

THE PREVENTION OF RESPIRATORY TRACT BACTERIAL INFECTIONS

BY SULFADIAZINE PROPHYLAXIS IN THE UNITED STATES NAVY

COMMANDER ALVIN F. COBURN, MC-V(S) U.S.N.R.
WASHINGTON, D. C.

The struggle between bacterial flora and the human host is a continuous one. Survival of the two has been determined by a balanced relationship. In time of war, living conditions of the host are such that this relationship is disturbed, and the balance is now already tipped in favor of respiratory pathogens. In the first year of World War II a significant development in the armed forces was the increasing morbidity rate from respiratory infections, and in the U. S. Navy the majority of the important respiratory diseases were caused by the hemolytic streptococcus. At U. S. naval training centers situated in Northern states these infections have handicapped recruit training. The experiences of one of these stations will illustrate the importance of streptococcal infections in the U. S. Navy.

Early in 1943 a training center with an average strength of 43,000 had an outbreak of measles. This was followed by many types of respiratory infections, including in one year 4,973 cases of scarlet fever, 1,375 cases of rheumatic fever, 1,383 cases of pneumonia, 131 cases of meningitis and at least 50,000 infections of the nasopharynx or tonsils. During the summer months the activity of the meningococcus and the pneumococcus subsided. However, the hemolytic streptococcus maintained its pathogenicity, and late in 1943 this bacterium manifested an increased virulence. It became highly communicable; it produced rather intense scarlet fever; it precipitated severe rheumatic attacks in susceptible subjects; it became invasive. The acquisition of invasiveness by this micro-organism was accompanied by the rapid development of lytic phenomena in the patient, e. g. vomica formation, pericarditis, empyema and other suppurative lesions. Furthermore, strains of this bacterium identified serologically as types 17, 1 and 19 maintained their pathogenicity when transplanted by carriers to other geographic environments and even initiated streptococcal outbreaks at naval activities situated in Southern states.

ECONOMIC LIABILITIES OF STREPTOCOCCIC INFECTIONS

Each man who is taken up on the sick list with a streptococcal infection becomes a liability to the Navy. Not only are his services lost but, in addition, the services of two well persons are required to care for him. The duration of his time on the sick list is determined by the streptococcal syndrome manifested. The average man-days loss for common diseases induced by the hemolytic streptococcus in 1942 and 1943 is presented in table 1. This table shows that the average time spent on the Sick List for scarlet fever was 21.9 days, for rheumatic fever 92.1, for pneumonia 26.4 and for tonsillitis 5.7 days.

From the Bureau of Medicine and Surgery, Navy Department. U. S. Navy Epidemiology Units numbers 67 and 89 supplied data used in this report.

Read before the joint meeting of the Section on Practice of Medicine and the Section on Experimental Medicine and Therapeutics at the Ninety-Fourth Annual Session of the American Medical Association, Chicago, June 16, 1944.

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the U. S. Navy. The opinions and views set forth in this article are those of the writer and are not to be considered as reflecting the policies of the Navy Department.

Bacterial respiratory tract infections are costly not only in man-days loss but also in dollars expended. For example, the liability incurred for just four of these diseases at a single training station is conservatively estimated as shown in table 2.

A PROGRAM FOR THE CONTROL OF STREPTOCOCCIC INFECTIONS

The Navy's enormous loss to *Streptococcus haemolyticus* was only one of the compelling reasons for instituting a streptococcus control program. For military and civilian welfare it became essential to prevent the dissemination of the streptococcus among naval personnel, to prevent the induction of rheumatic fever with the development of incapacitating heart disease, to prevent the invasion of the streptococcus into deep tissues with the formation of suppurative lesions and to prevent the spreading of this highly virulent organism from one naval activity to another. To attain these objectives the U. S. Navy instituted a long term streptococcus control program in November 1943.

The first objective in this program was to check the dissemination of respiratory pathogens in the winter of 1944. For this purpose the use of prophylactic doses

TABLE 1.—Average Days Spent on the Sick List in 1942-1943 for Diseases Initiated by Respiratory Tract Pathogens

Diagnosis	Man-Days Loss
Scarlet fever	21.9
Tonsillitis, acute	5.7
Pharyngitis, acute	5.5
Catarrhal fever, acute.....	4.9
Laryngitis, acute	6.2
Bronchitis, acute	8.5
Tracheitis, acute	6.8
Tracheobronchitis, acute	10.5
Rhinitis, acute	5.2
Angina, Vincent's	8.4
Sinusitis, acute, group (pansinusitis, sinusitis: ethmoidal, frontal, maxillary, sphenoidal)....	15.8
Otitis media, acute.....	10.8
Mastoiditis, acute	60.6
Pneumonia, bronchial	26.4
Pneumonia, lobar	25.8
Cerebrospinal fever (meningococci).....	39.5
Rheumatic fever	92.1

of sulfadiazine seemed the method of choice. Other investigators had previously indicated the effectiveness of sulfonamide prophylaxis;¹ nevertheless, it seemed wise to control the administration of sulfadiazine with caution. To test the applicability of mass prophylaxis under controlled conditions and to determine a standard prophylactic dose of sulfadiazine, programs were designed for five large Northern training stations with high respiratory disease rates. Groups of trainees were then selected to receive sulfadiazine prophylaxis and comparable groups to serve as untreated controls. At each station these groups were placed under the surveillance of a Navy epidemiology unit consisting of two to five medical officers and four to ten pharmacist

1. Watson, R. F.; Schwentker, F. F.; Fetherston, J. E., and Rothbard, S.: Sulfadiazine Prophylaxis in an Epidemic of Scarlet Fever, *J. A. M. A.* **122**: 730-733 (July 10) 1943. Thomas, C. B., and France, R.: Preliminary Report of Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever, *Bull. Johns Hopkins Hosp.* **64**: 67-77 (Jan.) 1939. Thomas, C. B.; France, R., and Reichman, F.: The Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever, *J. A. M. A.* **116**: 551-560 (Feb. 15) 1941. Hansen, A. E.; Piatow, R. V., and Dwan, P. F.: Prolonged Use of a Sulfonamide Compound in Prevention of Rheumatic Recrudescences in Children: Evaluation Based on Four Year Study of 64 Children, *Am. J. Dis. Child.* **64**: 963-976 (Dec.) 1942. Kuttner, A. G., and Reyersbach, G.: The Prevention of Streptococcal Upper Respiratory Infections and Rheumatic Recurrences in Rheumatic Children by the Prophylactic Use of Sulfanilamide, *J. Clin. Investigation* **22**: 77-85 (Jan.) 1943. Chandler, Caroline A., and Taussig, Helen B.: Sulfanilamide as a Prophylactic Agent in Rheumatic Fever, *Bull. Johns Hopkins Hosp.* **72**: 42-53 (Jan.) 1943.

mates, all of whom had been trained in epidemiology. The duties of each unit included the following:

- (a) To supervise the distribution of sulfadiazine by line officers.
- (b) To administer the collection of clinical data on all men reporting to sick bay with respiratory symptoms.

TABLE 2.—Liability Incurred for Four Diseases at One Training Station

Disease	No. of Cases	Estimated Days Lost
Scarlet fever	4,973	108,908
Rheumatic fever	1,375	126,637
Pneumonia	1,383	36,511
Tonsillitis or pharyngitis.....	50,000	285,000
Total days lost to four diseases.....		557,056
Days consumed by personnel caring for these diseases.....		1,114,114
Estimated cost in salaries.....		\$5,000,000
Estimated cost in pensions for disabilities.....		\$10,000,000
Total cost for four streptococcus manifestations at one naval training station.....		\$15,000,000
Total man-days loss for four streptococcus manifestations at one naval training station.....		1,671,171

(c) To check the diagnoses of all men receiving sulfonamide compounds who were admitted to the sick list with respiratory infections.

(d) To obtain throat cultures on all such individuals and a sample (10 per cent) of individuals contracting respiratory infections in untreated control groups.

(e) To isolate the beta hemolytic streptococcus and ship these organisms in pure culture to the National Naval Medical Center, Bethesda, Md., for grouping, typing and testing of drug fastness.

On Dec. 1, 1943 this controlled program was initiated at five training stations. Data on the incidence of respiratory infections in the "treated" and control groups were collected for three months. With the accumulation of these data the effectiveness of mass prophylaxis was manifest. It was then decided to extend the program to three other naval activities experiencing a high incidence of streptococcal infections.

TABLE 3.—Monthly Morbidity for Certain Diseases Activity A

Rates per Thousand Men During the Winters of 1943 and 1944

Diagnosis	1943			1944		
	January	February	March	January	February	March
Tonsillitis.....	15.1	8.6	25.3	25.0	13.0	2.9
Catarrhal fever.....	75.1	58.2	76.3	54.2	26.6	5.6
Scarlet fever.....	0.5	2.8	9.3	16.6	4.4	0.8
Rheumatic fever.....	3.5	3.9	3.2	8.6	4.3	1.3
Septic sore throat.....	0.0	0.0	0.1	3.5	1.6	0.5
Pneumonia, bronchial.....	0.0	0.0	0.0	1.6	3.4	0.4
Pneumonia, lobar.....	0.5	0.0	0.6	1.3	1.7	0.2
Pneumonia, atypical.....	2.1	2.7	5.2	0.1	0.3	0.5
Sinusitis.....	3.7	3.6	5.1	6.7	5.0	1.8
Pharyngitis.....	1.7	0.8	4.5	1.4	6.0	1.3
Laryngitis.....	0.2	0.4	0.4	0.9	0.5	0.2
Otitis media, acute.....	2.3	3.2	6.3	6.0	5.6	1.8
Vincent's angina.....	2.5	2.0	1.8	0.1	0.0	0.5
Bronchitis.....	0.6	0.4	1.1	0.4	0.0	0.4
Meningitis.....	0.1	0.6	0.2	1.7	0.2	0.1
Mastoiditis, acute.....	0.0	0.0	0.1	0.4	0.2	0.1

and to discontinue the use of untreated controls in the five naval activities at which the sulfadiazine program was already in operation. Continuous mass prophylaxis was accordingly extended to about fifty camps of eight naval activities, and this program was continued throughout the spring months. The effectiveness of the overall program will be appraised in a forthcoming monograph.^{1a} The present paper is a preliminary report limited to observations on sulfadiazine prophylaxis instituted under three different conditions at three naval training camps.

1a. Nav. Med. 284.

THE EFFECT OF SULFADIAZINE PROPHYLAXIS INITIATED DURING A STREPTOCOCCIC OUTBREAK AT ACTIVITY A

Naval Activity A, situated in the city of Chicago, had experienced a high rate of infections occasioned by the great expansion of intensive training with a rapid turnover in personnel. Early in the winter its training program was seriously handicapped by a high incidence of streptococcal infections, which were subsequently identified as due to types 17, 3 and 30. During December 1943 more than 25 per cent of the station's complement were admitted to the sick list with respiratory infections, in all 27,966 man-days, or about 10 per cent of the available man power, were lost. The incidence of these infections continued to be high in January, and a large number of men developed rheumatic fever. By February 1944 the hospital admission rates² for respiratory diseases and sequelae had reached extraordinary heights: for catarrhal fever 988, for tonsillitis 426, for scarlet fever 171 and for rheumatic fever 70. The urgency of the situation and the expectancy of an increase in these rates during February and March

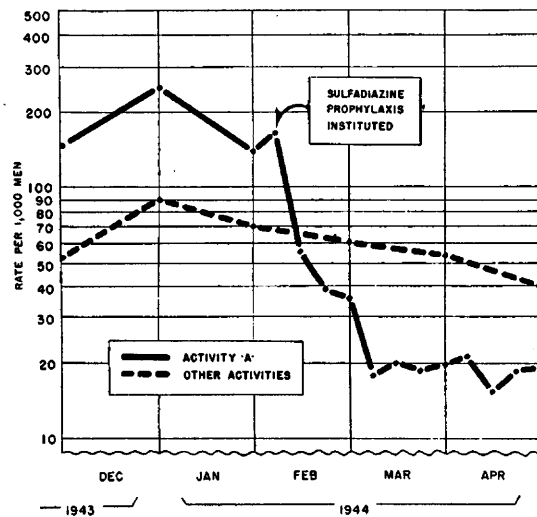


Chart 1.—A comparison of the monthly morbidity rates for respiratory tract infections at Activity A with those of other naval activities in the Chicago area.

were cogent reasons for placing all station personnel on sulfadiazine prophylaxis.

Results of Sulfadiazine Prophylaxis.—The institution of prophylaxis, 1 Gm. of sulfadiazine daily, on February 8 was followed by a rapid fall in the incidence of disease. For example, the scarlet fever rate² fell weekly to 70, to 45 and to 0 during the third week. The rheumatic fever rate rose during the first week of prophylaxis to 87 and then fell progressively by weeks to 45, 19 and 6. The fall in incidence of respiratory diseases observed in February became even more pronounced in March and April 1944. That this was not to be expected from the experience of 1943 is shown in table 3. And it is seen in table 4 that this phenomenal change was not observed at other naval activities in Chicago during March and April 1944. A comparison of the monthly morbidity rates for respiratory infections at Activity A receiving sulfadiazine prophylaxis after February 8 and for five other naval activities in Chicago receiving no prophylaxis is shown in chart 1.

In summary, the institution of sulfadiazine prophylaxis 1 Gm. daily to all hands at Activity A on

2. Annual admission rates per thousand strength.

February 8 during a severe streptococcic outbreak was accompanied by a precipitous, contraseasonal decline in streptococcic infections and was followed by a striking drop in the incidence of rheumatic fever.

EFFECT OF SULFADIAZINE PROPHYLAXIS INSTITUTED IN HALF A CAMP AT THE ONSET OF A SCARLET FEVER OUTBREAK

Camp 1 of a naval training station had served as an untreated control group for the prophylactic program during the early winter months of 1943-1944. The

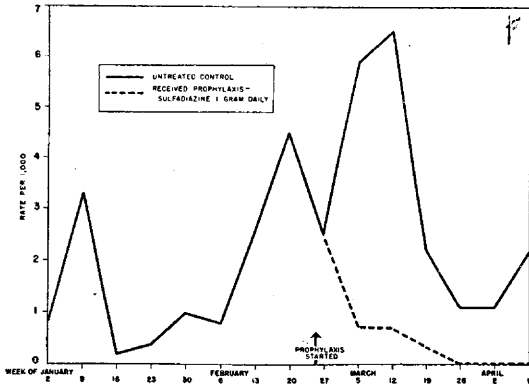


Chart 2.—The effectiveness of sulfadiazine prophylaxis as reflected by the incidence of scarlet fever in Camp 1 during the winter and spring months of 1944.

incidence of streptococcic infections among these 5,000 men had been moderate during December and January. About the middle of February the scarlet fever rate began to rise rapidly, and this was accompanied by a decided increase in the occurrence of other streptococcic respiratory diseases. Most of these infections, irrespective of the presence or absence of a scarlatinal rash, were caused by hemolytic streptococcus group A, type 19. On February 25 one half of the complement of this camp was placed on a prophylactic dose of 1 Gm. of sulfadiazine daily; the other half remained untreated. The effectiveness of sulfadiazine in preventing further

TABLE 4.—Acute Respiratory Tract Infections* at Various Naval Activities in Chicago
Admission Rates per Thousand Strength, Winter of 1943-1944

Naval Activity in Chicago	1943			1944		
	November	December	January	February	March	April
A	146	254	130	74	19	19
B	176	145	210	89	89	54
C	64	71	61	49	54	35
D	40	71	64	44	33	26
E	27	88	61	76	54	43
F	17	100	39	52	46	48

* Includes: tonsillitis, acute; pharyngitis, acute; catarrhal fever, acute; bronchitis, acute; laryngitis, acute; Vincent's angina; pneumonia, all forms; scarlet fever; septic sore throat; influenza; rheumatic fever.

spread of this highly communicable strain of hemolytic streptococcus in recruits receiving prophylaxis is shown in chart 2.

EFFECTIVENESS OF SULFADIAZINE IN PREVENTING IMPLANTATIONS OF HEMOLYTIC STREPTOCOCCUS IN A RECRUIT CAMP

The foregoing observations indicated that 1 Gm. of sulfadiazine administered daily was effective in checking a streptococcic outbreak, either when well advanced (Activity A) or in its early stage (Camp 1). The following observations will serve to show that as little as 0.5 Gm. of sulfadiazine administered daily prevents the implantation of the hemolytic streptococcus in a

recruit group (Camp 2) with a complete turnover of personnel every four to six weeks.

Camp 2 was situated about 1 mile from Camp 1 on the same naval training station. In November 1943, when the incidence of streptococcic infections was low, this camp was divided into two groups for the purpose of this investigation. All even numbered companies were placed in group A, which received no chemo-

TABLE 5.—The Incidence of Respiratory Infections (Probably Hemolytic Streptococcus) in Camp 2

Four Week Period Ended	All Respiratory Illness with Positive Hemolytic Streptococcus Cultures				x/σ	P
	A. Control		B. Treated			
	Number Cases	Rate per 1,000	Number Cases	Rate per 1,000		
2/6/44	77	46.88	9	5.27	7.43	<0.0001
3/5/44	113	79.02	9	6.05	9.60	<0.0001
4/2/44	18	6.88

TABLE 6.—The Incidence of Frank Streptococcic Infections in Camp 2

Four Week Period Ended	Scarlet Fever, Tonsillitis and Pharyngitis				x/σ	P
	A. Control		B. Treated			
	Number Cases	Rate per 1,000	Number Cases	Rate per 1,000		
2/6/44	26	15.83	2	1.17	4.56	<0.0001
3/5/44	64	44.75	2	1.34	7.06	<0.0001
4/2/44	3	1.15

prophylaxis, and all odd numbered companies were placed in group B, which received 0.5 Gm. of sulfadiazine daily. On March 1 both groups were placed on a prophylactic regimen of sulfadiazine 1 Gm. daily. The incidence of respiratory symptoms and respiratory diseases of groups A and B is shown in chart 3. Data on the incidence of probable and frank hemolytic

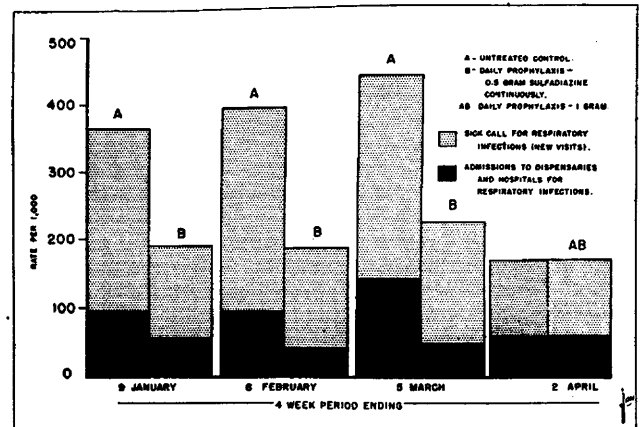


Chart 3.—The effectiveness of continuous sulfadiazine prophylaxis in preventing respiratory tract infections in Camp 2.

streptococcus infections of the two groups are summarized in tables 5 and 6.

It is seen in chart 3 and tables 5 and 6 that the group receiving sulfadiazine prophylaxis had a low incidence of respiratory infections. This low incidence in group B was maintained for three months, and perhaps greater protection was afforded during March, when the prophylactic daily dose of sulfadiazine was increased from 0.5 to 1.0 Gm. The incidence of sick call visits for respiratory symptoms in the untreated group was twice

that in the treated group, and the incidence of respiratory diseases requiring bed care in the untreated group was about three times that in the treated group. In both the difference in incidence between untreated and treated groups is statistically significant. This difference is even more striking for streptococcal infections. The incidence of respiratory disease probably caused by the hemolytic streptococcus in the untreated group was eleven times the incidence of the treated group. Frank streptococcal infections in the untreated group had an incidence twenty-four times that of the treated group.

EVALUATION OF THE POTENTIAL LIABILITIES AND ASSETS OF SULFADIAZINE PROPHYLAXIS

When this program was initiated, there appeared to be three potential dangers inherent in sulfadiazine prophylaxis: (a) sensitization of patients to sulfonamide compounds, (b) induction of severe, irreversible drug reactions, (c) development of drug fastness by respiratory pathogens.

Sensitization of Patients.—Mild evanescent dermal drug sensitization phenomena occurred in all three groups receiving sulfadiazine. The incidence of symptoms ascribed to the drug varied between 0.2 and 0.7

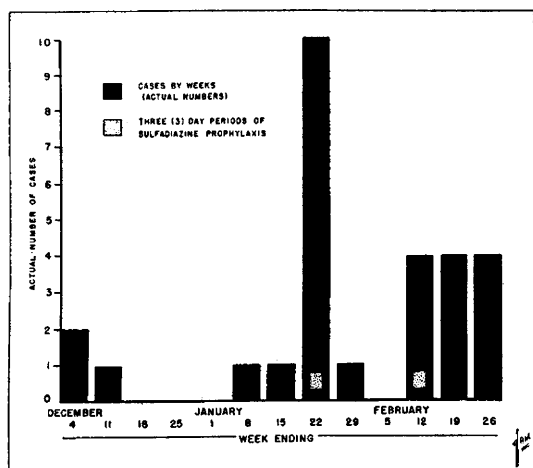


Chart 4.—The ineffectiveness of two short courses of sulfadiazine in checking an outbreak of scarlet fever at a small naval activity.

per cent. Approximately half of these reactors when retested had no drug symptoms and were replaced on the prophylactic program. The large majority of all reactions occurred in the second and third weeks of prophylaxis following the total dosage of 7 to 20 Gm. of sulfadiazine. The reinstitution of prophylaxis in groups who had been without sulfadiazine for a period of one to four weeks did not increase the incidence of drug reactions. A few individuals who had manifested sensitivity to sulfonamide compounds and who subsequently contracted severe respiratory infections were treated with penicillin. The collected findings indicated that a small percentage of persons have an idiosyncrasy to sulfonamide compounds administered in therapeutic or prophylactic doses and that sulfadiazine prophylaxis per se does not sensitize.

Severe Irreversible Drug Reactions.—Dangerous untoward reactions occurred in 0.01 per cent of individuals receiving sulfadiazine prophylaxis. These were of two types and about equally divided between exfoliative dermatitis and granulocytopenia. With supportive treatment these disease processes appeared reversible. The administration of therapeutic doses of sulfonamide to one man with a sulfonamide rash and bronchitis was

followed by death. This was the only instance in which death occurred. The autopsy showed lymphadenopathy, which on microscopic examination proved to be leukemia.

Development of Drug Fastness by Respiratory Pathogens.—Fastness to sulfadiazine was apparently not initiated during the first four months of this prophylactic program. The evidence is:

1. There was no increase in the prevalence of any serologic type of hemolytic streptococcus in the groups on prophylaxis.
2. There was no increase in the proportion of hemolytic streptococci in the throat flora of individuals throughout the period of prophylaxis.
3. There was no increase in streptococcal morbidity throughout the period of prophylaxis.
4. There was no difficulty in obtaining a satisfactory therapeutic effect from sulfadiazine in individuals who contracted streptococcal infections while receiving prophylaxis.

In summary, the only liability incurred in this program was the development of a few severe drug reactions, 1 in 10,000 individuals receiving prophylaxis.

The gains from the program included prevention of disabilities, saving in man-days loss and a reduction in the costs for care of the sick and for pensions. The size of these gains was proportional to the incidence of bacterial infections of the respiratory tract. Among recruits with a high incidence of infections it was estimated that 343 man-days were saved per thousand weekly from bacterial infections. Most of these man-days were saved through the prevention of streptococcal infections. Since these infections are prone to cause debilitating sequelae, their prevention obviously created enormous benefits to Naval personnel and to the United States government in a state of war.

COMMENT

A number of observers have pointed out the effectiveness of a short course of sulfadiazine prophylaxis in checking outbreaks of meningococcal infections.³ This measure not only breaks the epidemic process but also eliminates the meningococcus from the throat flora of carriers. Because of this misconception has arisen in the handling of streptococcal outbreaks. Sulfadiazine administered for a few days, either in prophylactic or in therapeutic doses, does not check a streptococcal outbreak and has little or no effect on the throat flora of individuals in the carrier state. This fact was demonstrated by a small naval activity experiencing an outbreak of scarlet fever. Sulfadiazine was given for three days in January with apparently good results; however, the outbreak recurred in February when another three day period of prophylaxis was administered with little effect. All personnel were subsequently placed on a continuous prophylactic program of sulfadiazine 1 Gm. daily, early in March. The streptococcal outbreak then subsided and only 2 new cases of scarlet fever occurred in the following ten weeks. The ineffectiveness of short courses of sulfadiazine at this activity is shown in chart 4. This experience illustrated that a three day course of prophylaxis, which will effectively check a meningococcal outbreak, is not adequate for preventing streptococcal infections. The presence of sulfadiazine on the surface of mucous membranes prevents

3. Cheever, F. S.; Breese, B. B., and Upham, H. C.: The Treatment of Meningococcus Carriers with Sulfadiazine, *Ann. Int. Med.* **19**: 602-608 (Oct.) 1943. Thomas, H. M., Jr.: Meningococcal Meningitis and Septicemia: Report of Outbreak in Fourth Service Command During Winter and Spring of 1942-1943, *J. A. M. A.* **123**: 264-272 (Oct. 2) 1943. Kuhns, D. M.; Nelson, C. T.; Feldman, H. A., and Kuhn, L. R.: The Prophylactic Value of Sulfadiazine in the Control of Meningococcal Meningitis, *ibid.* **123**: 335-339 (Oct. 9) 1943.

implantation of hemolytic streptococci but does not modify the streptococcus flora already implanted.

The exact concentration of sulfadiazine in the nasopharyngeal secretions required to prevent implantation of bacterial respiratory pathogens is still unknown. In the course of the present studies it was found that individuals receiving a daily dose of 1 Gm. of sulfadiazine had blood values ranging between 2.6 and 1.7 with a median of 2.2 mg. per hundred cubic centimeters and that with a daily dose of 0.5 Gm. the blood values ranged between 1.8 and 0.8 with a median of 1.4 mg. per hundred cubic centimeters. The findings of others⁴ have shown that the concentration of sulfadiazine in the secretions of the upper respiratory tract is about 60 per cent of blood levels. The observations made in Camp 2, therefore, indicate that these secretions containing less than 1 mg. of sulfadiazine per hundred cubic centimeters were adequate to prevent the implantation of most bacterial respiratory tract pathogens.

SUMMARY

1. The United States Navy is engaged in a long term program for the control of streptococcal infections and their disabling sequelae.

2. One component of this program involves mass prophylaxis with sulfadiazine.

3. Prophylactic doses of this drug were given continuously to about 250,000 naval trainees between December 1943 and April 1944.

4. This preliminary report deals with observations on only 30,000 men at three camps.

5. These observations indicate that the continuous ingestion of 1 Gm. of sulfadiazine daily is adequate (a) to check a well advanced streptococcal epidemic, (b) to check a streptococcal outbreak at its onset and (c) to protect 85 per cent of susceptible recruits from implantation with bacterial respiratory pathogens.

6. These observations also suggest that a continuous daily dose of 0.5 Gm. of sulfadiazine (affording a mean level of 1.4 mg. per hundred cubic centimeters in the blood and perhaps 0.8 mg. per hundred cubic centimeters in secretions of the respiratory tract) is almost 85 per cent effective in preventing implantation by *Streptococcus haemolyticus*.

7. The only untoward effect of mass sulfadiazine prophylaxis is the occurrence of evanescent rashes in 0.5 per cent and dangerous constitutional disturbances in 0.01 per cent.

8. Mass sulfadiazine prophylaxis is effective (a) in checking bacterial infections of the respiratory tract, (b) in preventing the development of disabling sequelae caused by these bacteria and (c) in aiding the economy of a nation at war.

ABSTRACT OF DISCUSSION

ON PAPERS OF COLONEL HOLBROOK AND
COMMANDER COBURN

DR. T. DUCKETT JONES, Boston: I have no doubt that the general contentions of both speakers are absolutely true. There can be little doubt that sulfadiazine in dosages as indicated and administered as indicated will definitely affect the illness rates, particularly those caused by hemolytic streptococci. I do not think the question of sensitivity to these drugs is yet answered. Sensitivity may not develop until many months after the cessation of the preventive administrations. That is a serious problem, and I wonder if either speaker had any means whereby he might evaluate the question of development

4. Norris, C. M.: Sulfonamides in Bronchial Secretion: The Effect of Sulfonamides in Bronchiectasis, *J. A. M. A.* 123: 667-670 (Nov. 13) 1943.

of sensitivity in any of the men receiving the drug. Commander Coburn showed some stations that were control stations. In my experience there have been great differences in illnesses, so that this type of control must be difficult. Neither presentation showed bacteriologic charts, but apparently the charts included bacteriologic infections. The only data at present with regard to rheumatic fever are those of Colonel Holbrook, and I saw no significant difference in the group as he presented it. In conclusion I should like to suggest that perhaps we may control the major features of streptococcal illness by giving the drug to small groups of men who constitute a single epidemiologic unit and base conclusions on the actual illness experiences in these groups. We know that at least 50 per cent of the men will not need preventive measures. It is possible that the drug can be used intelligently to prevent the maximum amount of disease by giving the drug to the minimum number of men.

CAPTAIN RICHARD G. HODGES, M. C., A. U. S.: In evaluating an epidemiologic experiment on respiratory disease it is necessary to exercise considerable caution because there are a number of factors which can cause considerable variation in the respiratory disease rates. In the military population the seasoning of the troops is extremely important. The living conditions of the troops, particularly as pertain to ventilation and dust, the duties of the troops and finally the inflow of new material into the population may also cause profound changes. It is possible that the mass of Commander Coburn's material makes careful control of these factors somewhat unnecessary. However, to substantiate his contentions I should like to mention my experience at an Army Air Force technical school where a considerable degree of control was possible. The school was almost ideally set up for a controlled experiment, being divided into two teaching shifts of approximately 5,000 men each. The duties, the living conditions and even the recreations of the two groups were identical. They were on different time schedules, and thus mixing between the two was at a minimum. Percentage distributions according to length of stay on the field, according to the length of service and according to age were approximately the same for the two. The inflow of new troops into these two groups was approximately equal. Finally, for the preceding fifteen months component squadrons of the school were found to have behaved similarly toward respiratory disease and to an approximately similar degree. During January both groups showed a progressive rise in rate. On the 2d, 3d and 4th of February the members of one teaching shift received 2 Gm. of sulfadiazine per day. Their rate dropped sharply, while the control group's continued to rise. The drop lasted ten days. Then the other group was placed on 2 Gm. a day for two days and showed a corresponding but somewhat less prolonged response. Finally one group was placed on a continuous dosage of 1 Gm. a day and the other group was placed on 2 Gm. a day for two days, and then that was repeated one week later. Both dropped sharply. The response was greatest in streptococcal infections. The streptococcus disease rate was lowered almost to zero by each administration. Thus I believe that the effectiveness of the treatment with sulfadiazine is established.

COMMANDER ALVIN F. COBURN (MC), U.S.N.R.: There are two points that I should like to mention before the conclusion of this discussion. One is that conditions in naval training camps lend themselves well to controlled studies. Alternate companies can either be given prophylaxis or serve as untreated groups. Accurate data can be obtained. Except for the one program which, as I stated, was instituted during an epidemic at a naval activity here in Chicago, all of the navy studies were controlled. Companies selected in random fashion mingled and slept in the same barracks, used common mess halls and exercised together in common drill halls. These studies in the effectiveness of chemoprophylaxis were made under ideal conditions. The second point, which was mentioned only briefly, is that sulfadiazine prophylaxis was effective in preventing rheumatic fever. The incidence of rheumatic fever among men receiving chemoprophylaxis was 15 per cent of the incidence in control groups. Approximately 85 per cent of the expected rheumatic fever cases appeared to be eliminated by sulfadiazine.

DR. ROY W. SCOTT, Cleveland: Are there any advantages of sulfadiazine over sulfathiazole?

COLONEL W. PAUL HOLBROOK, M. C., A. U. S.: Dr. Jones asked about what is being done to determine the question of sensitivity. The possibility of individuals becoming sensitized to the drug has been considered. As yet, evidence for an increasing sensitivity in individuals who are on the prophylactic program is not available. Repeated periods of prophylaxis on the same groups have shown in each instance a decreased number of reactors for the second or third prophylactic period rather than an increase. Once the known positive reactors are eliminated, no further difficulty is encountered during subsequent periods of prophylaxis. We also now have a rather large number of troops who have had prophylactic sulfadiazine and who have subsequently developed an acute illness requiring the administration of sulfadiazine therapeutically. These patients have responded as well as those not having had a prophylactic period. These experiences do not appear compatible with an increasing sensitivity. A long range study is planned by means of recording each individual's prophylactic record on his immunization register, so that in six months or a year a rather large accumulation of information should be available on this subject. I have not used sulfathiazole, largely because of the general reports in the literature as to its increased toxicity, but I have no experience in its use for this type of prophylaxis.

THE TREATMENT OF TONSILLITIS WITH SMALL DOSES OF SULFONAMIDES

CAPTAIN EDWARD D. FREIS

MEDICAL CORPS, ARMY OF THE UNITED STATES

From both military and economic aspects, any relatively nontoxic therapy which will shorten the course of a prevalent disease, if even for a few days, is worthy of application. Since it is generally acknowledged that tonsillitis is responsible for a significant number of the total man hours lost to industry and the armed forces, the advisability of treating acute follicular tonsillitis with sulfonamides has been the subject of a variety of studies. From the medical point of view, chemotherapy would be desirable because of the possibility that such complications as peritonsillar abscess and such sequelae of tonsillitis as nephritis and rheumatic fever might be prevented or at least minimized.

The advisability of using large doses of sulfonamides (2 Gm. or more per day) in the treatment of tonsillitis remains controversial. Some believe that, since this disease is relatively benign and self limited, chemotherapy is unnecessary and even dangerous.¹ This view is supported by the number of serious toxic reactions that have resulted from the indiscriminate use of the sulfonamides. Others believe with Gettelman and Kaiz² that early treatment with sulfonamides (2 Gm. per day) appreciably shortens the course of the disease.

From the AAF Rheumatic Fever and Streptococcal Disease Control Program.

Lieut. Col. Robert King, M. C., and Dr. Chester S. Keefer cooperated with suggestions and criticisms.

From the Medical and Laboratory Services, AAF Regional Station Hospital, U. S. Army Air Field, Lincoln, Neb.

1. Rhoads, P. S., and Afremow, M. I.: Sulfanilamide in the Treatment of Sore Throat Due to Hemolytic Streptococci, with Controls, *J. A. M. A.* **114**: 942 (March 16) 1940. Richards, L. G.: Treatment of Diseases of the Throat, *ibid.* **115**: 501 (Aug. 17) 1940. Hughes, L. W.: Diseases of the Nasopharynx, *Mississippi Doctor* **18**: 261 (Oct.) 1940. Kernan, J. D.: Infections of the Mouth, Pharynx, and Respiratory Tract, *Bull. New York Acad. Med.* **17**: 674 (Sept.) 1941. Beckman, H.: Treatment in General Practice, ed. 4, Philadelphia, W. B. Saunders Company, 1942.

2. Gettelman, E., and Kaiz, S. P.: The Treatment of Severe Tonsillitis in a Naval Dispensary, *U. S. Nav. M. Bull.* **42**: 399 (Feb.) 1944.

A middle of the road point of view is taken by Janeway,³ who prescribes chemotherapy only for those patients whose temperature exceeds 102 F.

In addition to systemic therapy, the local treatment with sulfonamide sprays has become popular. Many investigators have reported effective therapeutic results and an absence of drug reactions following the use of local sprays in the treatment of various upper respiratory infections.⁴

In order to establish the relative efficacy of the local and systemic administration of sulfonamides in the treatment of acute follicular tonsillitis we considered it necessary to study this question under controlled conditions using hospitalized patients.

METHOD

During the winters of 1943 and 1944 a series of 405 young men of military age who had definite clinical evidence of acute follicular tonsillitis were hospitalized to a separate ward devoted to their care. During the first year of the study the patients were divided into two groups, alternate patients being treated by one of two methods. One group (1) of 100 patients were given only hot saline irrigations every four hours and received no chemotherapy. The other group (2) of 100 patients were treated with hot saline irrigations every four hours and in addition received sulfanilamide spray to the tonsils and pharynx every two hours except while asleep. Powdered sulfanilamide was sprayed into the throat until an even white coating of the mucous membranes was produced, the patient being then instructed to swallow, following which the throat was again sprayed.⁵ The amount of sulfanilamide used per dose varied from 75 to 100 mg. and, as eight applications were administered daily, the total daily dosage varied from 500 to 800 mg. With this dosage blood sulfanilamide levels were never found to be above 1 mg. per hundred cubic centimeters and usually were too low to be read by standard methods.

During the second year group 3, consisting of 115 patients, received saline irrigations every four hours and, in addition, 125 mg. of sulfadiazine by mouth four times a day (500 mg. daily). The sulfadiazine was in tablet form and was swallowed immediately. Another group (4) of 90 cases was treated in the same way as group 2 except that "microform crystals" of sulfadiazine⁶ were substituted for sulfanilamide powder.

On admission a throat culture and white blood count were obtained. Patients who showed peritonsillar abscess, fusospirochetal ulcers of the tonsil, scarlet fever, acute glomerulonephritis or rheumatic fever on admission were not included in this study. Similarly excluded were patients who had the common cold with nasopharyngitis and tonsillar swelling without pronounced redness or follicles.

As indicated in the table, the four groups were essentially similar in regard to admission temperature, infecting organism and average admission leukocyte counts.

3. Janeway, C. A.: *Medical Progress: The Sulfonamides*, New England J. Med. **227**: 1029 (Dec. 31) 1942.

4. Freeman, M. S.: Local Use of Sulfathiazole Powder for Acute Pharyngeal Infections, *Arch. Otolaryng.* **37**: 496 (April) 1943. Silcox, L. E., and Schenck, H. P.: Use in Otolaryngology of Microcrystals of Drugs of the Sulfanilamide Group, *ibid.* **36**: 171 (Aug.) 1942. Dolowitz, D. A.; Loch, W. E.; Haines, H. L.; Ward, A. T., and Pickrell, K. L.: The Prevention of Ear and Nasal Sinus Complications of the Common Cold, *J. A. M. A.* **123**: 534 (Oct. 30) 1943. Turnbull, F. M.; Hamilton, W. F.; Simon, E., and George, M. F.: Sinusitis and Infections Secondary to the Common Cold, *ibid.* **123**: 536 (Oct. 30) 1943.

5. The DeVilbiss standard atomizer-type powder blower No. 175 was used.

6. Smith, Kline and French laboratories supplied the sulfadiazine microform crystals.