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THE PHARMACOLOGIC AND CHEMOTHERAPEUTIC ACTION OF SOME NEW SULFONES AND STREPTOMYCIN IN EXPERIMENTAL TUBERCULOSIS [1] [2]

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In 1940 Rist and associates showed that 4,4′-diaminodiphenyl sulfone (DDS) had a favorable effect in experimental tuberculosis in rabbits infected with an avian strain (1). Later the same was shown to be true for experimental tuberculosis in guinea pigs infected with a human strain (2). Since then many attempts have been made to develop compounds chemically related to or derivatives of DDS with the objectives of decreasing toxicity and increasing activity. The first objective has been realized, for there are now many derivatives of DDS that are less toxic than the parent compound. The second objective has not met with as much success.

Generally speaking there are two types of derivatives of DDS: (*a*) The disubstituted derivatives, in which a hydrogen in each of the two amino groups is replaced by a substituent, e.g., promin, diasone and the more recent sulphetrone (4); and (*b*) the monosubstituted derivatives in which one of the amino groups remains free. In the latter class, the alkyl monosubstituted derivatives have been found to be the least toxic and most effective (5). These compounds, however, are characterized by low absorbability. Further experimentation showed that the introduction of a hydroxyl group into the alkyl substituent in-

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[1] Presented at the Tuberculosis Study Section Meeting, September 21, 1948.

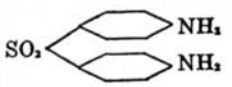
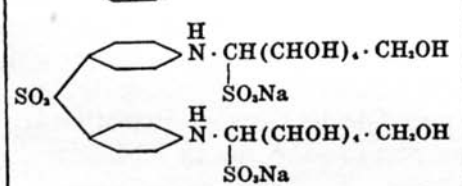
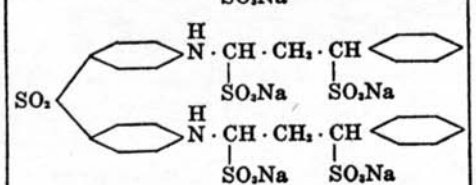
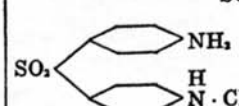
[2] Reprinted with permission from the *American Review of Tuberculosis* **60** (1949) 62-77, with the elimination of one paragraph dealing with streptomycin but otherwise with no essential change. Photographic copies of the original text-figures were supplied by the authors.

[3] Watumull Foundation Fellow.

creased absorbability without sacrifice with respect to toxicity and activity.

The present paper is a report on the actions of the newer disubstituted derivative sulphetrone (4)[4] and the monosubstituted 4-amino-4′-β-hydroxyethylaminodiphenyl sulfone (6)[5] synthesized in this laboratory and hereafterdesignated hydroxyethyl. For comparison, data are also included on the older and better known disubstituted derivative promin and the parent substance DDS. Promin and sulphetrone are water soluble and can be administered parenterally; DDS and hydroxyethyl are only slightly soluble in water and are usually administered orally.

TABLE 1.—*Structural formulas and analyses of 4,4′-diaminodiphenylsulfone (DDS) and three derivatives.*

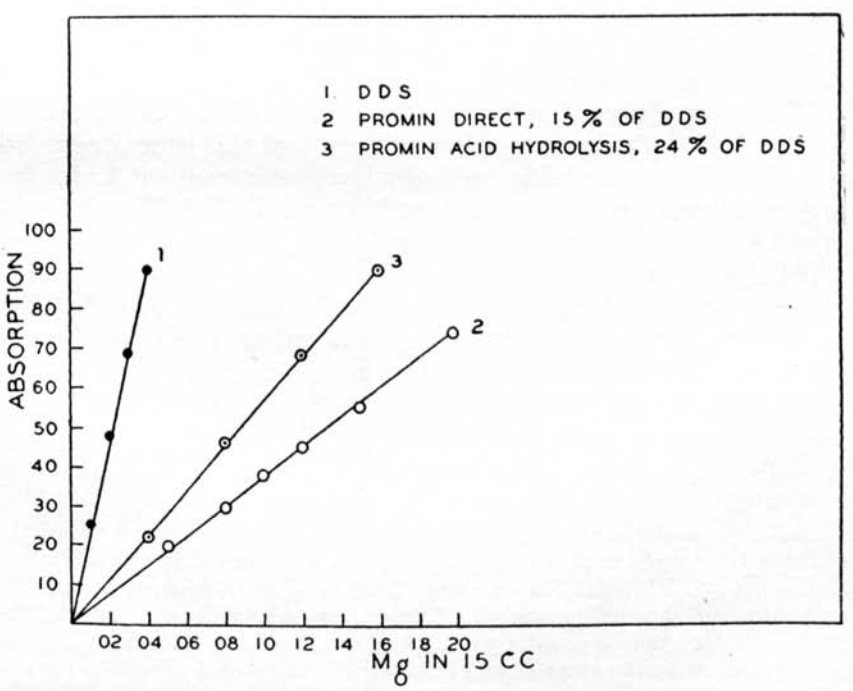
Substance	Formula	DDS Equivalent		
		Theory	Analysis	
			Direct	After 1 hour at 100°C.
DDS		100	100	100
Promin		31	15	24
Sulphetrone		27.8	13	22
Hydroxyethyl		42.4	46	0

[4] 4,4′-bis(y-phenyl-n-propylamino)diphenylsulfone-tetrasodium sulfonate. Supplied by Dr. Edwin J. de Beer, the Wellcome Research Laboratories.

[5] 4-amino-4′-β-hydroxyethylaminodiphenyl sulfone crystallizes as dimorphic forms melting at 130.5-131.5°C. and 143.5-144.5°C. The two forms have shown about the same absorption, toxicity and chemotherapeutic activity, the latter tested in experimental pneumococcus infection in mice. We are indebted to Dr. Augustus Gibson and Dr. Max Tishler of Merck & Company for the supply of a large quantity of the compound.

EXPERIMENTAL

Table 1 shows the structural formulas of these compounds and their DDS equivalents. Hydroxyethyl on direct diazotization at room temperature, according to the Bratton and Marshall technique, is 46 per cent of DDS, close to the theoretical value. Promin and sulphetrone are 15 and 13 per cent, respectively, showing their instability, for theoretically, having no free amino group, they should have no diazotization value. Both of these compounds in 0.25 *N* hydrochloric acid containing some trichloroacetic acid are decomposed at 100°C., the diazotization values being short of the theoretical values, probably because of the presence of impurities. Under similar conditions, there is no splitting of the molecule of hydroxyethyl. This was demonstrated by keeping a solution of 0.3 gm. of hydroxyethyl in 0.25 *N* hydrochloric acid containing 2.5 per cent trichloroacetic acid at 100°C. under a reflux condenser for one hour. Concentration



TEXT-FIG. 1. Diazotization curves of DDS and promin on direct diazotization and after acid hydrolysis at 100°C. for one hour. Values for DDS are identical; two sets of values are obtainable with promin. Similar analysis of blood and urine of animals receiving promin orally yield nearly identical values as with DDS, suggesting the degradation of promin to DDS.

and neutralization of the solution by sodium hydroxide yielded 0.3 gm. of pure hydroxyethyl, identified by its melting point and a mixed melting point determination with the authentic compound.

Text-figure 1 illustrates the values obtained on direct diazotization of DDS and promin at room temperature and after acid hydrolysis, as described in a previous report (7). Plotting light absorption obtained with a Fisher electrophotometer against concentration in mg. per 15 cc., Curve 1 represents values obtained for DDS. The direct values and those obtained after heating were identical. Curve 2 represents the values obtained for promin on direct diazotization, and Curve 3 after acid hydrolysis.

When the blood or urine of an animal receiving DDS is analyzed by the two procedures the values are identical, as expected if the DDS is unaltered in the animal body. When the blood or urine of an animal receiving promin by oral administration is analyzed in the same manner the values are also identical, which suggests that promin is metabolized in the body to DDS. Sulphetrone gives similar results.

The properties of a metabolite isolated from the urine of man receiving the hydroxyethyl indicate that this is not degraded to DDS. This metabolite was obtained, by a method to be described later, in solid condition melting at 170-174°C. and showing diazotization and coupling with the Bratton-Marshall reagents. A mixture of this material with authentic DDS crystals of m.p. 176-177°C. melted at 142-145°C., which shows that the metabolite is not DDS. Although the quantity of material available was insufficient for complete purification and identification, the possibility of the oxidation of hydroxyethyl in the human body to the previously described glycine derivative (6) is mentioned.[6]

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[6] Using a similar technique of isolation, DDS was recovered nearly quantitatively and identified by melting point when added to normal urine. In like manner DDS was also recovered from urine of rabbits receiving DDS and identified by melting point. Moreover, a substance with m. p. 199-200°C was isolated from the urine of a cat receiving hydroxyethyl and when mixed with the pure glycine derivative

it gave a m.p. of 201-202°C. The pure glycine derivative melts at 202-203°C. This isolated material also gave a diazotization curve identical with that of the glycine derivative. These experiments will be described in detail in a later publication.

Toxicity studies.—Data in Table 2 give the approximate LD_{50} in rats on oral administration as 1.0 gm. per kg. for DDS, 3 to 4 gm. per kg. for promin, and more than 4 gm. per kg. for sulphetrone and hydroxyethyl. On intravenous injection the LD_{50} for promin is between 3 and 3.5 gm. per kg., for sulphetrone 4.5 gm. per kg. In terms of DDS equivalent, the toxicity of the two disubstituted derivatives is almost identical and considerably greater than that of hydroxyethyl.

TABLE 2.—*Acute toxicity of 4,4'-diaminodiphenylsulfone (DDS) and derivatives in rats weighing 125 to 175 gm.*

Dose gm/kg	Route	Mortality, Number Died Number Used			
		DDS	Promin	Sulphetrone	Hydroxyethyl
0.8	Oral	3/10			
1.0	Oral	*6/10*			
3.0	Oral		4/10		
4.0	Oral		*6/9*	2/10	0/10
3.0	I.V.		3/10	0/10	
3.5	I.V.		*7/10*		
4.0	I.V.		*5/5*	2/10	
4.5	I.V.			*7/15*	

The chronic toxicity in rats when fed on a semisynthetic diet is shown in Table 3. The tolerated concentration of DDS is 0.2 per cent of the diet. At this concentration the blood levels were 1.2 to 2.6 mg. per 100 cc. Promin is tolerated at a concentration of 0.8 per cent, almost exactly the same as DDS when computed on the basis of DDS content. Sulphetrone under the same conditions is much less toxic, for it is tolerated in concentrations of 3 to 5 per cent. The blood levels at the high concentrations of sulphetrone in the diet were not significantly higher, however, than those of promin at the concentration of only 0.8 per cent in the diet, suggesting that the relatively low toxicity of sulphetrone may be due to lower absorbability.

The same appears to be true from the data on cumulative toxicity in guinea pigs, shown in Text-figure 2. Three groups of ten guinea pigs each were fed by stomach tube, twice daily, 1.0 gm. per kg. of promin, sulphetrone and hydroxyethyl respectively. All the animals in the promin group were dead after 10 doses. Only one of the ten in the sulphetrone group died

after 14 doses, and two in the hydroxyethyl group after 20 doses. All the others survived 30 doses. However, blood level determinations made at comparable periods after the administration of the respective compounds indicated much higher values for promin than for sulphetrone or hydroxyethyl. The average blood levels in the promin group were 26-48 mg. per 100 cc., sulphetrone 5-10 mg. per 100 cc., and the hydroxyethyl group 1-7 mg. per 100 cc.

TABLE 3.—*Chronic toxicity of 4,4'-diaminodiphenylsulfone (DDS) and derivatives in young white rats weighing 60 to 80 gm. when fed in the diet in the concentrations indicated.*

Mortality in relation to number used (M) and blood levels mg. per 100 cc. (BL) at the end of the experimental period.

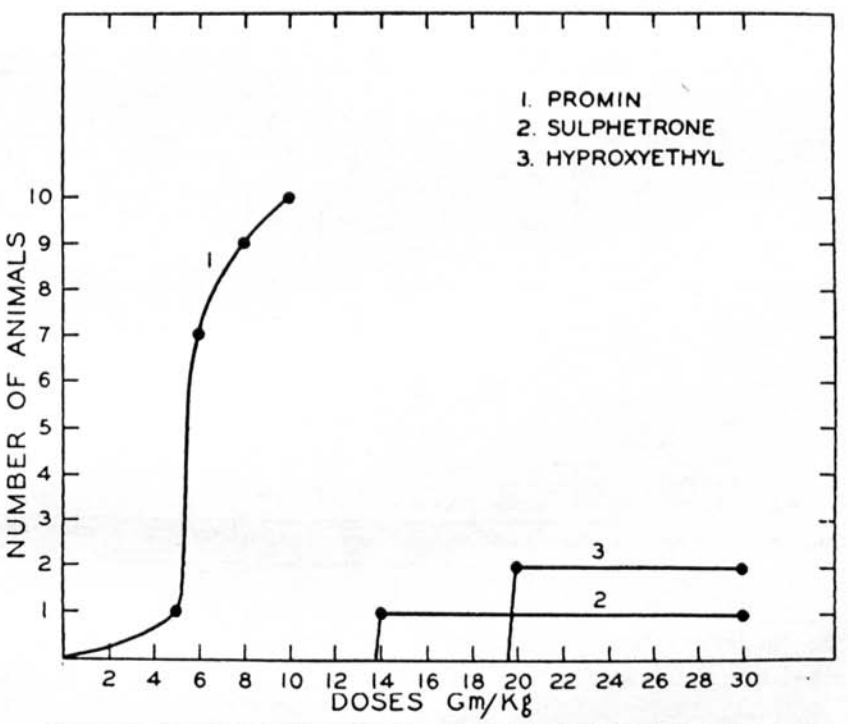
Per Cent Drug In Diet	DDS			Promin			Sulphetrone		
	M	Days	BL Mg. per 100 cc.	M	Days	BL Mg. per 100 cc.	M	Days	BL Mg. per 100 cc.
0.2	*0/10*	50	1.2-2.6						
0.3	10/10	2 to 11							
0.5	10/10	4 to 10							
0.8				*0/10*	46	9-26			
1.0	10/10	1 to 6		4/10	11 to 38				
1.5				8/10	3 to 38	6.4-22.0			
3.0				10/10	3 to 43		*0/9*	105	10.8-34.0
5.0							2/10	46[1]	12 -33

[1] Subnormal growth.

Hemoglobin determinations showed a reduction on an average of from 14.3 to 12.0 gm. per 100 cc. during treatment for the promin group, from 14.8 to 12.5 gm. per 100 cc. for the sulphetrone group, and from 14.9 to 13.3 gm. per 100 cc. for the hydroxyethyl group.

In Table 4, data of the chronic toxicity of some of these compounds in cats are given. The compounds were administered daily, incorporated in a ration of 100 to 200 gm. ground lean beef, for voluntary consumption. Two animals in the first group received 50 mg. per kg. of DDS, the second group of two animals received the DDS equivalent as promin, the third group of two animals received first the DDS equivalent as sulphetrone followed by twice the DDS equivalent, and the last three animals in the fourth group were given from 1 to 4 times the DDS equivalent as the hydroxyethyl compound. The DDS animals lost weight rapidly and developed anorexia, frequently refusing to consume their ration and thus failing to ingest the drug. One

of these animals died after 30 doses. The promin animals held up somewhat better, but on the whole they displayed similar effects and one died after 70 doses. The sulphetrone and hydroxyethyl animals accepted the drugs well, showed no visible effects, and appeared to be in good health. Spectrophotometric



TEXT-FIG. 2. Cumulative toxicity of promin, sulphetrone and 4-amino-4'-β-hydroxyethylaminodiphenyl sulfone in guinea pigs; mortality curves. Dose: 1.0 gm. per kg. daily, orally.

analysis of blood pigments towards the end of the observation period by the method of Evelyn and Malloy (8) revealed more methemoglobin and sulfhemoglobin in the DDS, promin, and sulphetrone animals than in the hydroxyethyl animals. The reduction in oxyhemoglobin in relation to the total hemoglobin was more pronounced in the first three groups.

Blood level determinations made uniformly at about 18 hours after feeding, at the time when the animals were receiving 200 mg. per kg. of sulphetrone and 100 to 200 mg. per kg. of hydroxyethyl, indicated much higher drug concentrations in the promin and sulphetrone groups than the hydroxyethyl group.

Summing up the data on toxicity it may be concluded that promin is about as toxic as DDS when dosage is computed on

TABLE 4.—*Chronic toxicity and effect on blood pigments in cats, oral administration.*

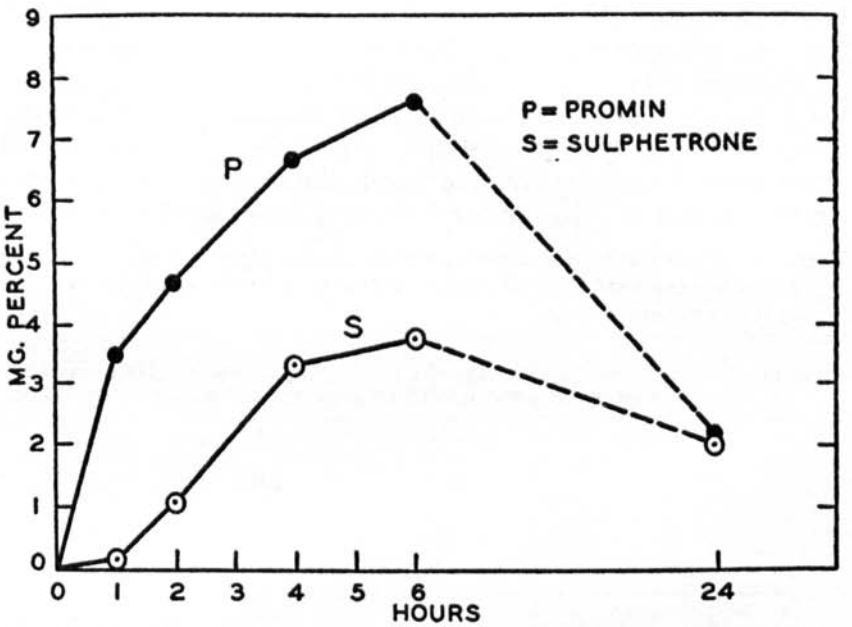
Compound	Number	Weight Kg.		Doses mg/kg	Total Dose gm/kg	Blood Levels mg per 100 cc.	Blood Pigments, Gm. Per 100 cc.			
		Initial	Final				Total Hb	HbO_2	MHb	SHb
DDS	1	4.2	2.3	30 x 50[1]	1.5					
	2	3.5	1.7	65 x 50	3.25	3.0	11.7	8.6	0.9	2.8
Promin	3	3.2	2.7	70 x 200	14.0	16.0	12.1	10.0	0.9	1.5
	4	3.4	1.5	70 x 200[1]	14.0	19.5	11.7	8.9	1.1	2.1
Sulphetrone	5	2.9	3.2	68 x 200	20.0	14.0	12.6	9.7	1.0	2.5
				16 x 400						
	6	2.9	3.5	68 x 200	20.0	11.6	15.5	13.2	0.9	1.9
				16 x 400						
Hydroxyethyl	7	3.2	2.7	34 x 100	9.0	3.0	12.6	11.9	0.8	1.2
				14 x 400						
	8	3.9	3.7	5 x 100	12.7					
				29 x 200		3.5	13.0	11.4	0.7	1.1
				16 x 400						
	9	3.7	3.2	5 x 100	11.5					
				29 x 200		2.4	13.3	13.2	0.5	0.5
				13 x 400						
Controls, average of 9 determinations in 5 normal cats							14.3	13.9	0.3	0.4

[1] Died.

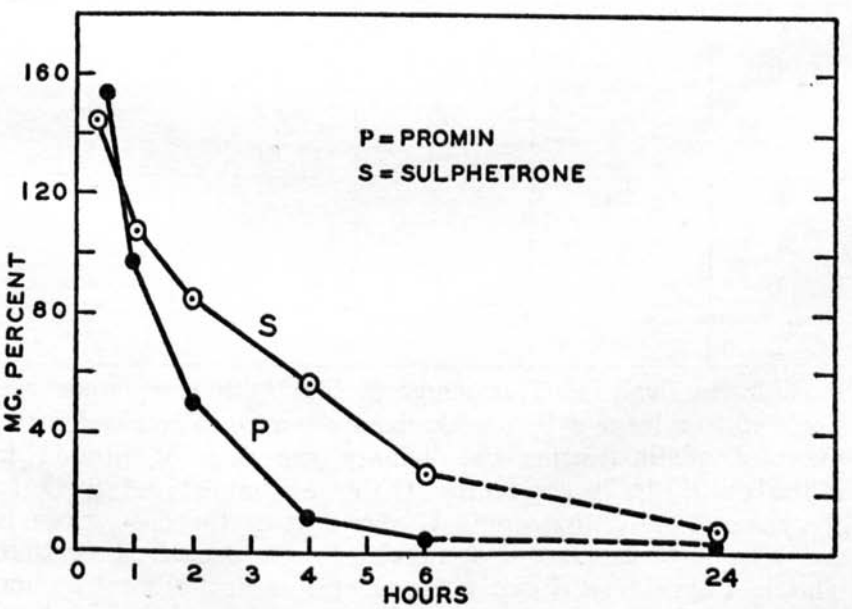
the basis of DDS equivalent, while sulphetrone and hydroxyethyl are much less toxic. Since the blood levels were generally lower for the last two compounds the question of absorption, tissue distribution and excretion was considered next.

Metabolism studies.—Data on the absorption of these compounds from the gastrointestinal tract of the guinea pig, as judged by drug concentration in the blood, are given in Table 5. Blood level determinations were made at various intervals up to 24 hours following a single dose of 0.1 to 1.0 gm. per kg. of promin and sulphetrone and up to 2.0 gm. per kg. of hydroxyethyl. The highest blood levels were obtained with promin, the lowest with hydroxyethyl. In rabbits given 0.5 gm. per kg. of either promin or sulphetrone orally, the promin blood levels were more than twice as high as the sulphetrone, as shown in Text-figure 3.

To determine the relative retention of promin and sulphetrone, each was injected intravenously in rabbits in doses of 0.5 gm. per kg. and blood levels were determined at stated intervals during 24 hours, with the results shown in Text-figure 4. It



TEXT-FIG. 3. Blood levels following oral administration of promin and sulphetrone in rabbits. Significantly higher blood levels of promin suggest better absorption.



TEXT-FIG. 4. Blood levels following intravenous injection of promin and sulphetrone in rabbits. Results indicate better retention of sulphetrone.

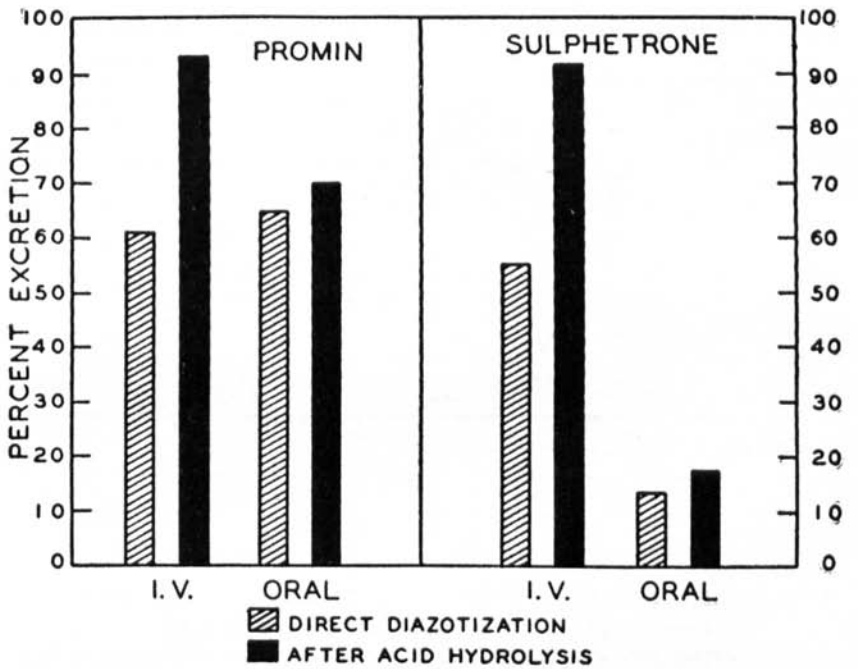
is evident that both drugs leave the blood stream rapidly, though sulphetrone appears to be retained somewhat better than promin.

Further data on the metabolic fate of promin and sulphetrone are given in Text-figure 5. Both drugs are excreted in the urine to the extent of about 60 per cent of the dose administered when given intravenously. Moreover, the acid hydrolysis diazotization values are higher for both drugs compared with direct

TABLE 5.—*Blood levels in mg. per 100 cc. in guinea pigs at various intervals following the oral administration of three sulfone derivatives in doses of 0.1 to 2.0 gm. per kg.*

Hours	Dose gm/kg	Promin mg. per 100 cc.	Sulphetrone mg. per 100 cc.	Hydroxyethyl mg. per 100 cc.
1	0.1	2.0	2.1	1.2
3		2.4	2.6	0.8
5		2.7	3.0	0.5
24		1.1	trace	0
1	0.5	3.6	2.4	2.4
3		8.0	4.0	3.2
5		13.0	4.6	2.9
24		2.8	2.6	0.7
1	1.0	7.3	4.3	3.4
3		9.1	5.5	4.0
5		9.0	6.3	5.0
24		13.0	3.6	1.6
1	2.0			6.1
3				7.5
5				4.7
24				2.4

diazotization values. This suggests that both compounds are excreted to a large extent unchanged when given intravenously. On oral administration the urinary excretion of promin is still about 60 to 70 per cent of the dose administered, while in the case of sulphetrone only 15 per cent of the dose given is recoverable in the urine, indicating much poorer absorption. The acid hydrolysis diazotization values on oral administration are nearly identical with the direct diazotization values in both drugs, suggesting their degradation to the parent substance.



TEXT-FIG. 5. Urinary excretion of promin and sulphetrone after intravenous and oral administration in rabbits, in relation to dose administered (0.5 gm. per kg.) and metabolic fate. Results indicate degradation of both to DDS on oral administration and poorer absorption of sulphetrone.

The urinary elimination of hydroxyethyl in relation to the dose administered was studied in rabbits and in man. The experiments in rabbits are summarized in Table 6 and show that, regardless of the dose administered orally, nearly 50 per cent of it is recoverable from the urine in 24 hours. An experiment in three human subjects to whom the compound was administered orally in 2 gm. doses three times during the day (approximately 0.1 gm. per kg.) gave results, shown in Table 7, which almost paralleled the results obtained in rabbits. From 40 to 60 per cent of the dose administered was excreted in the urine, and most of it during the first day.[7]

The low blood levels compared with the relatively high urinary excretion following the oral administration of hydroxyethyl suggested the possibility of a preferential distribution of the compound in the tissues. This was studied in several guinea

[7] We are indebted to Drs. Howard M. Payne of Freedman's Hospital and Philip Kilbourn of the Tuberculosis Division, Public Health Service, for their cooperation.

TABLE 6.—*Absorption and excretion of hydroxyethyl in rabbits after different doses.*

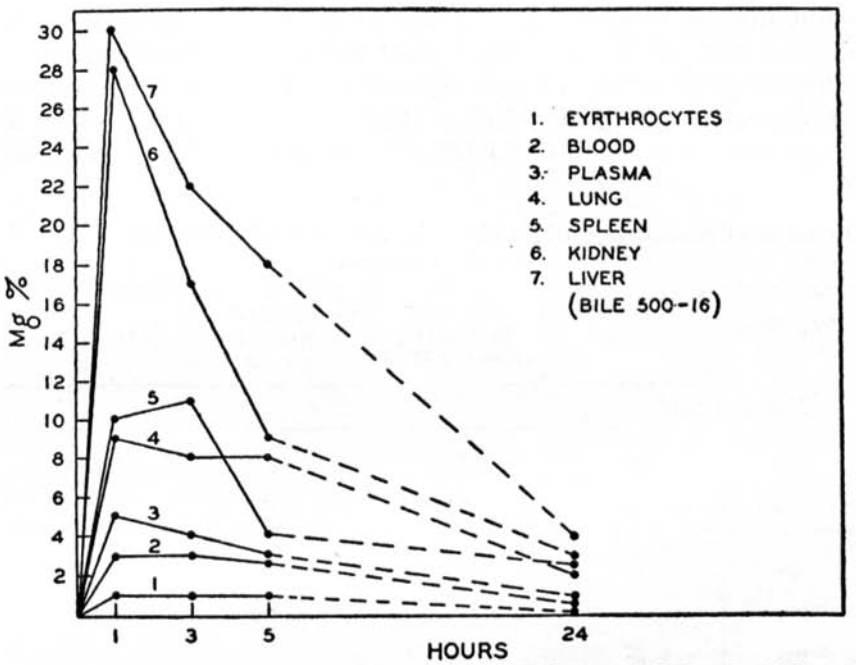
Hours	Blood Levels Mg. Per 100 cc.		
	0.1 gm/kg	0.5 gm/kg	1.0 gm/kg
1	1.2	2.3	3.7
2	0.9	1.9	3.7
4	0.9	1.9	4.2
6	0.7	1.5	3.7
24	trace	trace	1.3
Urinary excretion, percentage of dose.			
24	45	46	52

TABLE 7.—*Blood levels and urinary excretion of hydroxyethyl in man.* Dose: 2 gm.—8:00 a. m., 12:00 m. and 4:00 p. m.

Subject	Blood Levels, Mg. Per 100 cc., Hours				Urinary Excretion, Per Cent Of Dose		
	2	4	7	24	First day	Second day	Total
HB	0.4	0.5	0.9	0.6	43	0.9	43.9
AK	0.5	0.6	1.0	0.7	55.8	4.6	60.4
GK	0.7	0.6	0.9	0.6	38.5	1.5	40.0

pigs after a single dose of 0.5 gm. per kg., and the average results are given in Text-figure 6. The lowest concentrations, estimated as hydroxyethyl, were found in the erythrocytes; the plasma showed somewhat higher concentrations than whole blood; and the liver, kidney, spleen and lungs gave values ranging from 3 to 10 times those of whole blood. Estimations of the compound in the bile indicated as high a concentration as 500 mg. per 100 cc. at 1 to 3 hours after the administration of the compound, and 16 mg. per 100 cc. 24 hours later.

Thus it may be concluded that promin is better absorbed than sulphetrone; that both drugs are apparently metabolized to DDS when given orally; that the low blood levels following the oral administration of hydroxyethyl are not due to poor absorbability but rather to a preferential localization of the compound in certain tissues and organs of the body.



TEXT-FIG. 6. Distribution of 4-amino-4'-β-hydroxyethylaminodiphenyl sulfone in the tissues of guinea pigs. Average of 3 to 4 animals. Highest concentration in the liver and kidney, lowest in erythrocytes.

Chemotherapeutic activity.—This was studied in experimental pneumococcus infection in mice and experimental tuberculosis in guinea pigs. Brownlee and associates (4) state that sulphetrone was inactive in experimental pneumococcus infection in mice. In our experience with monosubstituted derivatives of DDS, such compounds have usually shown considerable activity, frequently comparable with that of DDS, and because of their lower toxicity such compounds have often shown a more favorable chemotherapeutic index (9).

In the case of the hydroxyethyl compound, 50 per cent survival of infected mice [8] was obtained with a total dose of 3.0 gm. per kg. orally and 2.0 gm. per kg. subcutaneously, suspended in olive oil, when given in eight divided doses over a period of four days. In normal mice a single dose of 8.0 gm. per kg. orally and 4.0 gm. per kg. subcutaneously failed to kill any animals. In the case of the parent substance DDS, approximately 0.5 gm. per kg. protected 50 per cent of infected mice when given in

[8] Mice of 18 to 22 gm. were used and the infecting dose was 0.5 cc. of 10^{-6} dilution of a six-hour broth culture of Type I pneumococcus given intraperitoneally, which kills all controls within 24 hours (9).

eight divided doses over a period of four days, but the single dose of 0.25 gm. per kg. killed about 50 per cent of normal mice, whether given orally or subcutaneously. Thus the chemotherapeutic ratio of hydroxyethyl (LD_{50}/SD_{50}) is more than 4 to 6 times greater than that of DDS. These data are shown in Table 8.

TABLE 8.—*Chemotherapeutic activity in experimental pneumococcus type I infection in mice.*

Total Dose gm/kg	Route	Per Cent Survival Of Infected Mice	Toxicity LD^{50} In Normal Mice gm/kg	LD^{50}/SD^{50}
Hydroxyethyl				
4.0	os	73	>8.0	>8/3
3.0	os	*51*		
4.0	sc	75		
3.0	sc	68	>4.0	>4/2
2.0	sc	*50*		
1.0	sc	30		
DDS				
1.0	os	92		
0.6	os	69	0.25	
0.4	os	*41*		
1.0	sc	87	0.25	1/2
0.5	sc	*49*		

The results obtained in experimental tuberculosis in guinea pigs are summarized in Table 9. These data concern the activities of sulphetrone and hydroxyethyl when used alone or in combination with streptomycin. The hydroxyethyl compound was used at the relatively low dose levels of 100 and 300 mg. per kg. because of the limited supplies at the time this work was done. The sulphetrone experiments were so planned as to give some information on the question as to which is the more critical, streptomycin or the supplementary sulfone, in combined therapy. The results indicate greater activity for hydroxyethyl than sulphetrone when used alone, and potentiation of action in the

case of the hydroxyethyl compound comparable with that reported previously for promin and other sulfones (3, 10). An additive effect in the instance of sulphetrone was obtained when used with the small dose of 5 mg. per kg. per day of streptomycin. When used with the larger dose of streptomycin, 25 mg. per kg. per day, some potentiation of action was obtained. The chemotherapeutic effectiveness of 25 mg. per kg. streptomycin plus 500 mg. per kg. sulphetrone was somewhat greater than that of double the dose of streptomycin when used alone.

TABLE 9.—*Activity in guinea pig tuberculosis; 0.5 mg. H37 Rv I. P; treatment day after infection and continued 80 days.*

Date of Inoculation	Number of Animals	Therapy, Mg/Kg/Day		Mortality Per Cent	Average Weight Gain gm	Average T. B. Index[1]	Chemo-Therapeutic Effectiveness[2]
		Sulfone orally	Streptomycin intramuscularly				
November, 1947	10	0	0	80	40	15.5	
	10	Hydroxyethyl-300	0	10	118	6.2	2.5
	10	0	20	10	276	1.5	10.3
	10	Hydroxyethyl-100	20	0	304	0.8	19.4
June, 1948	15	0	0	86	13	12.2	
	15	Sulphetrone-100	0	53	78	8.6	1.4
	15	Sulphetrone-500	0	66	10	9.9	1.2
	15	0	5	27	108	6.5	1.9
	15	0	25	7	204	2.0	6.1
	15	0	50	7	188	0.8	15.2
	15	Sulphetrone-100	5	0	175	3.6	3.4
	15	Sulphetrone-500	5	7	184	3.6	3.4
	15	Sulphetrone-100	25	0	240	1.3	9.4
	15	Sulphetrone-500	25	0	248	0.7	17.4

[1] Average tuberculous involvement for the group, each animal being graded 0 to 20 according to the extent of lesions in (*a*) omentum and mesenteric glands, (*b*) spleen, (*c*) liver, (*d*) peritoneum, kidneys and testes, (*e*) lungs and mediastinal glands, each graded 0 to 4 on the basis of no visible lesions, slight, moderate, generalized, or extensive.

[2] Average TB index of controls/treated.

SUMMARY AND CONCLUSIONS

A comparative study is presented of the pharmacologic and chemotherapeutic properties of (1) 4,4′-diaminodiphenyl sulfone (DDS), (2) promin, (3) sulphetrone, and (4) 4-amino-4′-β-hydroxyethylaminodiphenyl sulfone (hydroxyethyl).

The intravenous toxicities of promin and sulphetrone in rats are almost identical if computed on the basis of DDS equivalent.

The oral toxicities of sulphetrone and hydroxyethyl are much

less than that of promin. The low toxicity of sulphetrone appears to be due to poor absorbability.

The blood levels following oral administration of hydroxyethyl are relatively low. This is not due to poor absorbability but rather to a preferential localization of the compound in certain organs and tissues of the body, *e.g.*, liver, kidney, lungs and spleen. About 50 per cent of the dose administered is excreted in the urine in 24 hours, and undetermined but appreciable amount, possibly 25 per cent, is eliminated in the bile.

There is evidence to indicate that promin and sulphetrone are metabolized in the body to the parent substance DDS. There is evidence that hydroxyethyl is not metabolized to DDS.

Hydroxyethyl has a good chemotherapeutic activity in experimental pneumococcus infection in mice. Its activity in experimental tuberculosis in guinea pigs compares favorably with promin. Like promin it potentiates the action of streptomycin. Sulphetrone has a lower activity when used alone and, when used with 5 mg. per kg. per day of streptomycin, the effect was additive. When used with the large dose of 25 mg. per kg. per day of streptomycin, some potentiation of action was obtained.

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