PHARMACODYNAMICS OF A RADIOPROTECTIVE DRUG: 2-(1-DECYLAMINO)ETHANETHIOSULFURIC ACID

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FOREWORD

This study was carried out in the Radiobiology Division under task No. 775708 and partially under subtask 8716-RMD 2068, DASA (STMD). The work was performed between February and May 1969. The statistical data were analyzed by the Biometrics Division. The paper was submitted for publication on 20 February 1969 to fulfill the research requirement of phase II of the Residency in Aerospace Medicine.

The assistance of Horace E. Hamilton in preparing the report is gratefully acknowledged.

The animals involved in this study were maintained in accordance with the "Guide for Laboratory Animal Facilities and Care" as published by the National Academy of Sciences-National Research Council.

This report has been reviewed and is approved.

JOSEPH M. QUASHNOCK
Colonel, USAF, MC
Commander
ABSTRACT

One phase of the search for radioprotective agents is the study of the physiologic and pharmacologic mechanisms responsible for toxic and protective effects. In this study, the drug N-(1-decylamino)ethanethioic acid (WR-1607) was injected, according to different dose schedules, into control and irradiated Macaca mulatta monkeys. Changes in hemograms and blood chemistries were measured, and clinical observations were recorded. The response in control animals appeared to be that to a temporary chemical challenge with prompt recovery within one week. In the irradiated animals, the response corresponded to a subacute radiation syndrome. In this experiment, WR-1607 failed to mobilize physiologic mechanisms for protection against radiation injury. Further investigation of this drug as a radioprotectant should consider a different approach in method of administration.
I. INTRODUCTION

The increasing use of atomic energy with its potential hazard of exposure of man to high dosages of ionizing radiation has generated the search for chemical preparations possessing protective characteristics against radiation injury. Testing the ability of such chemical agents to reduce lethality in irradiated experimental animals is one phase of the endeavor to obtain practical methods for modification of radiation injury. Another phase of the scientific effort is the study of physiologic and pharmacologic mechanisms responsible for the toxic and protective effects of the radioprotective agents.

The compound 2-(1-decylamino)ethanethiosulfuric acid (WR-1607), developed by the Walter Reed Army Institute of Research, has been tested in mice with promising results—50% to 90% protection in doses of 5 mg./kg. Results in initial studies with dogs have not been so encouraging. Toxicity studies in rhesus monkeys have been few (2). The potential use of this drug as a radioprotective agent requires prior consideration of its pharmacodynamics. In the present study an attempt was made to evaluate the physiologic effects of WR-1607 in primates, in conjunction with a recent investigation of the radioprotective effectiveness of the compound (3). The parameters selected for evaluation were: (1) clinical picture, (2) hemograms, and (3) blood chemistries.

II. MATERIALS AND METHODS

Adult Macaca mulatta, ranging in weight from 6.5 to 9 lb., were used in this investigation; all but 2 were males. The primates were screened for evidence of existing disease and acclimatized for 2 weeks. They were caged individually in air-conditioned quarters and maintained as described by Young et al. (4). The 28 primates were randomly distributed

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of animals</th>
<th>Drug dosage (mg./kg.)</th>
<th>Pre-irradiation interval (hr.)*</th>
<th>Radiation dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>A₁</td>
<td>4</td>
<td>10</td>
<td>1</td>
<td>Sham</td>
</tr>
<tr>
<td>A₂</td>
<td>4</td>
<td>20</td>
<td>1</td>
<td>Sham</td>
</tr>
<tr>
<td>B₁</td>
<td>5</td>
<td>10</td>
<td>1</td>
<td>850 R</td>
</tr>
<tr>
<td>B₂</td>
<td>5</td>
<td>10</td>
<td>3</td>
<td>850 R</td>
</tr>
<tr>
<td>C₁</td>
<td>5</td>
<td>20</td>
<td>1</td>
<td>850 R</td>
</tr>
<tr>
<td>C₂</td>
<td>5</td>
<td>20</td>
<td>3</td>
<td>850 R</td>
</tr>
</tbody>
</table>

*Time interval between drug administration and irradiation period.
into six groups as presented in table I. In addition, each irradiated group included 1 radiation control (irradiated but not administered drug) to confirm lethality of the radiation dose. No clinical, chemical, or hematologic studies were performed on the radiation controls.

The compound WR-1607, obtained from the Walter Reed Army Institute of Research, was dissolved in warm Carbowax just before injection. The concentrations were adjusted so that each animal received approximately 3 ml of solution. The dissolved drug was administered intraperitoneally by use of standard procedures.

Whole-body irradiations were performed with a Maxitron-300 machine at a dose rate of 18 ± 2 R/min, for a total dose of 850 R.

Hematologic data were obtained by the methodologies described by Wintrobe (6).

The clinical evaluation presented in this paper is limited to body weights and rectal temperatures (tables II and III); a more extensive clinical evaluation of the compound WR-1607 in Macaca mulatta is available (3).

Data on the following 14 variables were collected pretreatment and on days 1, 3, and 7 postinjection:

- Leukocytes
- Hematocrit
- Platelets
- Lymphocytes
- Neutrophils
- SGOT
- SGPT
- Alkaline phosphatase
- Bilirubin (direct)
- Bilirubin (total)
- Total protein
- Albumin
- Sodium
- Potassium

For each variable the mean values for each time and for each group are shown in tables IV through XVI.

One-way analyses of variance were computed from the baseline data for each variable in order to check for differences between the groups before treatment. Since the animals

<table>
<thead>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A₁</td>
<td>7.5</td>
<td>98</td>
<td>91</td>
<td>95</td>
<td>93</td>
<td>93</td>
<td>95</td>
<td>92</td>
<td>91</td>
<td>93</td>
</tr>
<tr>
<td>A₂</td>
<td>7.2</td>
<td>99</td>
<td>89</td>
<td>88</td>
<td>94</td>
<td>92</td>
<td>89</td>
<td>86</td>
<td>86</td>
<td>88</td>
</tr>
<tr>
<td>B₁</td>
<td>6.9</td>
<td>100</td>
<td>101</td>
<td>96</td>
<td>93</td>
<td>81</td>
<td>82</td>
<td>83</td>
<td>82</td>
<td>77</td>
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<td>B₂</td>
<td>7.0</td>
<td>101</td>
<td>97</td>
<td>101</td>
<td>90</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>C₁</td>
<td>6.7</td>
<td>102</td>
<td>89</td>
<td>88</td>
<td>85</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>C₂</td>
<td>6.9</td>
<td>97</td>
<td>101</td>
<td>94</td>
<td>99</td>
<td>100</td>
<td>80</td>
<td>88</td>
<td>89</td>
<td>87</td>
</tr>
</tbody>
</table>

In group B₁, survival ratio at day 3 was 6/6; at day 7, 2/3; at day 14, 1/6 and at day 17, 1/6.

In group B₂, survival ratio at day 7 was 4/6.

In group C₁, survival ratio at day 17 was 4/6.

In group C₂, survival ratio at day 7 was 2/3; at day 10, 2/3; at days 14, 17, and 19, 1/3; and at day 21, 1/3.

*Days after drug administration.
†Percent = group mean weight/mean baseline weight.
### TABLE III

*Mean rectal temperature (in degrees Fahrenheit) of irradiated and sham-irradiated primates*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A_1</td>
<td>102.9</td>
<td>101.6</td>
<td>102.0</td>
<td>102.1</td>
<td>102.2</td>
<td>102.2</td>
<td>99.8</td>
<td>100.6</td>
<td>102.6</td>
<td></td>
</tr>
<tr>
<td>A_2</td>
<td>102.6</td>
<td>101.5</td>
<td>102.8</td>
<td>102.2</td>
<td>102.8</td>
<td>102.8</td>
<td>99.8</td>
<td>101.5</td>
<td>101.5</td>
<td></td>
</tr>
<tr>
<td>B_1</td>
<td>102.4</td>
<td>102.6</td>
<td>102.2</td>
<td>102.5</td>
<td>101.4</td>
<td>102.8</td>
<td>102.0</td>
<td>104.4</td>
<td>102.8</td>
<td></td>
</tr>
<tr>
<td>B_2</td>
<td>102.6</td>
<td>103.1</td>
<td>101.8</td>
<td>102.5</td>
<td>99.1</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>C_1</td>
<td>103.0</td>
<td>102.3</td>
<td>100.3</td>
<td>102.3</td>
<td>102.1</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>C_2</td>
<td>102.5</td>
<td>102.7</td>
<td>102.7</td>
<td>102.0</td>
<td>101.8</td>
<td>102.6</td>
<td>100.0</td>
<td>101.4</td>
<td>102.2</td>
<td></td>
</tr>
</tbody>
</table>

*See table II for survival data.

*Days after drug administration.

### TABLE IV

*Change in leukocytes with WR-1607 and radiation*

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Day 1*</th>
<th>Day 3</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>A_1</td>
<td>7,800</td>
<td>17,500</td>
<td>9,700</td>
<td>10,800</td>
</tr>
<tr>
<td>A_2</td>
<td>8,200</td>
<td>11,600</td>
<td>12,800</td>
<td>11,300</td>
</tr>
<tr>
<td>B_1</td>
<td>8,700</td>
<td>10,800</td>
<td>1,700</td>
<td>600</td>
</tr>
<tr>
<td>B_2</td>
<td>10,900</td>
<td>11,900</td>
<td>5,300</td>
<td>400</td>
</tr>
<tr>
<td>C_1</td>
<td>8,600</td>
<td>1,800</td>
<td>900</td>
<td>600</td>
</tr>
<tr>
<td>C_2</td>
<td>9,100</td>
<td>16,700</td>
<td>1,400</td>
<td>600</td>
</tr>
</tbody>
</table>

*Time postinjection.

### TABLE V

*Change in hematocrit with WR-1607 and radiation*

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Day 1*</th>
<th>Day 3</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>A_1</td>
<td>42</td>
<td>44</td>
<td>38</td>
<td>36</td>
</tr>
<tr>
<td>A_2</td>
<td>40</td>
<td>40</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>B_1</td>
<td>40</td>
<td>27</td>
<td>25</td>
<td>38</td>
</tr>
<tr>
<td>B_2</td>
<td>42</td>
<td>39</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td>C_1</td>
<td>42</td>
<td>45</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td>C_2</td>
<td>45</td>
<td>44</td>
<td>40</td>
<td>42</td>
</tr>
</tbody>
</table>

*Time postinjection.

### TABLE VI

*Change in platelets with WR-1607 and radiation*

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Day 1*</th>
<th>Day 3</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>A_1</td>
<td>80,000</td>
<td>87,000</td>
<td>128,000</td>
<td>484,000</td>
</tr>
<tr>
<td>A_2</td>
<td>401,000</td>
<td>427,000</td>
<td>91,000</td>
<td>890,000</td>
</tr>
<tr>
<td>B_1</td>
<td>483,000</td>
<td>269,000</td>
<td>201,000</td>
<td>88,000</td>
</tr>
<tr>
<td>B_2</td>
<td>346,000</td>
<td>218,000</td>
<td>186,000</td>
<td>53,000</td>
</tr>
<tr>
<td>C_1</td>
<td>350,000</td>
<td>92,000</td>
<td>77,000</td>
<td>24,000</td>
</tr>
<tr>
<td>C_2</td>
<td>184,000</td>
<td>123,000</td>
<td>100,000</td>
<td>45,000</td>
</tr>
</tbody>
</table>

*Time postinjection.

### TABLE VII

*Change in lymphocytes (%) with WR-1607 and radiation*

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Day 1*</th>
<th>Day 3</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>A_1</td>
<td>75</td>
<td>19</td>
<td>64</td>
<td>63</td>
</tr>
<tr>
<td>A_2</td>
<td>66</td>
<td>11</td>
<td>50</td>
<td>46</td>
</tr>
<tr>
<td>B_1</td>
<td>78</td>
<td>10</td>
<td>58</td>
<td>0†</td>
</tr>
<tr>
<td>B_2</td>
<td>71</td>
<td>10</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>C_1</td>
<td>65</td>
<td>5</td>
<td>3</td>
<td>0†</td>
</tr>
<tr>
<td>C_2</td>
<td>69</td>
<td>4</td>
<td>12†</td>
<td>2‡</td>
</tr>
</tbody>
</table>

*Time postinjection.

†Survival ratio 4/6.
‡Survival ratio 3/6.
were randomly assigned to the treatment
groups, no differences would be expected be-
between the group means. As indicated in
table XVII, only the leukocyte data gave a
statistically significant (P < .05) difference
between group means. It seems reasonable to
assume that this difference was due to random
variation only and did not reflect any bias in
the way in which the animals were handled.

An analysis of variance of repeated meas-
urements was computed for the postinjection
data for each pair of groups (A₁ and A₂; B₁
and B₂; C₁ and C₂). This provided a test
(G x T) of whether the response curves for
the two groups in each pair were the same.
It also provided tests of whether the group
means (averaged over time) were the same,
and whether the means (averaged over groups)
for the three postinjection times (1, 3, and
7 days) were the same. These latter tests
are generally meaningful only if the G x T test
is not significant (P > .05). The probability
levels for these tests are given in table XVII.

<table>
<thead>
<tr>
<th>TABLE VIII</th>
<th>TABLE X</th>
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</thead>
<tbody>
<tr>
<td><strong>Change in neutrophils (%) with WR-1607</strong></td>
<td><strong>Change in SGPT with WR-1607</strong></td>
</tr>
<tr>
<td>and radiation</td>
<td>and radiation</td>
</tr>
<tr>
<td><strong>Group</strong></td>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td>A₁</td>
<td>23</td>
</tr>
<tr>
<td>A₂</td>
<td>22</td>
</tr>
<tr>
<td>B₁</td>
<td>25</td>
</tr>
<tr>
<td>B₂</td>
<td>29</td>
</tr>
<tr>
<td>C₁</td>
<td>34</td>
</tr>
<tr>
<td>C₂</td>
<td>30</td>
</tr>
</tbody>
</table>

*Time postinjection.
†Survival ratio 4/5.
‡Survival ratio 5/6.

<table>
<thead>
<tr>
<th>TABLE IX</th>
<th>TABLE XI</th>
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</thead>
<tbody>
<tr>
<td><strong>Change in SGOT with WR-1607</strong></td>
<td><strong>Change in alkaline phosphatase with WR-1607</strong></td>
</tr>
<tr>
<td>and radiation</td>
<td>and radiation</td>
</tr>
<tr>
<td><strong>Group</strong></td>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td>A₁</td>
<td>36</td>
</tr>
<tr>
<td>A₂</td>
<td>33</td>
</tr>
<tr>
<td>B₁</td>
<td>37</td>
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<tr>
<td>B₂</td>
<td>39</td>
</tr>
<tr>
<td>C₁</td>
<td>38</td>
</tr>
<tr>
<td>C₂</td>
<td>40</td>
</tr>
</tbody>
</table>

*Time postinjection.
†Survival ratio 4/5.
‡Survival ratio 5/6.
A combined analysis was done on the data of groups B₁, B₂, C₁, and C₂. This analysis provided tests for the following: 10-mg. dosage as compared to 20-mg.; 1-hour preirradiation interval versus 3-hour interval; 1-day versus 3-day versus 7-day postinjection measurements; and interactions among these variables. The tests which were significant (P < .05) are indicated in table XVIII. The standard deviations for comparing means within and between treatment groups for each variable are given separately below.

Each variable is discussed separately below.

III. RESULTS

Hemogram

Values for leukocytes, hematocrit, platelets, and relative lymphocytes and neutrophils are presented in tables IV through VIII. The values are the means for the survivors at the time of testing.

Leukocytes showed an initial increase in all animals. The initial leukocytosis was more
significant for the drug-control groups. By the 3rd day posttreatment the drug-control group was returning to the baseline while the irradiated animals were developing severe leukopenia as in untreated, irradiated monkeys.

A significant decrease in hematocrit can be seen from day 1 to days 3 and 7. Some differences appeared in the response between groups C1 and C2, and the B groups responded differently from the C groups.

Table XVI

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Day 1</th>
<th>Day 8</th>
<th>Day 7</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>4.8</td>
<td>4.2</td>
<td>4.5</td>
<td>4.8</td>
</tr>
<tr>
<td>A2</td>
<td>4.8</td>
<td>4.1</td>
<td>4.7</td>
<td>4.6</td>
</tr>
<tr>
<td>B</td>
<td>5.2</td>
<td>4.2</td>
<td>4.5</td>
<td>4.2†</td>
</tr>
<tr>
<td>B2</td>
<td>5.0</td>
<td>4.2</td>
<td>4.5</td>
<td>4.6</td>
</tr>
<tr>
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<tr>
<td>C2</td>
<td>5.4</td>
<td>3.0</td>
<td>6.2†</td>
<td>5.1</td>
</tr>
</tbody>
</table>

*Time postinjection.
1Survival ratio 2/6.
2Survival ratio 6/6.

Table XVII

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>A1 vs. A2</th>
<th>B1 vs. B2</th>
<th>C1 vs. C2</th>
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<tr>
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<td>&lt;.001</td>
<td>&lt;.001</td>
<td>NS</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>NS</td>
<td>&lt;.01</td>
<td>NS</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Platelets</td>
<td>NS</td>
<td>&lt;.001</td>
<td>&lt;.025</td>
<td>&lt;.001</td>
</tr>
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<td>Lymphocytes</td>
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<td>&lt;.001</td>
<td>&lt;.001</td>
<td>NS</td>
</tr>
<tr>
<td>Neutrophils</td>
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</tr>
<tr>
<td>SGOT</td>
<td>NS</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>NS</td>
</tr>
<tr>
<td>SGPT</td>
<td>NS</td>
<td>&lt;.001</td>
<td>&lt;.025</td>
<td>&lt;.005</td>
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<td>NS</td>
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<tr>
<td>Bilirubin (direct)</td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Bilirubin (total)</td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
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Probability levels in the analyses of variance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>A1 vs. A2</th>
<th>B1 vs. B2</th>
<th>C1 vs. C2</th>
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<tbody>
<tr>
<td>Leukocyte</td>
<td>&lt;.05</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>NS</td>
</tr>
<tr>
<td>Hematocrit</td>
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<td>&lt;.01</td>
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<td>NS</td>
<td>&lt;.001</td>
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<td>&lt;.001</td>
<td>NS</td>
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<tr>
<td>Neutrophils</td>
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<td>&lt;.001</td>
<td>&lt;.001</td>
<td>NS</td>
</tr>
<tr>
<td>SGOT</td>
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<td>SGPT</td>
<td>NS</td>
<td>&lt;.001</td>
<td>&lt;.025</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Alkaline phos</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Bilirubin (di</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>Bilirubin (to</td>
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<tr>
<td>Albumin</td>
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<td>Potassium</td>
<td>NS</td>
<td>&lt;.001</td>
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Neutrophils increased in all groups within the 1st day. By the 3rd day, those of group C had dropped to extremely low levels. Group B neutrophils returned to baseline levels by the 7th day, and those of group A approached the baseline level.

Manifestations in the hemograms of the irradiated-and-treated animals were comparable to the results from irradiation alone (6).

Blood chemistries

An immediate increase in SGOT and SGPT occurred in all groups, followed by a significant return to baseline by the 3rd day posttreatment and postirradiation (tables IX and X). One exception appeared on day 7 when the level of SGPT for C groups fell significantly below baseline levels.

The alkaline phosphatase values showed no significant variations through the 7-day period for the A groups, but the levels were significantly below baseline at days 3 and 7 for the C groups, and at day 7 for the B group (table XI).

The total bilirubin showed an increase in all groups lasting through the 7-day period while the direct portion showed a lasting rise in only the treated, nonirradiated group (table XII); however, the evidence for any real change in either direct bilirubin or total bilirubin was very weak. Rough nonparametric evaluations showed no significant effects.

There appeared to be little consistency in the total protein response between the groups; thus it is difficult to find an interpretable pattern. An initial decrease was seen in albumin

<table>
<thead>
<tr>
<th>TABLE XVIII</th>
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<tbody>
<tr>
<td>Significant sources of variation from analyses of B and C groups combined</td>
</tr>
<tr>
<td>Variables</td>
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<tr>
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<tr>
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</tr>
<tr>
<td>Neutrophils</td>
</tr>
<tr>
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</tr>
<tr>
<td>SGPT</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
</tr>
<tr>
<td>Bilirubin (direct)</td>
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<tr>
<td>Bilirubin (total)</td>
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<tr>
<td>Total protein</td>
</tr>
<tr>
<td>Albumin</td>
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<tr>
<td>Sodium</td>
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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>S.D. of means* within and between treatment groups for each variable</td>
</tr>
<tr>
<td>Variables</td>
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<td>Hematocrit</td>
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<td>Albumin</td>
</tr>
<tr>
<td>Sodium</td>
</tr>
<tr>
<td>Potassium</td>
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</tbody>
</table>

*T. E. of the difference between two means = S.D. \( \sqrt{\frac{1}{N_1} + \frac{1}{N_2}} \),

where \( N_1 \) and \( N_2 \) are the number of observations in each mean. Comparisons within a group should be made only where \( N_1 = N_2 \).
levels for the B groups, and an initial increase in albumin for the C groups, followed by a general decrease for all groups by day 3. The day-7 levels for all groups were lower than the corresponding baseline values but, for all groups other than B1 and C2, were higher than the corresponding day-3 values.

A general decrease in sodium levels and a corresponding increase in potassium levels occurred from day 1 to day 7 for all groups. Though some of the tests were significant, the reasons for the significance are not clear.

**Clinical parameters**

Weight remained essentially the same in the lightly treated drug-control group (A1). The heavily treated control group (A2) had a slight but significant weight loss in the 30-day period studied. Animals in irradiated, treated groups (B and C) experienced significant weight losses prior to their deaths (table II). The temperatures were quite variable within the groups, and no significant inference may be obtained (table III).

**IV. DISCUSSION**

The hematologic response of the drug-control group appears to be that of the ordinary brief reaction to a drug challenge with most parameters returning to the baseline values by the end of the 7-day period investigated. The treated, irradiated animals responded immediately to the challenge with a somewhat similar reaction, then gradually reacted in the typical manner of animals sustaining radiation injury. The eventual lack of survivors among the protected animals confirmed the absence of mobilization of physiologic mechanisms for defense against the radiation insult (3).

The blood chemistry response in both drug controls and treated, irradiated animals was similar, with the exception of the direct portion of the bilirubin which increased more lastingly in the drug controls. Elucidation of the reasons for this difference requires further investigation. This finding agrees with previous studies (2) which found degenerative changes in liver and kidneys of primates dying of toxic effects of WR-1607.

Of the clinical parameters, the change in weight appeared to be the only contributory factor, conforming to the general response to a chemical challenge and typical subacute radiation syndrome.

One may conclude that WR-1607, as utilized in this experiment, failed to effectively mobilize physiologic mechanisms for protection against the radiation injury. All treated, irradiated animals responded in the typical manner to the ionizing radiation as determined by the parameters evaluated. Further investigation of this drug as a potential radioprotective agent must consider a different approach to its administration.

**REFERENCES**


One phase of the search for radioprotective agents is the study of the physiologic and pharmacologic mechanisms responsible for toxic and protective effects. In this study, the drug 2-[(1-decylamino)ethanethiosulfuric acid (WR-1607) was injected, according to different dosage schedules, into control and irradiated Macaca mulatta monkeys. Changes in hemograms and blood chemistries were measured, and clinical observations were recorded. The response in control animals appeared to be that to a temporary chemical challenge with prompt recovery within one week. In the irradiated animals, the response corresponded to a subacute radiation syndrome. In this experiment, WR-1607 failed to mobilize physiologic mechanisms for protection against radiation injury. Further investigation of this drug as a radioprotectant should consider a different approach in method of administration.
<table>
<thead>
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<th>LINK C</th>
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