duce appreciable toxicity when approximately 150 mg/kg were taken daily in the drinking water by rats for 30 days. Benaglia *et al.*,[10] gave doses varying from 0.19 to 0.87 g/kg to rats with the food and doses between 0.1 and 0.5 g/kg to rabbits, monkeys, and dogs for 24 hours without finding appreciable toxicity, although some inhibitory effect on the growth rate was discernible.

Repeated intravenous injection with these solutions could not be carried out. Among the practicable routes in mice, intraperitoneal injection most closely approximates the intravenous route. Hence, 0.1 mg sodium tetradecyl sulfate in 0.1 cc was injected into 19 mice first intravenously, then 12 times intraperitoneally in the course of 3 weeks. Four mice died of peritonitis or intercurrent infection during the first week. The average weight of the remaining mice increased from 25.9 g to 31.3 g. Five of the surviving mice showed localized infections (abscess in the spleen, localized peritonitis, and adhesions). These were obviously due to perforation at the time of injection. Sections made of the lungs, liver, kidney, spleen, brain, intestine, stomach, testis, and heart of the remaining 10 mice showed no pathology attributable to the drug.†

Summary. The thrombogenic activity of some soaps and synthetic detergents was compared by injecting their solutions under standardized conditions into the tail vein of mice. Sodium tetradecyl sulfate (2-methyl-7-ethyl-undecyl sulfate-4) and Aerosol OT (di-2-ethylhexyl sodium sulfosuccinate) were found to be more potent agents than the soap solutions generally used to sclerose veins. Alkyl sulfates and sulfonates containing large branched chain hydrophobic residues were found to produce thrombus more readily than their straight chain isomers. Sodium tetradecyl sulfate produced less tissue reaction than sodium ricinoleate or sodium morrhuate. Its toxicity was not significantly greater than that of the soap solutions studied.

† Thanks are due Dr. I. E. Gerber, pathologist, for the preparation and examination of the slides.

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Sulfonamide and Penicillin Resistance of Group A Hemolytic Streptococci.*

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It has frequently been possible to establish satisfactory prophylaxis against Group A hemolytic streptococcus respiratory infection and its complications by the daily administration of a sulfonamide.[1] Such a technic, established by the U. S. Navy in many activities early in December, 1943, was uniformly satisfactory[2] until mid-summer of 1944. At that time strains of hemolytic streptococci that were resistant to the antibacterial action of these agents appeared[3] as the cause of disease among personnel in a station in the northwest and initiated an epidemic in spite of the widespread use of chemoprophylaxis. Later these organisms were transmitted widely to other Navy activities through the nor-

* This study was carried out under the auspices of the Commission on Hemolytic Streptococcal Infections, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, United States Army.

1 U. S. Department of Labor, Children's Bureau Publication No. 308, Washington, 1945, 64-87.

2 NAVMED 284, Bureau of Medicine and Surgery, Navy Department, Washington, D. C., 1944.

3 a. Epidemiology Unit No. 22, *J. A. M. A.*, 1945, **129**, 921; b. Damrosch, D. S., *J. A. M. A.*, 1946, **130**, 124; c. Eckles, L. E., personal communication, Sept. 28, 1945.

mal movements of men in training and have also established themselves among Army Air Force personnel.[4] Strains of only 3 Lancefield types, in order of degree of sulfonamide resistance, 17, 19 and 3, have been isolated under the circumstances just described.[3,4] Similar properties have been discovered in a few strains of other types, including 6 and 14.

The development of epidemics of respiratory infection caused by sulfonamide resistant hemolytic streptococci has been explained by 2 quite different hypotheses. One suggests that the etiological agents possessed a natural ability to multiply in the presence of sulfonamides and were therefore able to initiate outbreaks of disease in a host population in which sulfonamide prophylaxis had been established. Alternatively, it is proposed that mutants of previously sensitive strains appeared during rapid epidemic transmission which were resistant to the effect of sulfonamides. Such mutations were enabled to survive and spread because their new property was advantageous in the chemically altered host environment.

It seemed possible that a study of the sulfonamide resistance of a large number of strains of hemolytic streptococci collected during a study carried out between December 12, 1943 and April 20, 1944 in 2 army posts might give information as to which of the above concepts is correct. There was little possibility that sulfonamide resistant streptococci could have developed in naval activities and been transferred in so short a time to these particular army installations, since both were situated in an area remote from any naval training station. The nature and personnel of Post I has been described elsewhere.[5] Post II was an Army Air Base located about 10 miles from Post I. Contact between the 2 was possible through the intermingling of troops in a neighboring community.

Methods. Hemolytic streptococci were isolated from the upper air passages of infected men by technics described elsewhere.[6] The organisms were divided into groups and types by the precipitin technics of Lancefield. Sulfonamide sensitivity was determined by the method of Wilson;[7] penicillin sensitivity by streaking the streptococci on segments of blood agar plates containing appropriate amounts of the drug.

Results. Sulfonamide Sensitivity. The Group A hemolytic streptococci available for study consisted of 77 single, and 271 paired cultures of the same type, isolated from the upper air passages of 348 infected men at Post I. Each pair was recovered from the same individual, separate isolations having been made in the various cases at intervals from 1 to 25 days. In addition, 41 strains obtained from as many cases at Post II were tested.

Identical values for sulfonamide sensitivity were obtained with 225, and one-tube differences with 46, pairs. There were two-tube differences in 4 and these pairs were excluded. There was found no relationship between the time of isolation of the culture or the therapeutic administration of a sulfonamide and the variations between members of the pairs. It seems proper to assume that each pair of cultures represents the same organism recovered on 2 different occasions. The results indicate that the method for determination of sulfonamide sensitivity is quite precise and that relatively small differences in resistance may be satisfactorily compared.

The results of the determination of sulfonamide sensitivity of the single strains and of the nonidentical pairs (considering each member of the pair as a single strain) are presented in the first 4 columns of Table I. The values obtained for the 225 identical pairs are recorded in the 5th to 8th columns. The whole is summarized in columns 9 to 13.

No strain grew in the presence of more than 5 mg of sulfadiazine. Those of 5 types, 19, 24, 26, 30, and 36, as well as those included with the miscellaneous types, occasionally were

[4] a. Mitchell, R. B., Van Ravenswaay, A. I., Special Report, Office of the Air Surgeon, Oct. 8, 1945; b. Connor, A. R., Special Report, Office of the Air Surgeon, Oct. 8, 1945.

[5] Rantz, L. A., Rantz, H. H., Boisvert, P. J., and Spink, W. W., *Arch. Int. Med.*, in press.

[6] Rantz, L. A., Boisvert, P. J., and Spink, W. W., *Arch. Int. Med.*, in press.

[7] Wilson, A. T., PROC. SOC. EXP. BIOL. AND MED., 1945, **58**, 130.

TABLE I.
Ability of Strains of Group A Hemolytic Streptococci to Grow in the Presence of Sulfadiazine.

Type	Single strains and individual members of nonidentical pairs considered as single strains				Identical pairs (2 cultures of same type from same patient)				All strains (considering identical pairs as single strains)				
	No. of strains	Grew in control only	Grew in 1 mg	Grew in 5 mg	No. of pairs	Grew in control only	Grew in 1 mg	Grew in 5 mg	Total strains	Grew in 1 but not in 5 mg	Grew in 5 mg	% grew in 1 mg or more	% grew in 5 mg
1	14	3	11	0	12	3	7	2	26	18	2	76.9	7.5
3	23	7	9	7	17	7	6	4	40	15	11	65.0	27.5
6	9	2	5	2	3	0	3	0	12	8	2	66.6	16.7
17	16	1	5	10	20	0	3	17	36	8	27	97.5	75.1
19	21	12	9	0	38	30	8	0	59	17	0	28.8	0.0
24	2	2	0	0	8	7	1	0	10	1	0	10.0	0.0
26	5	3	2	0	15	15	0	0	20	2	0	10.0	0.0
30	10	6	4	0	19	19	0	0	29	4	0	13.8	0.0
36	24	13	9	2	33	33	0	0	57	9	2	19.3	3.5
44	5	4	1	0	6	3	1	2	11	2	2	36.4	18.2
46	8	0	4	4	12	2	7	3	20	11	7	90.0	35.0
Other types	32	17	13	2	42	30	11	1	74	24	3	35.5	4.0

resistant to the action of 1 mg per 100 ml of sulfadiazine but all but 5 strains failed to multiply in 5 mg per 100 ml of the drug. Strains of types 1, 3, 44, and 46 were often resistant to the action of 1 mg per 100 ml and, frequently, to that of 5 mg per 100 ml of sulfadiazine. Type 6 is represented by very few examples but nearly all were slightly sulfonamide resistant. The strains of type 17 were the least sensitive in that all but one grew in the presence of 1 mg per 100 ml and 27 of 36 in the presence of 5 mg of sulfadiazine per 100 ml.

Five strains of type 3 were collected at Post II; 4 grew in the control tube only, one in the 5 mg tube. Seventeen strains of type 19 were studied, only one of which grew in the 1 mg tube and none in the higher levels of sulfonamide. Seventeen of 19 strains of type 17 grew in the 1 mg and 4 in the 5 mg tubes.

The month of isolation of the resistant strains of types 3 and 17 was determined. All strains of type 3, able to grow in the presence of 5 mg of sulfadiazine, were isolated after March 1, 1944, since this type did not appear as a cause of disease in the post before this date. The results with type 17 were different in that 2 resistant strains were recovered in January and 6 in February of 1944.

Penicillin Sensitivity. The ability of all of the above listed strains to grow in the presence of penicillin was studied. Regarding them as individual strains, 54 were resistant to the action of 0.02, and 7 to that of 0.05 units per ml. All were inhibited by 0.1 unit per ml. If the paired strains only are considered, it is discovered that in only 5 of the 271 instances were both members of the pair able to grow in the presence of as much as 0.02 units of penicillin per ml. No relationship between the serological types of these slightly penicillin resistant strains was discovered.

Comment. This study has demonstrated that certain types of Group A hemolytic streptococci were significantly more resistant to the antibacterial action of sulfonamides than were others collected during the same period. It is unlikely that these strains had been transmitted through a host population undergoing sulfonamide prophylaxis. They

must, therefore, be regarded as having been naturally resistant to the action of these chemicals.

Strains of 2 of these types, 3 and 17, later became established as the etiological agents of epidemic hemolytic streptococcal respiratory infection in military establishments in which sulfadiazine was being administered prophylactically. When studied under these circumstances the degree of resistance of strains of type 3 was approximately that discovered in this study but that of strains of type 17 was much greater.[3,4]

It is probable, therefore, that both of the hypotheses previously mentioned, explaining the appearance of epidemic, sulfonamide resistant, hemolytic streptococci, are correct. Certain strains of Group A hemolytic streptococci were present in the national military population at the time that mass chemoprophylaxis was instituted that possessed two advantageous biological properties: moderate sulfonamide resistance and a high degree of communicability. These characteristics permitted these strains to spread and cause disease after their introduction into a host population undergoing sulfonamide prophylaxis. In some instances (type 17) mutation occurred and much more sulfonamide resistant variants appeared; in others (type 3) the resistance of the strain did not become greatly enhanced.

This study has not revealed a precursor for the resistant strains of type 19 that also caused epidemics. It is quite possible, however, that naturally resistant variants of this type were present in other areas.

The failure of other moderately resistant strains discovered during this study to establish epidemics may have been due to a lack of certain properties which permit a high degree of communicability or to the fact that they were never introduced into a group in which sulfonamide prophylaxis was in use.

No significantly penicillin-resistant strains of hemolytic streptococci were discovered during this study.

Summary. Strains of certain types of Group A hemolytic streptococci were discovered to be naturally resistant to moderate amounts of sulfadiazine. It is suggested that such organisms originated the epidemics of streptococcal disease among troops receiving sulfonamide prophylaxis, later becoming more resistant by mutation. No strains significantly resistant to penicillin were discovered.

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Effect of Atropine, Testosterone and Pitressin on Experimental Myocardial Infarction.*

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Recently Mokotoff and Katz[1] have made use of an experimental approach to determine the effect of drugs upon infarct size following coronary ligation. It was shown by this means that papaverine had a definite effect in reducing infarct size, while aminophyllin parenterally had a smaller, but definite effect. It was felt that other drugs might profitably be evaluated by this method. In the present report data obtained with atropine, testosterone, and pitressin are presented.

Atropine was chosen since it has been claimed recently to have a clinically beneficial effect in myocardial infarction.[2] This beneficial effect was attributed to an abolition of supposed vagus coronary constrictor tone.

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† Herbert G. Mayer Fellow.

1 Mokotoff, R., and Katz, L. N., *Am. Heart J.*, 1945, **30**, 215.

2 Leroy, G. V., Fenn, G. K., and Gilbert, N. C., *Am. Heart J.*, 1942, **23**, 637.