THE EFFECT OF BRITISH ANTI-LEWISITE ON SELENIUM TOXICITY IN RATS[1,2]

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British Anti-Lewisite (BAL) or 2:3-dimercaptopropanol is well known to be effective in the detoxification of arsenicals (1). Further work has revealed that although BAL is effective in the detoxification of antimony, bismuth, nickel, chromium, mercury and gold, it is by no means a universal antidote (2-5). For this reason its effect on selenium poisoning was of interest and experiments were designed to determine this effect.

Early work indicated that in rats, BAL and selenium had a synergistic effect (6). Since then, this synergism has been confirmed by other workers (2, 7).

Arsenic has been known since 1938 to reduce the toxicity of selenium (8), but the exact nature of this reaction is as yet obscure.

From these three points it was thought that some indications of the nature of the selenium toxicity might be disclosed.

Experimental

Three separate experiments were carried out over a period of three months.

In the first experiment 12 male rats approximately 120 days old, and ranging from 275-325 gm. in weight, were divided into six experimental groups and treated as follows:

1. Three groups of two rats each were treated as controls. The first group received a normal diet, distilled water, and sham injections with sesame oil; the second, a toxic

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selenium diet, distilled water, and sham injections; and the third, a toxic selenium diet, distilled water containing 5 parts per million (ppm.) of arsenic as sodium arsenite, and the sham injections.

2. Groups IV, V, and VI were paired to groups I. II, and III respectively and were treated likewise except that the rats of these groups received injections of 50 mg. per kg. of body weight of BAL.

The second experiment consisted of 9 mature male rats weighing 310-380 gm. Three of these rats were treated as controls, the others received the BAL injections. This experiment was a replica of the first with the exceptions that the water contained 10ppm. of arsenic, and the BAL injections were 35 mg. per kg. of body weight.

In the third experiment 18 male rats, 55-72 gm. in weight, were divided into six experimental groups as in the previous experiments. Each group of three rats was treated as in the second experiment with the exception of a reduction of the dosage of BAL from 35 to 25 mg. per kg. of body weight on the seventh day.

The normal diet contained the following ingredients:

	Per cent	
Wheat	84.25	
Casein	10.00	
Salts	1.00	Phillips-Hart No. 3
Yeast	1.00	
Lard	3.00	
Cod liver oil	0.75	

The toxic diet used differed only from the normal diet in that it contained a naturally seleniferous wheat assaying 23 ppm. of selenium. The water for groups III and VI in the first experiments contained 5 ppm. of arsenic as sodium arsenite ($NaAsO_2$) and in the second experiment 10 ppm. of arsenic.

The BAL was injected subcutaneously as a suspension in corn oil for a short time during the first experiment, but was subsequently changed to a suspension in sesame oil which was found to be more satisfactory to the animal.

Growth curves were plotted and the average daily food and water consumptions were computed for each rat in the experiments for a period of 4 weeks.

Results and Discussion

The mode of action of BAL has been the subject of many studies and has thrown much light on the toxic properties of certain metals. It is believed that these toxic actions are due to combinations of the metal with the thiol groups of certain enzymes (9), and that the therapeutic effect of BAL is due to its greater affinity for these metals than that exerted by the thiol groups of the enzyme. In the case of arsenic BAL is thought to form a 5 membered ring with arsenic (10). If the action of selenium **in vivo** is of this nature, it follows that BAL might exert its protective action as shown with many metals, by binding the selenium with its highly reactive sulfhydryl groups. A study in 1939 by DuBois, Rhian, and Moxon (11) showed that glutathione could protect against selenium poisoning. The fact that selenium forms a compound with the thiol group of this tripeptide **in vitro** indicates that its protective effect lies in its sulfhydryl group (12, 13). This suggests that a dithiol as well as a monothiol might have a positive effect in protecting against selenium poisoning. While glutathione gave maximum protection if injected before the selenium, it was hoped that BAL would furnish effective protection when given along with the selenium. This however, did not prove to be true.

The growth curves for the first experiment are seen in Figures 1 and 2 wherein the daily weight for each animal in each group is plotted. Figure 3 shows the individual daily weights for the animals in the second experiment and Figure 4 shows the daily average weights for each group in the third experiment. As seen from these growth curves, the results are similar to those of other workers. In these experiments, the growth curves of all rats receiving selenium and BAL showed little or no gain, in fact the younger rats used in the third experiment (Figure 4) had to have the BAL dosage decreased in order to prevent early deaths.

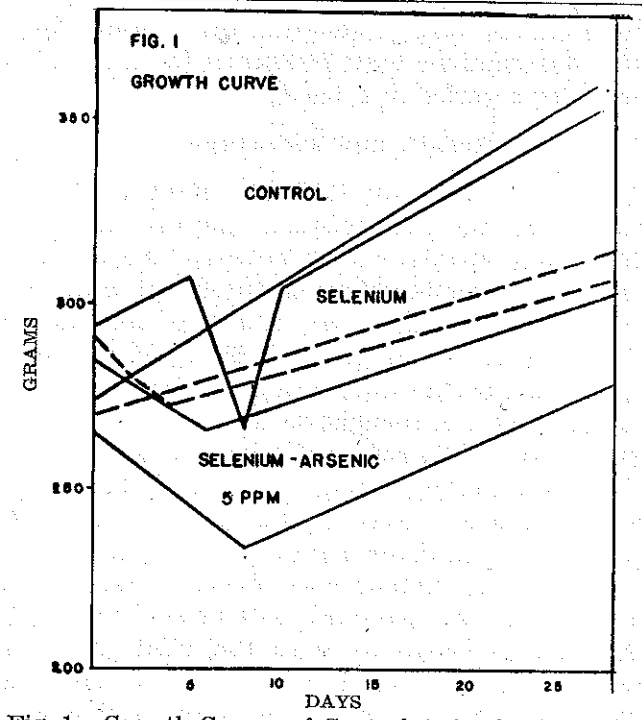

Fig. 1. Growth Curves of Control Animals Used in the First Experiment.

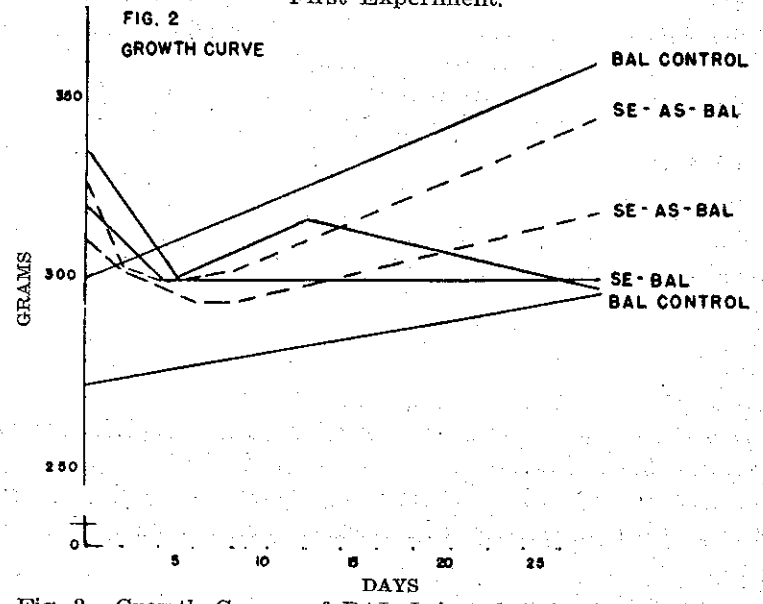

Fig. 2. Growth Curves of BAL Injected Animals Used in the First Experiment.

This synergism of selenium and BAL is especially emphasized in Figure 3. Likewise the importance of the correct arsenic to selenium ratio for alleviating the selenium toxicity is shown in Figures 1, 3 and 4. At the selenium level in the diet (19 ppm.), 5 ppm. of arsenic was not enough to correct for the toxicity.

Also in all three experiments, rats receiving selenium and arsenic have approximately the same rate of growth as those receiving selenium, arsenic and BAL. The molar ratio of BAL to arsenic ingested per day, computed for the second experiment, is approximately 5 moles of BAL per mole of arsenic, five times the required amount to neutralize any arsenic effect. It seems evident that in the presence of selenium, BAL is unable to exert its specificity for arsenic by interfering in the selenium-arsenic antagonism. The arsenic may be bound in the body in a form that is more stable than the BAL-arsenic complex.

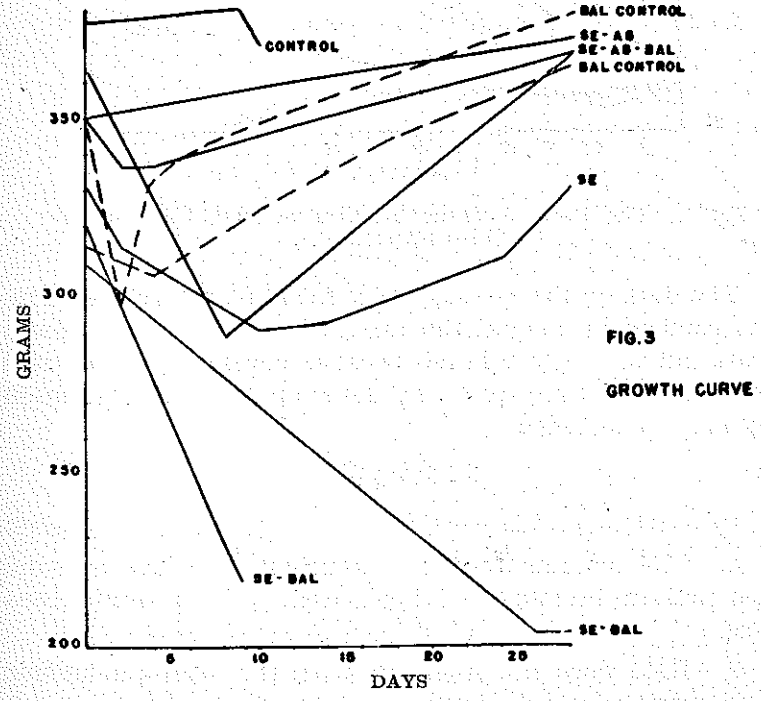

Fig. 3. Growth Curves of Rats Used in the Second Experiment.

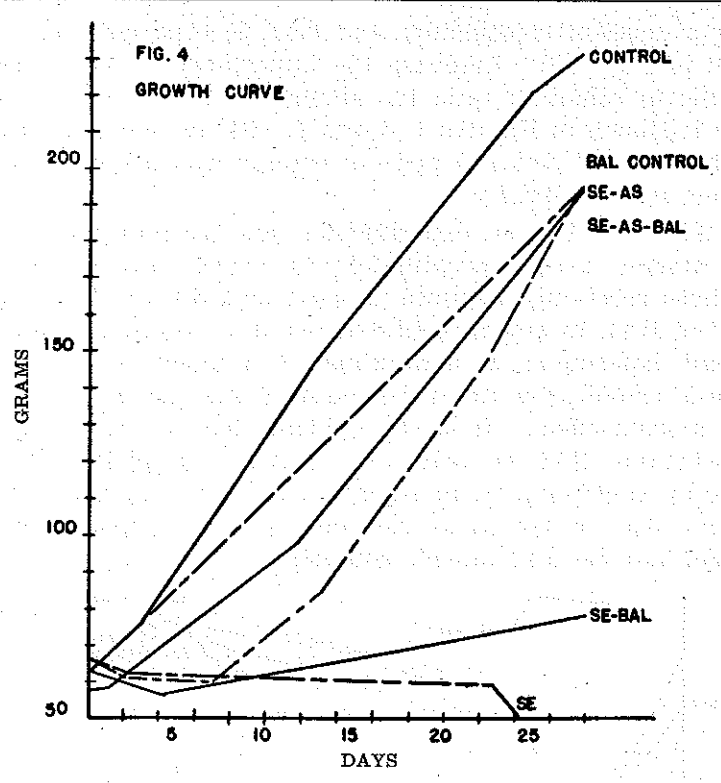

Fig. 4. The Daily Average Weights of Rats Used in the Third Experiment.

The data on the average daily food and water consumptions confirm in general the material shown in the growth curves but are only relative because considerable amounts of water and diet are spilled by the animals. For this reason they are not included.

SUMMARY

In conclusion, this work may be summarized as follows:

1. The synergistic effect of selenium and BAL is found to be present in rats receiving selenium from seleniferous wheat.

2. BAL does not interfere with the selenium-arsenic antagonism.

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