_2$/gm/hr (±SE) | | | | 1000 r Mortality |
|---|---|---|---|---|---|
| | Before Injection | 15 min | 70 min | 120 min | |
| No injection | 4.5 ± 0.2 (14)** | 4.1 ± 0.3 (15) | 4.22 ± 0.1 (15) | 3.4 ± 0.3 (16) | 95/14 |
| Saline | 4.4 ± 0.1 (12) | 4.1 ± 0.1 (14) | 4.2 ± 0.1 (13) | 4.1 ± 0.1 (14) | 95/14 |
| Pentobarbital 0.05 mg/gm | 4.6 ± 0.1 (16) | 2.3 ± 0.2 (23) | 4.4 ± 0.2 (17) | 3.9 ± 0.3 (17) | 95/14 |
| 2,4,5-TOH 0.2 mg/gm | 5.0 ± 0.2 (12) | 2.7 ± 0.2 (18) | 2.5 ± 0.1 (20) | 2.9 ± 0.2 (18) | 62/33 |

*Four or five mice per condition.

**( ) readings.

Saline vs. pentobarbital treatment: at 15 minutes post-injection, $p < 0.001$; not significant at other time points.

Saline vs. 2,4,5-TOH treatment: at 15, 70, and 120 minutes post-injection, $p < 0.001$.

Pentobarbital vs. 2,4,5-TOH treatment: at 70 and 120 minutes post-injection, $p < 0.001$ and $p < 0.02$, respectively; not significant at other time points.

The fact that the radiation-protective auxin analogues IoxBu(n) and MIBT and the synergist statolon have antiviral activity suggests that radiation sickness in mammals from 1000 r or less may be a phenomenon somewhat similar to the radiation induction of infectious virus in lysogenic bacteria. Monod, Changeux, and Jacob[10] have suggested that a hormone of small molecular weight is an allosteric effector that inactivates a specific genetic repressor. This allosteric transition removes or peels off the repressor from the operator gene of the operon and permits its cistrons to transcribe m-RNA. If this concept is correct, a hormone analogue of suitable structure could function as an antihormone to block this allosteric transition and prevent the operon from functioning. We suspect that our radiation-protective auxin analogues act in this manner to inhibit or repress the vegetative multiplication of initially latent but potentially cytopathic viruses that were activated by the radiation. This hypothesis is discussed in some detail in another paper.

## Section 3

## GLOSSARY

| Abbreviation | Compound |
|---|---|
| DMSO | dimethylsulfoxide |
| 4-HBPr(n) | n-propyl 4-hydroxybenzoate |
| IAA | indolyl-3-acetic acid |
| IOH | indolyl-3-ethanol |
| IoxBu(n) | n-butyl 4-hydroxy-3,5-diiodobenzoate |
| IoxBu(sec) | sec-butyl 4-hydroxy-3,5-diiodobenzoate |
| MIBT | N-methyl isatin-β-thiosemicarbazone |
| PABA | 4-aminobenzoic acid |
| PCBA | 4-chlorobenzoic acid |
| PIBA | 4-iodobenzoic acid |
| 2,4,5-T | 2,4,5-trichlorophenoxyacetic acid |
| TIBA | 2,3,5-triiodobenzoic acid |
| 2,4,5-TOH | 2,4,5-trichlorophenoxyethanol |
| SE | Standard error of the mean |
| p | Probability level of t according to R. A. Fisher.[11] |

## Section 4

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13. ABSTRACT

Although plant growth modifiers were found to be totally devoid of radiation-protective activity, their structural analogues were found to protect male Webster white Swiss mice against lethal doses of $^{60}Co$ $\gamma$-radiation. A broad-spectrum antiviral agent, statolon, which alone exhibited no activity, was found to synergize the protective action of certain growth modifying analogs. The possibility of latent virus involvement in radiation damage in a manner similar to bacterial lysogeny is also discussed.

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13. ABSTRACT: Enter an abstract giving a brief and factual summary of the document indicative of the report, even though it may also appear elsewhere in the body of the technical report. If additional space is required, a continuation sheet shall be attached.

It is highly desirable that the abstract of classified reports be unclassified. Each paragraph of the abstract shall end with an indication of the military security classification of the information in the paragraph, represented as *(TS), (S), (C), or (U)*.

There is no limitation on the length of the abstract. However, the suggested length is from 150 to 225 words.

14. KEY WORDS: Key words are technically meaningful terms or short phrases that characterize a report and may be used as index entries for cataloging the report. Key words must be selected so that no security classification is required. Identifiers, such as equipment model designation, trade name, military project code name, geographic location, may be used as key words but will be followed by an indication of technical context. The assignment of links, rules, and weights is optional.

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