7. Survival of rats and guinea-pigs after contamination of the skin with lethal amounts of lewisite has been obtained by the local application of BAL even when treatment was delayed for as long as 2 hr. after contamination.

8. Injections of saturated aqueous solutions of BAL have saved rats after the injection of lethal amounts of sodium arsenite or the contamination of the skin with lethal amounts of lewisite.

9. Vesication in man following the application of small amounts of lewisite to the skin can be prevented by treatment with BAL up to at least 1 hr. after contamination.

10. Rough toxicity tests of a number of dithiols

have been carried out and the LD₅₀ dose of BAL when given by intramuscular injection to white rats has been accurately assessed.

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British Anti-Lewisite

3. ARSENIC AND THIOL EXCRETION IN ANIMALS AFTER TREATMENT OF LEWISITE BURNS

By L. A. STOCKEN AND R. H. S. THOMPSON, *Department of Biochemistry, Oxford*

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Earlier work in this laboratory (Stocken & Thompson, 1941) has shown that 2:3-dimercapto-propanol (British Anti-lewisite or BAL) reacts with lewisite and other arsenicals of the types $RAsO$ and $RAsCl_2$ to form stable ring compounds:

the affinity of the dithiol for the arsenical being sufficiently great to bring about combination with the traces of lewisite dissociating from combination with the tissue proteins. Low concentrations of BAL have been shown to protect against and to reverse the toxic action of lewisite on the pyruvate oxidase system of brain, in this respect differing fundamentally from all the monothiols so far investigated. Further, small animals may be caused to survive after contamination with lethal

amounts of lewisite by the application of BAL to the burn as late as 1 hr. after contamination; and finally, vesication by lewisite or phenyldichloroarsine in man may be prevented by treatment with BAL after intervals up to 1 hr. following contamination.

In view of these results it is clearly desirable to know something of the metabolism and ultimate fate of lewisite absorbed from the skin, and of any changes in its metabolism or rate of excretion brought about by treatment of the contaminated skin with BAL.

The excretion of arsenic, and in particular of the organic therapeutic arsenicals, has been extensively studied in animals and man (Heiden & Navassart, 1913; Voegtlin & Thompson, 1922; Underhill & Davis, 1922; Bulmer, 1923). It is now known that arsenic appears in the urine within a few hours of its intravenous injection. In rats, trivalent arsenic oxides show the slowest rate of excretion; arsenobenzene derivatives (i.e. of the type $RA_s:AsR$) a much greater excretion rate, and pentavalent compounds greater still. The maximum excretion rate occurs on the day of the injection or on the following day, but small amounts continue to be excreted for a large number of days. In the case of certain compounds, notably arspenamine, a considerable quantity is excreted, via the biliary tract, in the faeces.

Calder (1941) studied the excretion of arsenic after the application of lewisite to the skin of rabbits, and found that 3–6% of the amount applied was excreted in the urine during the first day after contamination, with a further 6–7% during the second day. In all, he found that 15–20% of the amount applied was excreted by the kidneys during the first week, but that by the end of this time no further excretion was taking place. Arsenic was also present in the bile during the first few days, but all tests carried out on faeces were negative.

The influence of thiols in this connexion does not appear to have been studied, although an extensive literature exists on the effect of sodium thiosulphate on arsenic excretion. This compound was used by Ravaut in 1920 for the treatment of arspenamine dermatitis; since then, much conflicting evidence has been produced both for and against the value of this compound in the treatment of various conditions due to both acute and chronic arsenical intoxication. In 1925 Myers, Groehl & Metz claimed that patients with arspenamine dermatitis or jaundice excrete a large amount of arsenic in the urine after each injection of sodium thiosulphate, and they attributed the beneficial effect in part to the removal of stored arsenic from the body. Kuhn & Reese (1925) put forward similar claims, while Ayres & Anderson (1938) observed that an increase in the urinary excretion of arsenic usually follows

the injection of sodium thiosulphate. Other workers, however, have been unable to confirm this increased excretion of arsenic, and have, in some cases, found an actual decrease (Mattice & Weisman, 1937; Mattice, Baxt & Byrne, 1940).

Experiments are described below which were designed to compare the rates of urinary and faecal excretion of arsenic from the body after lewisite contamination in untreated animals and in animals which had received treatment with BAL. Further, since visible damage to the skin may be largely or completely prevented by treatment of the contaminated site with BAL after an interval sufficient to allow penetration of the skin by the lewisite, estimations were carried out to determine the effect produced by BAL on the amount of arsenic left in the skin 48 hr. after contamination.

Since, at the time when this work was first reported (Thompson & Stocken, 1941), no information was available concerning the biochemical effects or metabolism of dithiols in the animal body, preliminary experiments on the metabolism of BAL are also presented.

EXPERIMENTAL AND RESULTS

Excretion of arsenic after cutaneous application of lewisite to rats, and the effects of BAL treatment

Twenty-four hr. specimens of urine and faeces were obtained from rats following the cutaneous application of small amounts of lewisite, and the total quantity of arsenic excreted in these periods determined.

Adult white rats weighing from 150 to 350 g. were used throughout these experiments. A small area of skin (approx. 9 sq.cm.) was clipped free from fur with scissors. A dose of lewisite was then placed on the middle of the clipped area, and the animals either returned directly to metabolism cages, or treated with BAL after measured intervals and then placed in the cages. The BAL was dropped on to the contaminated area from a pipette and lightly spread over the clipped skin with a glass rod.

Owing to the small quantities of lewisite used in these experiments it was found necessary to place two or three rats in each metabolism cage, and to estimate the arsenic in the pooled excreta. This pooling had the additional advantage of diminishing the effects of the individual variations in the rate of excretion of arsenic that are known to exist among animals of the same species (Voegtlin & Thompson, 1922).

Arsenic was estimated by a modification of the titrimetric method of Allcroft & Green (1935), 97–100% recovery of amounts of arsenic varying from 50 to 300 μ g. being obtained with this method. The urine and faeces were each digested with a perchloric-nitric acid mixture, 93% recovery of added arsenic being obtained from urine using this digestion method, and 99% from faeces. All estimations were done in duplicate.

Table 1 shows the effect of BAL treatment on the excretion of arsenic in the urine of lewisite-contaminated rats. The untreated control rats were

contaminated with amounts equivalent to 10.0–12.7 mg./kg. body weight (i.e. approximately $0.5 \times LD_{50}$ dose); in the first 24 hr. the arsenic excreted in the urine corresponded to 2–4 % of the amount of lewisite applied to the skin.

The treated animals received an application of BAL 15 min. after contamination; in no case was any lewisite to be seen on the skin at the time of treatment. The urinary excretion of arsenic in the

from the untreated cages was in a few cases contaminated with small amounts of fluid or semi-fluid faecal matter, so that the true values obtained for the urinary excretion from the untreated animals may be slightly lower than those actually determined; estimations of the faecal excretion of arsenic, to be described later, indicate however, that the error arising from slight faecal contamination of the urine specimens would be insignificant.

Table 1. *Urinary excretion of arsenic after cutaneous application of lewisite to rats*

mg. lewisite/kg. body wt.	Total amount As applied (mg.)	Arsenic recovered in urine			
		mg./24 hr. specimen		Percentage of amount applied	
		0-24 hr.	24-48 hr.	0-24 hr.	24-48 hr.
		(1) Untreated			
11.7-12.7	4.54	0.12	0.07	2.5	1.5
10.0-10.8	2.82	0.10	—	3.5	—
10.3-10.7	3.38	0.07	0.05	2	1.5
10.2-10.9	3.31	0.14	—	4	—
10.0-10.4	2.70	0.08	0.08	3	3
(2) BAL treated (after 15 min.)					
49.5-57.0	5.40	0.78	—	14.5	—
49.2-50.8	6.49	1.55	—	24	—
45.5-50.0	4.87	0.69	0.17	14	3.5
17.4-19.6	2.16	0.44	0.08	20	4
12.9-15.0	4.54	0.50	0.10	11	2
10.9-13.1	3.49	0.38	—	11	—
10.8-11.8	3.75	0.60	—	16	—
10.0-10.4	2.27	0.29	0.10	13	4.5
(3) BAL treated (after 1 hr.)					
11.9-12.5	2.16	0.72	0.05	33.5	2.5
11.1-12.5	2.16	0.58	0.06	27	3

first 24 hr. in this group corresponded to 11–24 % of the amount applied. It will be seen (Table 1) that treatment after 15 min. caused a marked increase (approximately fourfold) in the urinary excretion of arsenic even when the same contamination (in mg. lewisite/kg. body weight) was used in the two groups of animals. Heavier contamination of the untreated rats was impossible owing to one or more of the animals dying within the first 24 hr. In the treated animals, however, contamination with more than $2 LD_{50}$ was carried out, the treatment resulting in the excretion of amounts of arsenic corresponding to 14–24 % of the amount of lewisite applied.

In a few experiments the urine was also collected throughout the second 24 hr. period after contamination, but the amount of arsenic excreted in the urine of the treated animals had fallen, although the few experiments that have been done suggest that even in the second 24 hr. excretion may be slightly higher in the treated group.

In contrast to the treated animals all the untreated rats showed varying degrees of diarrhoea, and in some cases visible amounts of mucus were passed with the faeces. For this reason the urine

Two experiments are also included in Table 1 in which BAL treatment was not begun until 1 hr. after contamination, as it was felt that although no liquid lewisite was visible on the skin after 15 min., treatment begun then might not have allowed sufficient time for the lewisite to have penetrated deeply into the skin, so that the application of BAL might have prevented the evaporation of further small amounts of lewisite from the superficial layers of the skin after 15 min. In these two experiments the urinary excretion in the first 24 hr. was even higher than in the animals treated after 15 min., amounting to 33.5 and 27 % respectively of the amount of arsenic applied to the skin. This higher excretion may be due merely to individual variations, but it is clear that treatment after an interval as long as 1 hr. also brings about a very significant increase in the renal elimination of arsenic from the system.

Large doses of BAL administered subcutaneously to rats have a diuretic effect, so that it might be argued that part of the increased excretion of arsenic in the treated animals is due to an increased urine flow; the urine volumes obtained in the above

experiments varied widely, but there was no obvious difference between the two groups of animals, so that BAL applied to the skin in the amounts used in these experiments does not appear to exert any significant diuretic action. Further, Underhill & Davis (1922) have shown that there is no relation between the amount of arsenic excreted and the volume of urine passed after administration of arspenamine or neo-arsphenamine.

In three experiments the faecal excretion of arsenic was also determined (Table 2); as BAL treatment did not significantly affect the small excretion of arsenic in the faeces, no further faecal analyses were made.

2.15 mg. As) had been injected into the animals, the recovery of 0.546 mg. in the first 48 hr. corresponds to a urinary excretion of 25 % of the arsenic applied.

Since lewisite vesication in man may be prevented by the application of BAL after erythema and oedema of the skin have already developed, it is evident that up to this stage of damage to the skin cells, BAL can reverse the toxic action of lewisite. It is of interest therefore to determine whether BAL causes any diminution in the amount of arsenic persisting in the skin. In untreated animals the visibly damaged skin, together with a surrounding ring of skin of normal appearance about 0.5 cm. in width, was therefore excised from the

Table 2. *Faecal excretion of arsenic after cutaneous application of lewisite*

	Total amount As applied (mg.)	Arsenic recovered in the faeces			
		mg./24 hr. faeces		Percentage of amount applied	
		0-24 hr.	24-48 hr.	0-24 hr.	24-48 hr.
Untreated	3.38	0.10	0.15	3	4.5
"	2.70	0.03	0.05	1	2
BAL-treated	5.40	0.04	—	0.75	—
"	2.27	0.07	0.07	3	3

One further experiment was carried out to study the excretion of arsenic after the subcutaneous injection of the lewisite-BAL compound (Stocken, 1946) into animals. Three rats, weighing 95, 97 and 106 g. respectively, each received a subcutaneous injection of 2.48 mg. lewisite-BAL compound dissolved in 0.1 ml. thiodiglycol. This amount is equivalent to 2 mg. lewisite, so that each rat received an amount of the compound, the lewisite equivalent of which was equal to 4 LD₅₀ doses (based on the Porton figure for the LD₅₀ dose for lewisite, viz. 5 mg./kg. body weight when administered subcutaneously in rats).

The rats were placed in one metabolism cage, and the pooled urine collected over the next three 24 hr. periods, and analyzed for arsenic. In the first two 24 hr. periods 0.504 and 0.042 mg. As respectively were excreted by the three rats. On the third day no arsenic could be detected in the urine. Since in all, 7.44 mg. lewisite-BAL compound (equivalent to

killed animal 48 hr. after contamination. In the case of the BAL-treated rats, visible trauma to the skin was in all cases much less, in some animals only slight puckering of the skin marking the site of contamination. From these animals an area of skin approximately equal in size to the pieces removed from the untreated animals was excised. The scars from the three (or two) animals in any experiment were digested together, and the arsenic estimated in the digest as in the excretion experiments, 94 % recovery of added lewisite to normal skin being obtained by this method. The results of these experiments are shown in Table 3.

With small doses of lewisite (9.4-12.5 mg./kg. body weight), the actual amount of arsenic left in the skin of the untreated animals 48 hr. after contamination is in all cases greater than in the treated animals. In one experiment (no. 354) the treated animals received 45-50 mg. lewisite/kg. body weight, yet even with this large dose the amount of arsenic

Table 3. *Effect of BAL treatment on the amount of arsenic remaining in the scar after 48 hr.*

Exp.	No. of rats	mg. lewisite/kg. body wt.	As applied (mg.)	As found (mg.)	Percentage of amount applied
450 Untreated	3	10.3-10.7	3.38	0.24	7.1
452 "	3	10.0-10.4	2.70	0.12	4.4
456 "	2	9.4-10.6	1.73	0.18	10.4
463 "	3	10.4-10.9	1.73	0.14	8.1
464 "	2	10.7-10.8	1.30	0.13	10.0
354 BAL-treated	3	45.5-50.0	4.87	0.12	2.5
452 "	3	10.0-10.4	2.27	0.06	2.6
456 "	3	10.8-11.2	2.27	0.04	1.8
461 "	3	11.9-12.5	2.16	0.09	4.2
462 "	3	11.1-12.5	2.16	0.045	2.1

present in the skin after 48 hr. was less than the amount present in four out of five of the untreated groups that had received only one-fifth of this dose of lewisite. In Exps. 354, 452 and 456 BAL treatment was begun 15 min. after contamination, in Exps. 461 and 462 1 hr. after contamination. Expressed as percentages of the amounts of arsenic applied to the skin (as lewisite) the difference between the two groups of animals becomes even more striking.

The metabolism of BAL

In the early treatment of lewisite contamination of the skin with BAL, present experience suggests that one application of the drug should suffice, so that the toxic action of large amounts of the compound should not be a complicating factor except in those cases where heavy contamination with lethal amounts of lewisite has occurred. It is possible however that BAL, or some related dithiol, may have an application in the late treatment of lewisite casualties at a time when symptoms of systemic arsenical poisoning are developing; in such cases it might be desirable to keep a low concentration of the drug in the blood for some time, along the lines of therapy with members of the sulphonamide group. In this connexion it was desirable to gain information concerning the length of time that BAL will persist inside the body.

An attempt was therefore made to follow the rate of excretion of BAL, or of a derivative of BAL or some compensatory thiol in the urine by iodine titration. Using rats, the normal daily excretion of thiols and of non-thiol substances titrating with iodine was found to fall within sufficiently narrow limits for the purpose of these experiments.

The procedure adopted was to place the rats in metabolism cages and to follow the excretion of thiols over a period of a few days, the 24 hr. urine samples being separated from faeces and food residues by means of glass separators. After establishing the normal thiol excretion rate, sub-lethal doses of BAL dissolved in thiodiglycol were then administered to the rats by subcutaneous injection, and the animals returned to the cages for the collection of further urine samples. The thiol content of the 24 hr. specimens of urine was estimated by titration with 0.02N or 0.01N-iodine. In order to obtain a satisfactory end-point it was found necessary to carry out the titration in strongly acid solution; 1 ml. of 25% (w/v) trichloroacetic acid was therefore added to each 5 ml. sample of urine. In the later experiments, 1 ml. of N-HCl was placed in the urine separator before beginning to collect each sample, in the hope of diminishing the loss of thiol by oxidation by air during the 24 hr. period; this was found however to have little effect on the amount of titratable thiol present.

The result of a typical experiment is shown in Table 4. It will be seen from these results that there is a marked rise in the iodine titre of the 24 hr. urine specimen following injection of BAL over the mean pre-injection level. Expressed in terms of BAL, the increases in the various experiments

Table 4. *Urinary excretion of thiols after injection of BAL into rats*

(Three rats, weighing 76, 81 and 112 g. resp.; 24 hr. specimens of urine collected for 22 days; 10 mg. BAL dissolved in thiodiglycol injected subcutaneously into each after 4, 14 and 17 days.)

Days	Vol. 24 hr. urine (ml.)	Vol. 0.02N-iodine/24 hr. specimen (ml.)	
1	17.0	0.54	Mean = 0.29
2	11.8	0.28	
3	10.6	0.17	
4	9.4	0.15	
BAL injected			
5	19.2	4.76	Mean = 0.43
6	15.0	0.56	
7	5.4	0.28	
8	12.5	0.81	
9	12.0	0.48	
10	9.6	0.29	
11	12.8	0.44	
12	10.5	0.46	
13	12.0	0.36	Mean = 0.54
14	7.0	0.20	
BAL injected			
15	20.0	3.66	
16	11.4	0.55	Mean = 0.49
17	11.6	0.53	
BAL injected			
18	27.5	4.73	Mean = 0.49
19	12.2	0.73	
20	10.6	0.49	
21	7.0	0.35	
22	13.0	0.39	

amount to 6.2, 4.95, 5.55, 4.0, 5.2, 1.59 and 4.58 mg. BAL corresponding to the excretion during the 24 hr. following injection of 21, 16.5, 18.5, 13, 17, 5 and 13% respectively of the amount of BAL injected.

The pre-injection samples of urine gave a negative nitroprusside reaction for thiol groups, the reaction remaining negative even after treatment with KCN to reduce any disulphide groups present. The 24 hr. specimen obtained following the injection of BAL gave in every case a strongly positive reaction for thiols. It cannot be claimed from these experiments that the rise in the iodine titre of the urine, following the injection of BAL, is due entirely to the excretion of thiols, but the strongly positive nitroprusside reaction given by the post-injection urine samples indicates that thiols are being excreted in markedly increased amounts. On account of the

small volume of urine obtained, no attempt was made in these experiments to identify the nature of the thiol excreted.

A further point of interest that emerges from these experiments is the rapidity with which the disturbance of thiol-disulphide equilibrium in the body produced by the injection of BAL is restored to normal; in every case except one, the thiol excretion had fallen to within the normal range 24 hr. after the injection. Moreover in two of the experiments the animals received repeated injections. The short duration of the metabolic disturbance produced by BAL is in agreement with the rapid return to normal in the general condition of the animals. It must be stressed that the dose injected into these animals was large, varying from 83–132 mg. BAL/kg. body weight, corresponding roughly to the subcutaneous injection of 7 g. of BAL into a 70 kg. man.

A few experiments were also carried out with male rabbits, the urine being obtained by catheterization. The rabbits were first catheterized, using a No. 3 soft rubber catheter, and the bladder emptied. A sub-lethal dose of BAL was then injected intraperitoneally, and the bladder contents drawn off at intervals thereafter. As in the previous experiments the urine samples were titrated with 0.02N or 0.01N-iodine; they were also tested for the presence of albumin and for —SH by the nitroprusside reaction. The results of three experiments are shown in Table 5. In rabbits also there is a rapid rise in the iodine titre of the urine following injection of BAL, a substantial increase occurring during the first hour. It will be noted that the thiol

excretion begins to fall again after 3–4 hr. Expressed in terms of BAL, and assuming that the pre-injection level of iodine-titrating substances other than BAL is maintained constant, a total of 10.33, 8.82 and 9.48 mg. BAL were excreted in 6 hr. in these three experiments, corresponding to 14, 13.5 and 12 % respectively of the amount injected. A control experiment was carried out to determine whether the injection of thiodiglycol alone influenced the excretion of thiols in the urine; it was found that the intraperitoneal injection of 0.2 ml. affected neither the iodine titre nor the nitroprusside reaction of the urine.

In each experiment the injection of BAL resulted in a transient albuminuria. In Exp. 390 a trace of albumin was present in the pre-injection specimen; this was probably brought about by struggling. The short duration of the albuminuria in these animals suggests that it is more the result of the vaso-dilator action of BAL on the renal vessels rather than the result of any serious damage to the glomeruli. In Exp. 409 the specimen obtained 1½ hr. after the injection was turbid and of a reddish brown colour; on centrifuging a clear, pale yellow supernatant was obtained, which contained a considerable quantity of albumin. The deposit was resuspended in 0.9 % NaCl, examined microscopically and identified as red blood cells of normal appearance. No clots were present in the specimen, and from its homogeneous appearance it was felt that the blood was renal in origin and not due to trauma to the urethra or bladder. It would appear therefore that although the injection of BAL resulted in glomerular vaso-dilatation to such an

Table 5. *Urinary excretion of thiols after injection of BAL into rabbits*

Sample	Vol. urine (ml.)	Vol. 0.02N- I ₂ /10 ml. urine (ml.)	Vol. 0.02N- I ₂ /whole specimen (ml.)	Mean rate/ hr. (ml. 0.02N-I ₂)	Nitroprusside	Albumin
Exp. 390. Wt. rabbit = 2905 g. 11.0 a.m. catheterized; bladder emptied. 11.20 a.m. 75 mg. BAL (=26 mg./kg. body wt.) injected intraperitoneally. Catheterized again at 12.20, 2.20 and 5.20 p.m.						
Pre-injection	7.2	0.66	0.475	—	—	Trace
1 hr. after BAL	2.5	27.5	6.87	6.87	++++	+
3 hr. after BAL	8.3	11.1	9.2	4.6	++++	+
6 hr. after BAL	25.2	1.2	3.02	1.01	++	Trace
Exp. 409. Wt. rabbit = 1752 g. 10.40 a.m. catheterized; bladder emptied. 10.45 a.m. 65 mg. BAL (=37 mg./kg. body wt.) injected intraperitoneally. Catheterized again at 12.15, 1.45, 3.15 and 4.45 p.m.						
Pre-injection	11.2	0.56	0.63	—	—	—
1½ hr. after BAL	3.5	7.8	2.73	1.82	+++	+ + (+ cells)
2 hr. after BAL	3.4	21.6	7.35	4.9	+++	Trace
4½ hr. after BAL	3.0	9.1	2.73	1.82	+++	—
6 hr. after BAL	5.5	4.1	2.26	1.51	++	—
Exp. 413. Wt. rabbit = 2129 g. 10.40 a.m. catheterized; bladder emptied. 10.45 a.m. 80 mg. BAL (=38 mg./kg. body wt.) injected intraperitoneally. Catheterized again at 12.15, 2.45 and 4.45 p.m.						
Pre-injection	4.6	1.0	0.46	—	—	—
1½ hr. after BAL	7.0	10.25	7.18	4.78	++++	Trace
4 hr. after BAL	4.0	18.60	7.44	2.97	++++	+
6 hr. after BAL	4.0	5.4	2.16	1.08	++	Trace

extent as to allow the passage of considerable quantities of protein, and possibly also of red blood cells, into the glomerular filtrate, it did not cause any detectable haemolysis.

DISCUSSION

The experiments described here show that the BAL treatment of lewisite burns in rats is followed by a marked increase in the elimination of arsenic in the urine during the succeeding 24 hr.; this increased excretion of arsenic is observed even when treatment with BAL is not begun until 1 hr. after contamination. The faecal excretion of arsenic does not appear to be significantly influenced by BAL. The severe diarrhoea invariably present in the control animals, however, was completely prevented by BAL treatment.

Analyses of the excised, contaminated skin showed that treatment with BAL causes a reduction in the amount of arsenic present in the skin 48 hr. after contamination. This finding is in agreement with the ability of BAL to prevent vesication in man after penetration of the skin by the lewisite.

No attempt was made at the time of this work to isolate or identify the derivative of lewisite excreted in the urine. It should be noted however that the subcutaneous injection into rats of the lewisite-BAL compound, prepared *in vitro*, is also followed by the urinary excretion of a large quantity of arsenic.

The disturbance of thiol-disulphide equilibrium caused by the subcutaneous injection of large amounts of BAL into rats or rabbits is rapidly readjusted by the excretion in the urine of an unidentified thiol. Although in rabbits a transient albuminuria accompanies the excretion of this thiol no evidence has been obtained of any serious or permanent functional damage to the kidney. A

brief preliminary review of this work has already appeared (Peters, Stocken & Thompson, 1945).

SUMMARY

1. Experiments are described showing that the treatment of lewisite burns in rats by 2:3-dimercaptopropanol (British Anti-lewisite, BAL) is followed by a marked increase in the urinary excretion of arsenic during the succeeding 24 hr., amounts up to 33% of the arsenic applied to the skin (as lewisite) being recovered in the 24 hr. urine sample.

2. This increased excretion of arsenic is observed even when treatment with BAL is not begun until 1 hr. after contamination.

3. The severe diarrhoea and passage of mucus shown by control animals were completely prevented by BAL treatment.

4. Treatment with BAL caused a diminution in the amount of arsenic left in the skin 48 hr. after contamination.

5. The subcutaneous or intraperitoneal injection of large amounts of BAL into rats or rabbits is rapidly followed by the excretion of an unidentified thiol (or thiols) in the urine. In rabbits the thiol excretion after a single dose of BAL begins to fall off after 3-4 hr., but is still above the pre-injection level after 6 hr.

6. In rabbits a transient albuminuria accompanies the excretion of this thiol, but no evidence has been obtained of any serious or permanent functional damage to the kidney.

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