differences in the 3-hour concentration of P^{32} from levels seen in the control animals. 4. The deleterious effects of thyroidectomy in the young animals with a high rate of tissue phosphate utilization was evidenced by the sharply decreased P^{32} concentration in the organs of those animals. Explanation for the markedly increased I^{131} concentrations in pituitary and adrenal of young and adult thyroidectomized animals is not readily apparent.

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Dithiol Antagonism and Potentiation of Chemotherapeutic Agents. (19038)

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Ehrlich(1) formulated the hypothesis that arsenicals act on pathogenic microorganisms through receptors formed by "conjugated" -SH or -OH groups.† Since then the participation of -SH groups in the mechanism of chemotherapeutic action has been widely studied, particularly after Voegtlin, Dyer and Leonard(2) demonstrated the antagonistic action of monothiols on arsenicals. The literature on this subject and the more recent conception that arsenicals act as thiol-enzyme inhibitors, has been reviewed by Findlay(3), Barron(4), Waters and Stock(5), Peters(6), Stocken and Thompson(7). The last 3 authors were "led . . . to the realization that the more stable form of arsenic with the enzyme must be a ring form in which two sulphur atoms are combined with one arsenic, as follows: $\left.\begin{matrix} R\text{—}S \\ \\ R\text{—}S \end{matrix}\right\} > As\text{—}$"(6). This idea was confirmed in the successful use of dimercaptopropanol (BAL) as an antidote in lewisite, and more generally, in metal poisoning. We reported(8) that BAL interferes to a much greater extent with the therapeutic action of arsenoxide against *T. equiperdum* than with its toxic effect on the host.‡ The intensive reversal of the therapeutic effect could not be explained alone with the formation of an arsenoxo-BAL compound, since this compound, prepared and studied in various laboratories, maintains a definite therapeutic activity and toxicity(9-12). Searching for an explanation, we assumed that BAL determines the reversal of the therapeutic effect by acting

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1. Ehrlich, P., *Ber. dtsche Chem. Ges.*, 1909, v42, 17.

† Ehrlich was referring explicitly to the dithiol function: "dass vielleicht solche orthoständigen Hydroxyloder Sulphhydrylgruppen durch geeignete Bedingungen befähigt sein können, als Metallreceptoren zu fungieren". Note the analogy with the expression used by modern biochemists (Stocken and Thompson, *Biochem. J.*, 1946, v40, 529): "it seems probable that the arsenic has combined with two -SH groups closely placed in space on the same molecule, to form a ring".

2. Voegtlin, C., Dyer, H. A., and Leonard, C. S., *J. Pharmacol.*, 1925, v25, 297.

3. Findlay, G. M. *Recent advances in chemotherapy*, Vol. I. Churchill, London, 1950.

4. Barron, G. E. S., *Advances in Enzymology*, 1951, v11, 201. Interscience, New York.

5. Waters, L. L., and Stock, Ch., *Science*, 1945, v102, 601.

6. Peters, R. A., *Symp. Soc. Exp. Biol.* III. 36, Cambridge University Press, 1949.

7. Stocken, L. A., and Thompson, R. H. S., *Physiol. Rev.*, 1949, v29, 168.

8. Ercoli, N., and Wilson, W., *J. Pharmacol.*, 1948, v92, 121.

‡ This finds a certain analogy in observations made by Voegtlin on monothiols: "it is more difficult to counteract the toxic effect of As in the higher animals than that exerted on protozoa"(2).

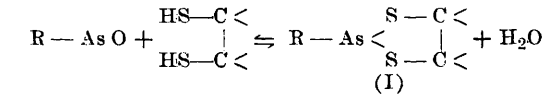
9. Peters, R. A., and Stocken, L. A., *Bioch. J.*, 1947, v41, 53.

10. Friedheim, E. A. H., and Vogel, H. J., PROC. SOC. EXP. BIOL. AND MED., 1947, v64, 418.

11. Friedheim, E. A. H., and Berman, R. L., PROC. SOC. EXP. BIOL. AND MED., 1947, v65, 180.

12. Sawyers, J. L., Burrows, B., and Maren, H. T., PROC. SOC. EXP. BIOL. AND MED., 1949, v70, 194.

directly on the parasite, thus interfering with the chemotherapeutic process itself, and consequently other drugs than the metal containing ones might be also reversed by the dithiol. We speculated that the antagonistic effect of BAL in the case of arsenicals might have two phases: (a) the dithiol intervenes in the "protection" of the -SH groups of the parasite; (b) it forms an As-BAL compound according to the equilibrium



(I)

In the presence of a sufficient excess of dithiol, the "BAL-OXO" compound (I) is stable enough to acquire different characteristics of penetration, fixation and elimination than the original arsenoxide. In fact, according to Peters and Stocken(9) the BAL-OXO compound itself is more toxic for the host than the original arsenical, but it becomes detoxified by additional BAL. According to Eagle and coworkers(13,14) BAL treatment increases noticeably the elimination of the arsenical from the host organism and this is undoubtedly one of the principal mechanisms responsible for detoxification. However, we considered it possible that as far as the antiparasitic effect is concerned, this formation of dithio-arsenate is only an additional factor contributing to the process of antagonism, while the main underlying phenomenon is the "protection" given by BAL to the -SH groups considered involved in the chemotherapeutic mechanism. This direct "protection" of the parasite, whatever its mechanism may be (competitive replacement of -SH groups, or else) should determine an antagonistic effect also in cases where the formation of a compound between therapeutic agent and BAL would not easily occur. This assumption implied that the mechanism of the BAL antagonism is not necessarily of the same nature for the host and for the parasite. Following this hypothesis, we investigated during the years 1948-1951 the influence of the mono- and dithiol functions on the majority of the therapeutic agents in use, in different types of experimental infections.

TABLE I. Effect of BAL on Therapeutic Activity of Fuadin in the *Tr. equiperdum* Infection of Mice.

Fuadin, mg/kg	BAL, mg/kg	No. of mice Cleared	No. of mice Cured
8	0	4/10	0/10
8	50	0/5	
16	0	8/10	3/10
16	1.5	1/5	0/5
16	6.25	0/5	
16	25	0/5	
16	2 x 50	0/5	
32	0	15/15*	5/15
32	12.5	5/5†	0/5
32	2 x 50	0/5	

* Within 3 hr.
† " 24 ".

Methods. The technics used to obtain the *T. equiperdum*(8), *Borrelia novyi*(15) and *duttoni*(16), *Streptococcus hemolyticus* and *E. coli*(17) infections of mice were described. The minimal effective and average curative doses have been precisely determined both in the protozoan(16) and bacterial infections (17). Dermal syphilis of the rabbit was induced by injecting intradermally 0.25 cc of a testicular suspension containing 5 *Tr. pallidum* per dark field: lesions developed within 14 to 21 days. The influence of BAL on the chemotherapeutic action has been established as follows: (a) in protozoan infections, by the influence of various BAL doses on the effectiveness of active dosages of the drug on the parasitemia following treatment and the rate of cure; (b) in bacterial infections, by the mortality rate change induced by BAL on protective (CD_{50} and CD_{90}) drug doses. From all dead animals heart cultures were made, and the bacteriological findings were considered in interpreting the results. BAL was injected subcutaneously in oil at the same time when therapeutic treatment was given; if a second injection of BAL was made, this was done

13. Eagle, H., Magnuson, H. J., and Fleischman, R., *J. Clin. Invest.*, 1946, v25, 451.

14. Wexler, J., Eagle, H., Tatum, H. J., Magnuson, H. J. and Watson, E. B., *J. Clin. Invest.*, 1946, v25, 467.

15. Ercoli, N., and Lafferty, L. C., PROC. SOC. EXP. BIOL. AND MED., 1944, v57, 4.

16. Carminati, G. M., and Ercoli, N., *Boll. Ist. Sieroter. Milanese,* 1951, v30, 97.

17. Carminati, G. M., *Boll. Ist. Sieroter. Milanese,* 1951, v30, 349.

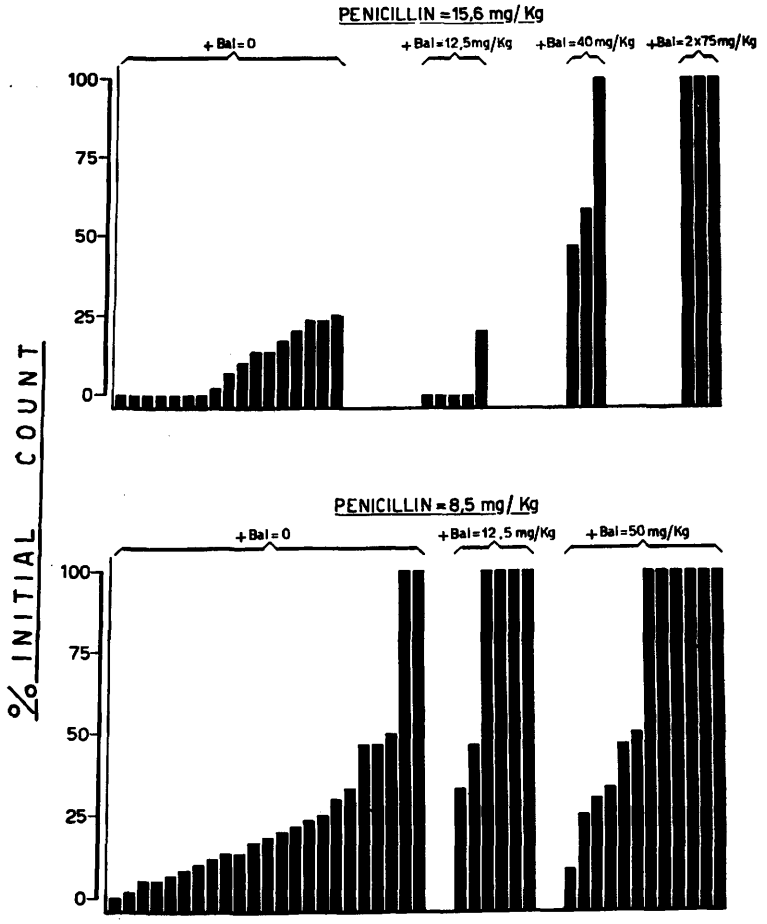


FIG. 1. Antagonistic effect of BAL on therapeutic activity of penicillin in *B. novyi* infection. (Each column represents one mouse.)

after 2 to 4 hours, the approximate duration of the dithiol effect. If not stated otherwise, drugs were administered subcutaneously. Freshly opened ampuls of oily BAL solutions, diluted as required, in oil, just before treatment are recommended.

Results. 1. *Trypanosoma equiperdum infection.* Therapeutic doses of Acriflavine (2.8 diamino-acridinium-10-metho-chloride) (4 x 25 mg/kg), Stilbamidine (4,4-diamidinostilbene) (25 mg/kg), and Naphuride (Trisodium salt of 8,8′ [3″,3‴ -ureylenebis(3‴-bensamido-4‴ methylbensamido)] bis 1,3,5-naphthalene-trisulfonic acid) (16.5 mg/kg) were not influenced in their effectiveness by BAL doses as high as 2x50 mg/kg. Fuadin (Antimony-pyrochatecol-sodium disulfonate) doses which cause disappearance of the trypanosomes within 24 hours, without permanent cure, (8-16 mg/kg) have been inhibited by 6.0, and occasionally by 1.5 mg/kg BAL. A higher Fuadin dose, 32 mg/kg, which causes complete disappearance of the parasites within 3 hours and sterilizes 30% of the mice, has been completely inhibited by 2 x 50 mg/kg BAL. With lower BAL doses, 12.5 mg/kg, the disappearance of the parasites was delayed from 3 to 20 hours and the survival period was shortened from 18 to 10 days. In general, Fuadin reacted to BAL in a manner similar to that reported for oxophenarsine(8); with a progressive increase of the BAL dosage the curative effect decreased, as revealed by the length of the relapse period and the percentage of relapsing animals (Table I).

2. *Borrelia novyi and duttoni infections.*

TABLE II. Influence of BAL and Glutathione on Therapeutic Activity of Penicillin G (50 mg/kg) in *B. duttoni* Infection.

Treatment	No. spirochetes/100 dark fields after				
	Before	2½ hr	4½ hr	21 hr	42 hr
Penicillin alone	300	12	0	4	0
	450	4	0	2	0
	260	8	0	4	0
	300	0	0	2	0
Penicillin + BAL, 62.5 mg/kg	300	350	100	80	800
	200	400	170	100	1000
	150	350	100	60	550
	200	500	180	100	1000
Penicillin + glutathione, 150 mg/kg	200	2	0	0	0
	270	4	0	0	0
	200	0	0	0	0
	170	4	0	0	0

TABLE III. BAL Antagonism of Bacitracin in *B. duttoni* Infection of Mice.

Bacitracin, mg/kg	BAL, mg/kg	No. spirochetes/100 dark fields after				
		Before	3 hr	6 hr	24 hr	48 hr
3	0	200	72	0	400	
		170	48	0	30	
		200	32	12	50	
3	50	200	200	600	2000	
		200	180	400	1200	
		200	216	200	1500	
10	0	300	8		8	100
		80	0		0	40
		250	0		0	100
		350	0		0	0
10	2 × 50	200	100		600	3000
		200	130		1300	2000
		180	45		1000	500
		300	100		32	3000
20	0	250	0		0	0
		280	0		0	0
20	2 × 50	150	80		50	1000
		300	350		400	1500

BAL had no influence on therapeutic doses of streptomycin (75-160 mg/kg), aureomycin (2-8 mg/kg) and terramycin (4-10 mg/kg). BAL doses of 4-8 mg/kg inhibited completely the clearing effect of 10 mg/kg oxophenarsine. Penicillin was completely or partially inhibited§ according to the penicillin/BAL dose relationship. The effect of a penicillin dose (30-50 mg/kg) which results in a rapid (2-3 hours) disappearance of the spirochetes has been practically destroyed by a single dose of 50-65 mg/kg BAL. Typical experiments showing the reversal of the antispirochetal action of penicillin by BAL are presented in Fig. 1 (*B. novyi*) and Table II (*B. duttoni*). The inhibition of the therapeutic action could not be obtained if BAL treatment was delayed by 2 hours or more. Multiples (20-50 mg/kg) of the therapeutic bacitracin dose (7-13 mg/kg) were completely inhibited by BAL as shown in the experiment presented in Table III. Chloromycetin doses above the minimal effective one (35 mg/kg) up to 80 mg/kg were inhibited by a single dose of 60 mg/kg BAL (Table IV). Higher doses of chloromycetin (100-150 mg/kg) were not influenced by 2 x 40 or 50 mg/kg BAL. With penicillin and bacitracin the BAL reversal was very regular and the doses required were the same in the *B. novyi* and *duttoni* infections (used respectively in the American laboratory and abroad) at the point that we

§ This observation was reported by Ercoli, Whitehead and Schwarz at the 48th Gen. Meeting Soc. Am. Bact., Minneapolis, Minn., 1948.

TABLE IV. BAL Antagonism of Chloromycetin in *B. duttoni* Infection of Mice.

Date	Chloromycetin, mg/kg	BAL, mg/kg	No. spirochetes/100 dark fields after — Before	3 hr	21 hr	44 hr
XII/20/50	30	0	300	32	12	—
			500	12	0	—
	30	2 × 60	500	300	72	—
	,,	,,	900	790	800	—
I/3/51	45	0	300	4	12	0
			500	20	0	300
			400	8	32	200
			400	12	8	500
			200	40	80	80
	45	75	800	1500	1000	2000
			600	1800	2500	2200
			400	600	200	2000
			600	600	1000	5000
			700	500	1200	2000
XI/27/50	70	0	300	0	0	0
			300	0	0	0
			400	0	24	0
	70	60	300	4	80	100
			500	48	30	80
			200	32	60	200
X/30/50	80	0	200	0	0	0
			400	0	0	0
	80	2 × 60	400	32	8	1500
			300	200	16	100

TABLE V. BAL Potentiation of Subtilin in *B. duttoni* Infection of Mice.
(Exp. 70/E–III/3/51.)

Subtilin, mg/kg	BAL, mg/kg	No. spirochetes/100 dark fields after — Before	3 hr	20 hr	30 hr	48 hr
Controls		400	600	1000	1400	1800
		500	800	1200	1600	2000
8	0	200	72	12	48	200
		300	100	60	300	800
		150	60	100	100	19
		300	100	800	800	1000
		200	22	300	400	600
8	50	300	0	72	8	1500
		300	0	64	24	600
		400	0	8	20	500
		300	0	4	12	200
		400	8	0	4	800
16	0	300	32	200	40	500
		400	200	500	1000	2300
		300	100	400	80	200
		400	0	300	40	10
		300	40	500	1200	2000
16	50	1500	4	0	0	0
		400	0	0	0	0
		300	0	0	0	0
		300	0	0	4	0
		400	0	0	0	0

have used this phenomenon for a rapid titration of BAL preparations; with chloromycetin the reversal did not reach the same degree of regularity. In contrast to the effect of BAL on the antispirochetal activity of the above antibiotics, subtilin (8-16 mg/kg) in some experiments was potentiated not only by the dithiol, but also by monothiol cysteine (150 mg/kg). However, for reasons which we cannot explain, the response of subtilin to

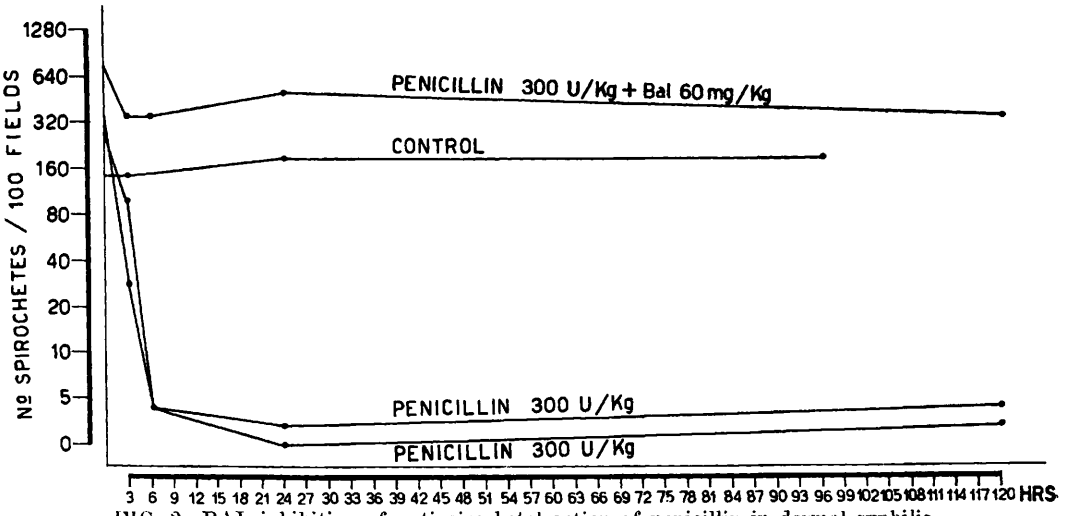


FIG. 2. BAL inhibition of antispirochetal action of penicillin in dermal syphilis.

the thiols is not constant. So far, potentiation with cysteine and BAL has been obtained in 2 out of 6 experiments while in the other 4 experiments the effect of subtilin has not been influenced by the thiols. One of the 2 practically identical experiments in which the subtilin potentiation appeared is presented in Table V. Cysteine had no effect on the antibiotic inhibited by BAL: in doses of 150 mg/kg it did not influence the activity of bacitracin, chloromycetin (and aureomycin); cysteine and glutathione doses as high as 500 mg/kg were without any effect on the therapeutic activity of penicillin (8-32 mg/kg). Cysteine doses of 150 mg/kg did not influence the therapeutic activity of 5 mg/kg oxophenarsine hydrochloride; but the same dose had a slight effect on a lower dose of arsenical: 2 out of 5 mice treated with 2.5 mg/kg oxophenarsine + cysteine were not cleared, while in the control groups this dose of arsenical gives in all cases complete (or 90%) reduction of the spirochetes within 24 hours. The therapeutic effect of gold thiomalate (Myochrysin)—which in doses of 25 mg/kg clears the blood stream within 24 hours and in doses of 75 mg/kg is curative—has been completely inhibited by 2 x 60 mg/kg BAL.

3. *Dermal syphilis of rabbit.* We controlled on *Tr. pallidum* the results obtained with penicillin in relapsing fever infections. Fig. 2 shows that in this infection too the therapeutic action of penicillin is reversed by BAL.

4. *Streptococcal infection.* The average protective dose of penicillin, 1-1.3 mg/kg (*i.e.* about 1/20th of the clearing dose in Borrelia infections) was not inhibited by BAL doses as high as 2 x 60 mg/kg. The average protective doses of the other antibiotics tested, namely subtilin (1.25-2.5 mg/kg), aureomycin (10 mg/kg), bacitracin (6 x 20 or single doses of 60-120 mg/kg), chloromycetin (150 mg/kg), streptomycin (140 mg/kg), terramycin (10 mg/kg) remained unaffected even by the highest tolerated BAL doses. The only anti-streptococcal agent inhibited by BAL is Myochrysin (Table VI). The doses required to inhibit the effect of 50-75 mg/kg Myochrysin is 50 mg/kg BAL, while a dose of 100 mg/kg requires for inhibition 2 treatments with 50 mg/kg BAL.

5. *E. coli infection.* BAL had no effect on streptomycin (6-40 mg/kg) terramycin (12-20 mg/kg), chloromycetin (160-230 mg/kg) and sulfadiazine (10-20 mg/kg). Aureomycin (30-40 mg/kg) given simultaneously with BAL (2 x 40 or 60 mg/kg) gave a larger number of deaths. This was found to be due to a combined toxic effect, and not to a decrease of therapeutic action: there was no difference in effectiveness between the series with and without BAL, when the animals which died with negative heart cultures were taken into account.

The effect of penicillin in this infection was significantly potentiated by BAL. In the

TABLE VI. Effect of BAL on Therapeutic Activity of Myochrysin in *Str. hem.* Infection of Mice.

Myochrysin, mg/kg	BAL, mg/kg	No. mice	% survivors
50–75	0	20	85
50–75	50–60	20	15
100	0	50	72
100	2 × 30	10	60
100	50–60	30	60
100	2 × 50	20	5

TABLE VII. Influence of BAL on Therapeutic Activity of Penicillin in *E. coli* Infection.

Penicillin, mg/kg	BAL, mg/kg	Alive/total mice	% survivors + sterilized
100	0	0/10	0
100	2 × 50	4/10	40
150–160	0	9/25	36
150–160	2 × 40–50	14/25	56
200	0	18/50	36
200	2 × 50 or 1 × 60	28/60*	66.6

* + 12 mice died with negative heart cultures.

TABLE VIII. Influence of BAL on Blood Levels of Mice Treated with 100 mg/kg Penicillin (Subcutaneously).

Date	BAL, mg/kg	μ/cc* ... hr after treatment 1½	3½	5½
V/23/51	0	7.9	.062	0
	62.5	69.5	.5	.031
V/28/51	0	3.9	.062	0
	40	16	.125	.062

* Average of 4 determinations.

group of mice treated with penicillin alone (100-200 mg/kg) 31.7% survived (27/85), in the BAL group 48.4% (46/95). However, in the BAL group 12 animals died with negative heart cultures, which brings the number of the sterilized animals to 61% (58/95). Thus, in spite a certain incidence of combined toxic effect, the survival rate was higher in the BAL treated series and the percentage of sterilized animals was about double (Table VII).

6. *In vitro experiments.* We considered it possible that the BAL potentiation of penicillin in the *E. coli* infection depends on a "pharmacological" and not on a "chemotherapeutic" mechanism. Therefore we decided to examine *in vitro* the antibacterial action of the blood of mice treated at high penicillin dose ranges, as required in the *E. coli* infection. We selected for these experiments *Strept. hem.* C203, an organism which by itself maintains its penicillin sensitivity under BAL treatment. Using the technic recommended by Rammelkamp(18), we found that the antibacterial action of the blood of mice treated with high penicillin dosages is increased by BAL treatment, both, as initial peak and duration of detectable blood concentration (Table VIII). This finding adds to the significance of the antagonism noted in the spirochetal infections: the therapeutic effect is inhibited in spite of the higher penicillin blood levels which may follow BAL treatment. This retention of penicillin is perhaps in relation to the antidiuretic and antichlorouretic effect of BAL reported by Earle and Berliner (19), and probably with the accumulation of the thiol in the kidney, as described for the radioactive material by Peters *et al.*(20).

Discussion. Summarizing our experimental results (Table IX), the known antiprotozoan agents can be divided in 2 classes according whether they are inhibited by BAL or not. *BAL reversible* are: the metal containing compounds (As, Au, Sb), penicillin, bacitracin and chloromycetin; *non BAL reversible* remain: streptomycin, aureomycin, terramycin, naphuride, stilbamidine, acriflavine. Subtilin in most cases was not affected, but occasionally was potentiated both by cysteine and BAL. It should be acceptable that a common inhibitor of the same physiological (antispirochetal) effect depends on an identical mechanism, or receptor system. Thus, such widely different chemical structures as metallic compounds, penicillin, bacitracin (a polypeptide) and chloramphenicol would have a similar antispirochetal mechanism. This inhibiting effect of the dithiol is specific under various aspects. First, the monothiols (cysteine and glutathione) do not possess the

18. Rammelkamp, C. H., PROC. SOC. EXP. BIOL. AND MED., 1942, v51, 95.

19. Earle, D. P., and Berliner, R. W., *Am. J. Physiol.*, 1947, v151, 215.

20. Peters, R. A., Spray, G. H., Stocken, L. A., Collie, C. H., Grace, M. A., and Wheatley, G. A., *Biochem. J.*, 1947, v41, 370.

TABLE IX. Effect of Mono and Dithiols on *in vivo* Activity of Chemotherapeutic Agents.

Drug	Effect of BAL on activity in . . . infection			
	Spirochetal	Trypanosomal	*E. coli*	*Strept. haem.*
Arsenoxide	Antagonized*	Antagonized		
Fuadin		,, ‖		
Acriflavine		None		
Stilbamidine		,,		
Naphuride		,,		
Bacitracin	,, †			None†
Penicillin	,, ‡		Potentiated	,, †
Chloromycetin	,, †		None	,,
Subtilin	Occasional potentiation§			None†
Aureomycin	None†		,,	,, †
Terramycin	,,		,,	,,
Streptomycin	,,		,,	,,
Sulfadiazine			,,	,,
Myochrysine	Antagonized			Antagonized

* Cysteine: very slight antagonism. † Cysteine had no effect. ‡ Cysteine and glutathione had no effect. § Same effect with cysteine. ‖ Toxicity for the host increased.

antagonistic activity of BAL. A similar specificity of the reversing effect of the dithiol has been reported for a number of enzymatic inhibitors: the inactivation of pyruvate oxidase by lewisite(21) and by therapeutic arsenicals (22) is reversed by BAL and not by monothiols. In the case of invertase inhibition by $HgCl_2$, BAL reverses, while cysteine even potentiates the effect of $HgCl_2$(23). This analogy of specificity suggests that an enzyme system of similar behavior ("dithiol enzyme") might be involved in the chemism of the therapeutic action of the *BAL-reversible* drugs. However, in view of the extremely complex and multiple participation of thiol functions in biological systems(4) and of the fact that BAL has other chemical properties (strong reducing agent), we do not feel authorized to express on the basis of the present experimental material a definite opinion on the intimate nature of this mechanism. We do feel though that our observations can be utilized as a base to explore with the methods of modern biochemistry and enzymology the mechanism involved in the antiprotozoan (antispirochetal) action of these drugs.

Another manifestation of specificity of the dithiol antagonism is that the drugs inhibited in the spirochetal infection are not affected by BAL in the bacterial infections. This proves that a chemical inactivation (of the drug by BAL) is not at play; otherwise the small—1 mg/kg—penicillin doses used in the coccal infection would have been totally inhibited.

At higher penicillin dose ranges it was found that BAL—probably due to a competitive renal elimination—increases the blood level and therefore the antagonism is higher than it appears considering the dose of penicillin injected. In fact, the increased penicillin levels cause the impression of a potentiation in the *E. coli* infection.

The lack of antagonistic effect of BAL in the bacterial infections proves that the therapeutic mechanisms responsible for antispirochetal and antibacterial actions of penicillin, chloromycetin, bacitracin are certainly not identical. The only drug inhibited by BAL in both, spirochetal and streptococcal infections is Myochrysin, which may be presumed, therefore, to act by the same mechanism in the two infections.

Interestingly, Fuadin which according to the finding of Van Dyke and coworkers(24) becomes more toxic by simultaneous BAL treatment (as confirmed repeatedly on mice

21. Stocken, L. A., and Thompson, R. H. S., *Biochem. J.*, 1946, v40, 535.

22. Stocken, L. A., Thompson, R. H. S. and Whittaker, V. P., *Biochem. J.*, 1947, v41, 47.

23. Gemmill, C. L., and Bowman, E. M., *J. Pharmacol.*, 1950, v100, 244.

24. Gammill, J. F., Southam, C. M., and Van Dyke, H. B., PROC. SOC. EXP. BIOL. AND MED., 1947, v64, 13.

in the present study) has been easily inhibited as a therapeutic agent in the trypanosomal infection. This forms another evidence for our initial hypothesis that drug toxicity and its inhibition (by BAL) in the case of the host and the parasite are not necessarily bound to the same mechanism. A similar specific inhibition of the trypanocidal and not of the toxic effect has been described by Schleyer and Schnitzer(25), who reported the antagonistic action of methyl-p-hydroxybenzoate against acriflavine and arsenicals.

With the experiments presented the participation of the dithiol function is extended to such widely different processes as, for instance, the antispirochetal activity of antibiotics, the diabetogenic action of alloxan (26), the plant-growth inhibiting effect of cumarin and protoanemonin(27), the detoxification of lewisite and metallic compounds in mammals, protozoans(7), and viruses(28), the activation of papain(29) and cathepsin (30) and their antagonization by carcinogenic hydrocarbons(30,31).

Summary and conclusions. (1) In experimental spirochetal infections BAL reverses the therapeutic activity of penicillin, bacitracin, chloromycetin, oxophenarsine and gold compounds (Myochrysin), while it has no influence on streptomycin, terramycin and aureomycin. (In most cases subtilin has not been affected, occasionally it has been potentiated by BAL and by cysteine). (2) Monothiols (cysteine and glutathione) do not induce the reversal obtained with BAL. (3) In trypanosomal infection BAL reverses the therapeutic activity of arsenicals and Fuadin, while it has no influence on Naphuride, Stilbamidine and Acriflavine. The toxicity of Fuadin for the host(24) is noticeably increased by BAL treatment. (4) In experimental streptococcal infection none of these antibiotics has been influenced by BAL (or monothiols), except Myochrysin, which has been inhibited by BAL. (5) In the *E. coli* infection only penicillin was influenced by BAL: its activity was *increased.* This apparent potentiation was found to be due to a blood level increase determined by BAL with higher penicillin doses. (6) It is concluded that a number of chemically different therapeutic agents (penicillin, bacitracin, chloromycetin, Au, Sb, As compounds) act by a similar mechanism involving the dithiol function in the protozoan infection, while their activity is of a different nature in bacterial infections (probably with the exception of the gold compound). It is considered that BAL inhibition of the drug does not take place with an identical mechanism for the host and the parasite. The specific BAL reversal in the spirochetal infection (and not in others) proves that this is due to a biological effect and not to a chemical inactivation of the drug.

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