Administration of BAL* in Selenium Poisoning.† (17376)

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Selenium causes "alkali disease" or "blind staggers" in livestock in the Dakotas, Kansas, Montana, Wyoming, and other Western States where the soil and vegetation are high in selenium content. Therefore the toxic properties of selenium and its compounds are of great importance in these areas.

As far as we know, there is no reliable agent which is of value in preventing or curing the symptoms of selenium poisoning, though protective action of arsenic has been demonstrated by Moxon *et al.*[1]

Peters, Stocken, and Thompson[2] described the effectiveness of BAL in counteracting the effects of arsenical poisoning. The protective action of this compound in arsenical poisoning was believed to be due to the release of SH groups by BAL which could compete with the tissue SH groups for the arsenic, and act as a detoxifying agent. The nature of the reaction between arsenic and BAL made it seem probable that BAL would react similarly with other metals, and Gilman, Allen, and Philips[3] have reported its effectiveness as an antidote for bichloride of mercury and cadmium poisoning, and Braun, Lusky, and Calvery[4] showed similar results against poisoning by antimony, bismuth, chromium and nickel. However, they demonstrated that lead and selenium were made more toxic by BAL.

Our experiments performed using BAL as an antagonist against selenium poisoning confirmed the results already described.[4] However, we have found no explanation in the literature of the apparent synergism between BAL and selenium, hence our work has been directed along this line.

Experimental. Healthy white rats 6 to 8 weeks old, 120 and 150 g of weight were used. Selenium was administered by intraperitoneal injections in the form of a freshly prepared aqueous solution of sodium selenite (SS). Intramuscular injections of BAL freshly dissolved in peanut oil were used. Each drug was administered daily for varying lengths of time.

A. *Toxicity of selenium.* The toxicity of selenium was determined by injections of (SS) in daily doses of 5 mg/kg of body weight. (This is equivalent to 2.2 mg of the element selenium). The animals were maintained on this regimen for a period of 28 days at which time they were sacrificed and the livers were examined for any possible pathology. All rats survived the full experimental period. (Table I). Microscopic examination showed a typical picture of liver necrosis and fatty degeneration (Fig. 1) as previously described by other workers.[6] Microscopic examination of the kidney was negative.

B. *Toxicity of BAL.* In this group all rats survived for the experimental period after receiving BAL in doses of 15 mg/kg of body weight. (Table I). Liver and kidney showed no abnormalities.

C. *Toxicity of SS and BAL.* 1. Combined treatment with BAL and SS. Rats injected simultaneously with BAL and selenium, 15 mg/kg and 5 mg/kg, respectively, had an average survival period of 8 days ranging from 6 to 10 days; those receiving doses of 7.5 mg/kg BAL and 5 mg/kg of selenium had

* BAL was kindly supplied by Hynson, Westcott and Dunning, Inc., of Baltimore, Md., and the Army Medical Center, Bethesda, Md.

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1 Rhian, M., and Moxon, A. L., *J. Pharm. and Exp. Therap.*, 1943, **78**, 249.

2 Peters, R. A., Stocken, L. A., and Thompson, R. H. S., *Nature*, 1945, **156**, 616.

3 Gilman, A., Philips, F. S., Allen, R. P., Koelle, E. S., *J. Pharm. and Exp. Therap.*, 1946, **87**, 85.

4 Braun, H. A., Lusky, L. M., and Calvery, H. O., *J. Pharm. and Exp. Therap.*, 1946, **87**, 119.

5 Durlacher, S. H., Bunting, H., Harrison, H. E., Ordway, N. K., and Albrink, W. S., *J. Pharm. and Exp. Therap.*, 1946, **87**, 28.

TABLE I.
Experiment with Selenium (Sodium Selenite, SS).*
Ten animals in each series.

Sex	Drug administered and method	Dosage (mg/kg)	Survival time (days)
♀	S.S.–(I.P.)	5	All survived
♂	,,	5	,, ,,
♀	,,	10	Avg—10
♂	,,	10	Avg— 6
	Experiment with BAL (British Anti-Lewisite)		
♀	BAL–(I.M.)	15	All survived
♂	,,	15	,, ,,

* Age of all rats used, 6 wk.

TABLE II.
Experiment with BAL and Selenium.*

No. of animals and sex	Drug administered and method	Dosage (mg/kg) BAL	SS	Survival time days (avg)
8 ♀	BAL (I.M.) + SS (I.P.)	15	5	10
8 ♂	,,	15	5	6
8 ♀	,,	7.5	5	6
8 ♂	,,	7.5	5	5
	(Using same animal after 20 days on BAL).			
10 ♀	BAL (I.M.) + SS (I.P.)	15	5	3
10 ♂	,,	15	5	3

* Age of all rats used, 6 wk.

a survival time of 5½ days ranging from 5 to 6 days (Table II). Microscopic examination of the liver showed no pathology but the kidneys exhibited a tubular necrosis.

2. Pre-treatment with BAL. Rats were pretreated 20 days with BAL, 15 mg/kg. On the 21st day and days after for as long as they lived, 5 mg/kg of SS was administered simultaneously with 15 mg/kg of BAL. The average survival time in this combined treatment was 3 days (Table II). Microscopic examination of the liver was normal but the kidney again exhibited moderate necrosis (Fig. 2).

Discussion. When SS was used alone a typical toxic picture was noted.[6] The livers of these animals were necrotic and showed moderate to severe fatty degeneration.

BAL alone did not produce any untoward results in our experience although Durlacher *et al.*[5] reported toxic reactions in mammals from the doses we used. The results of the combined doses of BAL and selenium led to a marked decrease in the survival time of the animals treated. This finding corresponds to the report of Braun, Lusky, and Calvery.[4] However, these investigators did not report any microscopic examination of the liver and kidney.

In our work, careful examination of the liver and kidney showed that, contrary to the usual findings in SS poisoning, there were no abnormalities in the liver tissue although the animals died rapidly. This might be regarded as due to the short survival time but it was noted that animals treated with SS alone for a period of 4 to 5 days *did* show the beginning of liver necrosis.

The results of our experiments would seem to indicate that the liver damage and death produced by SS may be entirely separate phenomena. As evidence in support of this contention BAL plus SS decreased the survival time of all animals as compared to those receiving SS alone. However, BAL protected SS animals from the liver damage usually produced by SS.

Seemingly, BAL does not antagonize the total toxicity of SS as it does other metals. However, it appears fair to propose that certain SH groups furnished by BAL prevent the liver damage caused by SS but are incapable

[6] Smith, M. I., Strohlman, E. F., and Lillie, R. D., *J. Pharm. and Exp. Therap.*, 1937, **60**, 449.

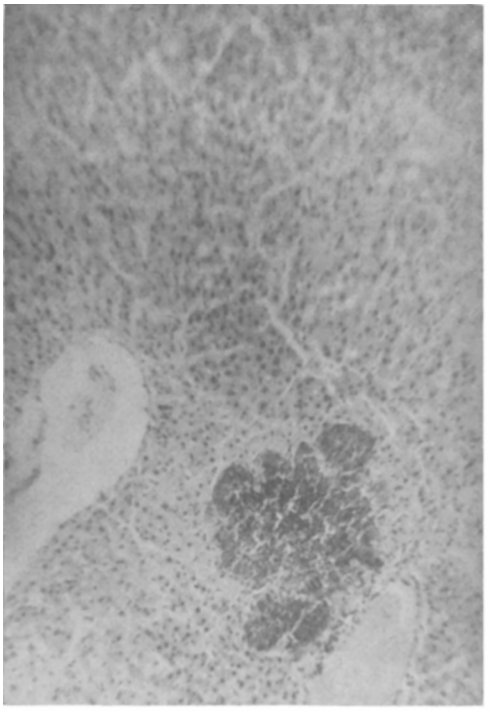

FIG. 1.
Rat liver: Typical focal necrosis and fatty degeneration following the administration of selenium in doses of 5 mg/kg for 10 days.

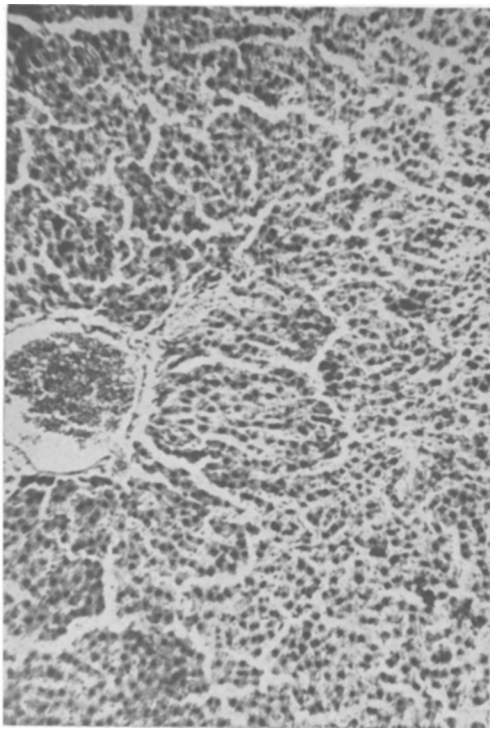

FIG. 2.
Rat liver: No abnormalities, following simultaneous administration of BAL 15 mg/kg and SS 5 mg/kg for 10 days.

of completely detoxifying the actions of SS.

It is now evident that BAL diminishes the toxicity of selenium for certain vital tissues and enhances the toxicity of the metal for the kidney. This corresponds to the findings of Gilman *et al.*,[3] who showed that cadmium becomes nephrotoxic with BAL. There are now evidently two such metals that have this property.

Our thanks are due Doctor R. L. Ferguson, Professor of Pathology, for reporting the microscopic findings in this paper.

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A Limited Feeding Regime for Rats.* (17377)

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For the past 5 years, a rat feeding regime has been in use by this laboratory which has proved so helpful under varied circumstances as to warrant this brief presentation. In carrying out metabolic research, some baseline of activity is needed. The definition of the "post-absorptive condition" has met this need in the human and dog, essentially daytime animals. However, the nocturnal feeding habits of the laboratory rat have led to the

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