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TREATMENT OF PNEUMOCOCCIC PNEUMONIA WITH SULFANILAMIDE

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DETROIT

Sulfanilamide has proved bacteriostatic against types I, II, III and XIV pneumococci in vitro and in laboratory animals, according to various authors.[1] While the drug probably has been used widely for human pneumococcic pneumonia, the reports to date are meager. Heintzelman, Hadley and Mellon [2] used it in nine cases of type III pneumonia and obtained seven recoveries, whereas among ten controls there were only two recoveries. Millett [3] reported one case of type III pneumonia in which a crisis occurred after the use of sulfanilamide. Louis [4] added six cases of pneumococcic pneumonia in which recovery occurred with sulfanilamide therapy.

The following report is based on 115 patients treated with sulfanilamide,[5] compared with forty patients receiving serum and ninety-four controls receiving identical symptomatic and supportive measures but no specific therapy. While this series is too small to be statistically significant, it is reported in the hope that an evaluation of the drug in the treatment of pneumonia may eventually be made by combining it with cases studied elsewhere.

METHOD OF STUDY

Diagnosis.—The diagnosis was confirmed by roentgenogram in every case. The admission sputum was typed directly by the Neufeld method, and the results were checked either by mouse inoculation or by the direct typing of a second specimen. Typing was repeated in the event of an extension. Blood for culture was taken on admission and cultures were repeated daily if positive. Hemoglobin estimations, white cell counts and differential counts were made daily during sulfanilamide therapy and at frequent intervals for the controls. Red cell counts were made twice weekly. Serum agglutinins were determined during convalescence.

Selection of Cases.—All patients over 12 years of age with pneumonia due to a single type of pneumococcus who were admitted between Oct. 1, 1937, and July 1, 1938, and remained in the hospital at least twenty-four hours were included in this study. Children under 12 were excluded because childhood and adult pneumonias are not strictly comparable. Patients who were moribund on admission and died within twenty-four hours were excluded because it was felt that they did not provide a fair trial of any form of therapy. Eight such patients were treated with sulfanilamide, three with serum and eight as controls. Two other patients treated as controls for three and six days respectively, with sulfanilamide therapy started within eight hours of death, were excluded from the tabulations.

Alternate patients with types I, II and VII pneumonia were treated with sulfanilamide and Felton serum, a few being reserved as controls. With types V and VIII pneumonia, serum was available for only a portion of the patients alternated with those receiving sulfanilamide. With the remaining types, patients receiving sulfanilamide were alternated with controls, who received similar symptomatic and supportive treatment. If for any reason the type could not be determined promptly, the patient was classed tentatively among those having nonpneumococcic pneumonia, who likewise were treated alternately with sulfanilamide. For several of these patients the type of invading pneumococcus was subsequently determined, thus causing discrepancies in the total number of patients treated by the two methods.

Dosage of Sulfanilamide.—The oral route was used as a routine, subcutaneous injections being substituted with those too ill to take or retain the drug by mouth. An initial massive dose of 15 grains (1 Gm.) to 20 pounds (9 Kg.) of body weight was given to all patients, those over 160 pounds (73 Kg.) receiving the maximum dose of 120 grains (8 Gm.). A similar total (15 grains to 20 pounds) was administered during the next twenty-four hours, divided into six equal doses, the first given four hours after the initial massive dose and the remainder at intervals of four hours around the clock. An equal amount of sodium bicarbonate accompanied each dose of sulfanilamide. The blood sulfanilamide

This study was aided in part by a grant from the Commonwealth Fund. From the Medical Department of the City of Detroit Receiving Hospital and Wayne University College of Medicine.

1. These include:
Rosenthal, S. M.: Chemotherapy of Experimental Pneumococcus Infections, Pub. Health Rep. **52:** 48 (Jan 8) 1937.
Gross, Paul, and Cooper, F. B.: P-Aminobenzenesulfonamide and Antipneumococcal Serum Therapy in Type I Pneumococcal Infections in Rats, Proc. Soc. Exper. Biol. & Med. **36:** 535 (May) 1937.
Kreidler, W. A.: Treatment of Pneumococcal Infections in Rabbits with Sulfanilamide, ibid. **37:** 146 (Oct.) 1937.
Cooper, F. B., and Gross, Paul: Sulfanilamide, Antipneumococcus Serum and Vitamin C Therapy in Type II Pneumococcal Pneumonia of Rats, ibid. **36:** 774 (June) 1937.
Cooper, F. B.; Gross, Paul, and Lewis, M.: Chemotherapy of Pneumococcal (Type II) Meningitis in the Rat, ibid. **38:** 835 (June) 1938.
Cooper, F. B.; Gross, Paul, and Mellon, R. R.: Action of P-Aminobenzenesulfonamide on Type III Pneumococcus Infections in Mice, ibid. **36:** 148 (March) 1937.
Cooper, F. B., and Gross, Paul: P-Aminobenzenesulfonamide Therapy in Experimental Type III Pneumococcal Pneumonia, ibid. **36:** 678 (June) 1937.
Schmidt, L. H.: Use of Sulfanilamide in Treatment of Type XIV Pneumococcus Infections in Mice, ibid. **37:** 205 (Oct.) 1937.

2. Heintzelman, J. H. L.; Hadley, P. B., and Mellon, R. R.: Use of P-Aminobenzenesulfonamide in Type III Pneumococcus Pneumonia, Am. J. M. Sc. **193:** 759 (June) 1937.

3. Millett, Joseph: Sulfanilamide: Report of a Case, New York State J. Med. **37:** 1743 (Oct. 15) 1937.

4. Louis, D. J.: The Treatment of Pneumonia with Sulfanilamide, Illinois M. J. **73:** 422 (May) 1938.

5. The sulfanilamide was furnished by Merck & Co.

level was determined within the first twenty-four hours and daily thereafter. An attempt was made to keep the blood concentration between 7 and 15 mg. per hundred cubic centimeters but preferably above 10 mg. As long as it was within this range, 15 grains to 20 pounds divided into six equal doses was given during each subsequent twenty-four hour period. If the blood level did changes in the blood picture, treatment with sulfanilamide was discontinued and transfusions were given.

Treatment of Patients Receiving Serum and of Controls.—This treatment was similar to that described by one of us (A. E. P.[6]) in a previous communication, except that serum was given in larger doses at intervals of two hours. The average total dose for type I pneu-

TABLE 1.—*Summary of Cases*

	Patients Treated with Sulfanilamide										Controls and Patients Treated with Serum									
Type	Number of Cases	Average Age	Chronic Alcoholism	Average Duration Before Therapy, Hours	Average Number of Lobes Consolidated	Extension	Bacteremia	Good Therapeutic Response	Average Time Until Therapeutic Response, Hours	Number of Deaths	Form of Treatment	Number of Cases	Average Age	Chronic Alcoholism	Average Duration Before Therapy, Hours	Average Number of Lobes	Extension	Bacteremia	Average Time Until Therapeutic Response, Hours	Number of Deaths
I	11	36	2	90.4	1.5	2	2	9	49	1	C.	6	41	2	122	2.3	1	2	132	3
											Ser.	10	32.3	1	69.3	1	3	4	36	0
II	18	42.8	6	100	1.5	3	3	14	53.3	3	C.	6	35.5	1	106.8	1.1	0	3	101.3	3
											Ser.	14	39.4	3	46.2	1.2	2	5	56	6
III	5	40	1	62.4	1.6	0	1	2	27	3	C.	9	65.6	0	77.4	1.3	0	2	88	6
IV	9	38.3	4	113.1	1.7	3	2	5	55.6	1	C.	5	50	2	189	1.4	0	1	96	2
V	11	37	3	74.9	1.1	2	2	11	48.4	0	C.	6	47	3	86	1	0	1	201.6	1
											Ser.	5	41.2	1	80	1	0	0	18.6	0
VI	3	53	1	56	1	0	1	2	52	1	C.	2	64.5	1	48	3.5	0	0	.....	2
VII	10	38.2	3	126.8	1.3	2	1	5	67.8	1	C.	3	52.3	0	38	2.3	0	0	64	0
											Ser.	9	45.4	3	60.3	1.4	1	3	65.2	5
VIII	7	33.4	1	77.8	1.4	0	0	6	45	1	C.	6	46	1	46.5	1.3	0	0	66	0
											Ser.	2	54	1	40	1	0	0	36	0
IX	1	35	1	48	3	0	0	1	84	0	C.	4	29.5	1	31	1.7	1	0	96	1
X	1	42	0	120	1	0	0	0	....	0	C.	1	77	1	0	1	1	0	192	0
XI	0										C.	1	12	0	0	1	0	0	.....	0
XII	5	33.4	0	105.2	2	0	1	5	49.8	0	C.	4	40	1	24.5	1	0	1	67	0
XIII	0										C.	1	36	0	72	2	0	0	4	0
XIV	4	29	2	138.2	2	0	4	3	64	0	C.	2	39	0	60	1	1	0	144	1
XV	3	34.7	2	64	1.3	0	0	3	56	0	C.	3	44.7	1	11.3	1	1	0	84	0
XVI	2	50	0	81	1	0	0	2	24	0	C.	2	37	0	72	2	0	0	72	0
XVII	4	39.5	2	87.2	1.5	0	0	3	23	1	C.	3	53	1	16	2.3	1	0	72	1
XVIII	3	36	2	65	1.7	0	0	2	15	1	C.	6	41	1	68	1.5	0	0	82.8	1
XIX	5	35.4	0	109.4	1.2	0	2	4	70	1	C.	6	44	0	32	1.8	0	1	168	2
XX	2	48	1	60	1.5	0	0	1	12	1	C.	3	50.6	0	52	1.3	0	1	84	1
XXI	1	36	0	24	1	0	0	1	48	0	C.	0								
XXII	0										C.	2	52	2	182	2.5	1	0	.....	2
XXIII	1	12	0	144	1	0	0	1	48	0	C.	1	66	0	86	1	0	1	168	0
XXIV	2	45	0	66	3	0	0	2	65.5	0	C.	1	47	1	96	1	0	0	120	0
XXV	2	48	0	126	3.5	0	1	1	120	1	C.	3	27	1	61	1.3	0	1	60	1
XXVIII	2	41	2	31.5	2	0	0	1	11	1	C.	2	27	0	36	1.5	0	0	60	0
XXIX	1	49	1	65	1	0	0	1	25	0	C.	4	46	2	96	2	0	1	18	2
XXXI	1	36	0	48	1	0	0	0	....	0	C.	1	52	0	144	2	0	0	72	0
XXXII	1	59	1	168	2	0	1	0	....	1	C.	1	49	0	0	1	1	0	120	0
	115	38.7	35	92.0	1.53	12	21	85	50.3	18	C.	94	45.6	22	71.7	1.51	8	15	98.9	29
											Ser.	40	39.9	9	59.1	1.16	6	12	42.5	11

TABLE 2.—*Effect of Sulfanilamide on Temperature*

Blood Sulfanilamide Level at the Time Temperature Level Fell to Normal	Hours Between Commencement of Sulfanilamide Therapy and Defervescence									Maximal Blood Sulfanilamide Level	No Response to Sulfanilamide		Totals
	0-11	12-23	24-35	36-47	48-59	60-71	72-83	84-95	96-120		Recovered	Died	
Below 4 mg. per 100 cc.	0	0	0	2	0	0	0	0	0		0	0	2
4- 6.9 mg. per 100 cc...	2	0	0	1	0	1	1	1	0		4	1	11
7- 9.9 mg. per 100 cc...	4	4	5	6	3	1	3	2	3		4	7	42
10-12.9 mg. per 100 cc...	3	4	3	5	2	1	3	2	3		3	4	35
13-15.9 mg. per 100 cc...	4	3	1	2	1	0	0	0	1		0	3	15
16-21 mg. per 100 cc.....	0	0	0	0	0	0	0	0	0		1	3	4
Not determined.....	0	2	0	0	1	0	0	1	2		0	0	6
Totals.....	13	13	9	16	7	3	7	6	11		12	18	115

not reach 7 mg. per hundred cubic centimeters, either the subcutaneous route was substituted or a larger dose was given by mouth. In most instances administration of the drug was discontinued after the temperature had been normal for twenty-four hours. If blood levels were maintained between 7 and 15 mg. per hundred cubic centimeters for five days without definite clinical response the case was classed as a therapeutic failure and the drug therapy was stopped. At the advent of serious toxic manifestations, particularly jaundice and monia was 210,000 units; for type II, 255,000; for type V, 124,000; for type VII, 175,000, and for type VIII, 110,000 units.

SUMMARY OF CASES

Race, Sex and Age.—Most of the significant data for the sulfanilamide, serum and control groups have been summarized in table 1. The racial distribution was as follows: sulfanilamide group, white 63.5 per cent and Negro 36.5 per cent; serum group, white 72.5

6. Price, A. E.: Modern Treatment of Pneumonia, J. Michigan M. Soc. **36**: 77 (Feb.) 1937.

per cent and Negro 27.5 per cent; controls, white 67 per cent and Negro 33 per cent. The proportion of males in the sulfanilamide group was 80.9 per cent, in the serum-treated group 82.5 per cent and in the controls 77.7 per cent. The age distribution was not as even as desirable, the average for the sulfanilamide group being 38.7 years as compared with 39.9 years for the serum-treated patients and 45.6 years for the controls.

Associated Diseases.—A history of daily consumption of alcohol was obtained from 30.4 per cent of the patients treated with sulfanilamide, from 22.5 per cent of those treated with serum and from 23.4 per cent of the controls. The Kahn reaction of the blood was positive for 23.5 per cent, 10 per cent and 14.9 per cent respectively. In the sulfanilamide group there was one patient with recent coronary thrombosis and four patients with congestive heart failure. The failure was secondary to hypertension in one, coronary sclerosis in two and syphilitic heart disease in one. There were four additional patients with definite clinical evidence of heart disease which remained compensated throughout their hospital stay. One of the patients treated with serum had failure of the right ventricle secondary to rheumatic mitral stenosis; another had well compensated mitral stenosis. Among the controls there were four patients with congestive heart failure secondary to hypertension and four others with compensated hypertensive or arteriosclerotic heart disease. Two controls and two of the patients treated with sulfanilamide had chronic asthmatic bronchitis. One of the patients treated with sulfanilamide had a compound fracture complicated by osteomyelitis, which was an important contributory factor toward his death. One of those in the control group had a carcinoma of the colon. The remainder had no associated diseases which were likely to affect the prognosis.

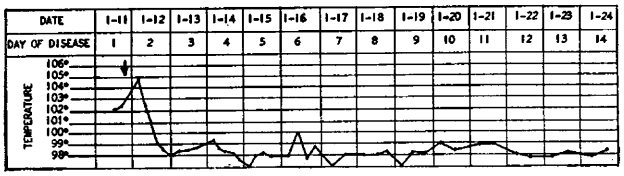

Chart 1.—Temperature in case 1.

TABLE 3 (case 1).—*Prompt Crisis Following the Use of Sulfanilamide, Type VII Pneumonia*

Patient a white youth aged 17; onset 8 p. m. January 10, admission January 11 and discharge Jan. 24, 1938.

Day of Disease	Sulfanilamide, Dose in Grains	Blood Level in Mg. per 100 Cc.	Blood Picture				Blood Culture	Agglutination	Miscellany
			Hb.	R.B.C.	W.B.C.	NF-F%			
1	140	8.7	....	....	.....	.....	Neg.	....	X-ray, consolidation of R.M.L. and portion of R.L.L.
2	120	8.1	12.5	4.99	38,000	65-32	.....	....	
3	120	8.6	12.5	....	20,100	61-37	.....	....	
4	60	8.2	....	....	.....	.....	.....	....	
5	...	4.3	11.5	....	10,400	37-48	.....	....	
8	...	...	....	....	.....	.....	.....	1:10	X-ray, considerable resolution
9	...	...	13.0	....	8,400	30-52	.....	....	
14	...	...	12.5	4.13	.....	.....	.....	....	

Duration and Extent of Pneumonia.—The average duration of the pneumonia before treatment was ninety-two hours in the sulfanilamide group, 59.1 hours for the serum-treated patients and 71.7 hours for the controls. The average number of lobes consolidated, as determined from the admission roentgenogram, was 1.53 in the sulfanilamide group, 1.16 in the serum group and 1.51 in the controls. The incidence of bacteremia was 19.1 per cent in the sulfanilamide group, 30 per cent for those treated with serum and 14.7 per cent for the controls. The admission leukocyte count was below 7,000 for four patients of the sulfanilamide group, for three serum-treated patients and for nine controls, and between 7,000 and 10,000 for twelve, four and eighteen patients, respectively.

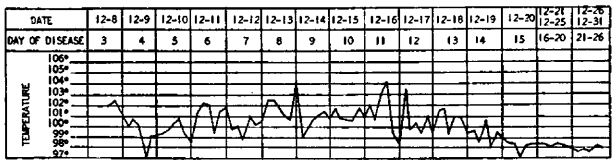

Chart 2.—Temperature in case 2.

TABLE 4 (case 2).—*Sulfanilamide Failure, Type IV Pneumonia with Bacteremia*

Patient a Negro aged 36; admission December 8 and discharge Dec. 31, 1937.

Day of Disease	Sulfanilamide, Dose in Grains	Blood Level in Mg. per 100 Cc.	Blood Picture				Blood Culture	Icteric Index	Miscellany
			Hb.	R.B.C.	W.B.C.	NF-F%			
3	120	...	13.6	4.4	6,800	33-55	IV	..	X-ray, pneumonia L.L.L.
4	120	15.6	11.4	3.79	9,250	86-8	Neg.	..	Liver extract 4 cc. 1 m. daily
5	120	9.9	11.8	....	20,700	87-8	.....	..	Sputum, type IV
6	120	11.0	12.2	....	40,600	.....	.....	..	
7	80	17.0	....	....	.....	.....	.....	..	
8	45	11.2	11.8	....	61,400	79-20	Neg.	38	X-ray, pneumonia L.L.L. and R.L.L.
9	30	8.2	10.2	3.34	27,700	70-28	.....	..	Sputum, type IV
10	0	4.1	10.6	....	41,000	71-28	.....	..	Urobilinogen in urine 1:300
11	0	0.9	....	....	.....	.....	Neg.	30	
12	0	0	....	....	.....	.....	.....	..	Urobilinogen 1:300
13	0	...	....	....	.....	.....	Neg.	..	X-ray, pneumonia R.L.L., R.U.L.; resolution L.L.L.
15	0	...	10.2	....	27,400	56-40	.....	16	Urobilinogen 1:50
21-26	0	...	9.6	....	8,000	20-67	.....	..	X-ray, slight resolution on right

RESULTS

Effect of Sulfanilamide on Temperature.—In table 2 the patients treated with sulfanilamide have been classed according to the number of hours elapsing between the commencement of the drug therapy and defervescence. The temperature fell to normal within twenty-four hours of the onset of sulfanilamide therapy in twenty-six cases (22.6 per cent), within forty-eight hours in fifty-one cases (44.3 per cent) and within 120 hours in eighty-five cases (73.9 per cent). On the other hand, the temperature reached normal within forty-eight

hours in only 16 per cent of the control cases. The effect of sulfanilamide on temperature was most striking when administration was started within thirty-six hours of the onset of the pneumonia. In fifteen of twenty-five such cases, the entire duration of the pneumonia, from onset to defervescence, was less than seventy-two hours. An example of an abortive crisis following sulfanilamide therapy is given in chart 1 and table 3 (case 1).

Twelve patients who did not show a temperature response within 120 hours but subsequently recovered from the pneumonia were classed as sulfanilamide failures. An example is given in chart 2 and table 4 (case 2). In this case, the blood culture became negative and a pseudocrisis occurred within twenty-four hours of the commencement of sulfanilamide therapy. In spite of adequate blood levels, the fever returned and the pneumonic process extended. The patient finally recovered, long after administration of the drug had been discontinued. Of the eighteen patients who died two had had a pseudocrisis, whereas the other sixteen showed no definite temperature response.

three of fifteen controls (20 per cent) and for seven of twelve patients (58.3 per cent) treated with serum. For those responding to sulfanilamide the blood culture usually became negative within twenty-four hours of the onset of therapy. The results were particularly good with type XIV, all four patients recovering. One of the most dramatic results is illustrated in chart 3 and table 6 (case 3). The patient was admitted on the seventh day of illness and was given no specific therapy during the first five days in the hospital. He showed roentgenographic evidence of an extension on the tenth day and positive blood cultures on the seventh, ninth, tenth and eleventh days. He was given a massive dose of sulfanilamide on the twelfth day and eight hours later had a crisis, eventually making a complete recovery. In chart 4 and table 7 (case 4) the course of type II pneumonia and bacteremia in a chronic alcoholic addict is illustrated. Sulfanilamide was started on the second day of illness. The blood culture was negative the following day and the temperature was normal from the fourth day. In chart 5 and table 8 (case 5) the course

TABLE 5.—*Results in Pneumococcic Bacteremia*

	Type of Pneumococcic Bacteremia															
	I	II	III	IV	V	VI	VII	XII	XIV	XIX	XX	XXIII	XXV	XXIX	XXXII	Total
Sulfanilamide																
Cases in which blood culture was positive	2	3	1	2	2	1	1	1	4	2	..	..	1	..	1	21
Cases in which blood culture became negative	2	2	0	2	2	0	0	1	4	2	..	..	1	..	1	17
Number of deaths	0	1	1	0	0	1	1	0	0	1	..	..	1	..	1	7
Controls																
Cases in which blood culture was positive	2	3	2	1	1	..	..	1	..	1	1	1	1	1	..	15
Cases in which blood culture became negative	1	0	0	0	0	..	..	1	..	0	0	1	0	0	..	3
Number of deaths	2	3	2	1	1	..	..	0	..	1	1	0	1	1	..	13
Serum																
Cases in which blood culture was positive	4	5	..	..	..	..	3	..	..	..	..	..	..	..	..	12
Cases in which blood culture became negative	4	3	..	..	..	..	0	..	..	..	..	..	..	..	..	7
Number of Deaths	0	3	..	..	..	..	3	..	..	..	..	..	..	..	..	6

In table 2 an attempt was made to correlate the temperature effect with the blood sulfanilamide level at the time of defervescence. No significant difference was noted between the group with blood sulfanilamide concentrations over 10 mg. per hundred cubic centimeters and the group with levels between 7 and 9.9 mg. When no therapeutic response occurred at low levels, larger doses were purposely given. One patient was observed who showed no improvement during three days when the blood level fluctuated between 4 and 7 mg. per hundred cubic centimeters but had a fairly prompt crisis after it rose to 10 mg. There were no definite examples of therapeutic failures at blood levels of from 7 to 9.9 mg. per hundred cubic centimeters followed by responses at higher levels. However, a much larger series will be needed to determine the optimal blood sulfanilamide concentration.

The effect of sulfanilamide on the pulse rate roughly paralleled that on the temperature. In some patients there was an associated symptomatic improvement but in many this was masked by the lassitude produced by the drug.

Effect of Sulfanilamide on Bacteremia.—The results in the cases of pneumococcic pneumonia complicated by bacteremia are given in table 5. For twenty-one of the patients treated with sulfanilamide the blood culture was positive on admission, and for seventeen (81 per cent) it became negative during treatment. On the other hand, the blood culture became negative for only

of type V pneumonia and bacteremia treated with sulfanilamide is illustrated. The blood was sterilized promptly and the temperature fell by lysis.

Five patients whose blood cultures became negative with treatment subsequently died. Three of these were in the sulfanilamide group, one in the serum group and one among the controls. In one of those whose blood culture became negative with sulfanilamide therapy hemolytic anemia subsequently developed, making it necessary to discontinue use of the drug. Ten days later the blood culture again showed the same organism and pneumococcic meningitis developed. At autopsy, it was seen that the pneumonia had completely resolved.

Effect of Sulfanilamide on the Consolidation.—Daily physical examinations were made to detect extensions and complications of the pneumonic process. The physical appearances were checked as often as necessary by x-ray examination. X-ray evidence of extension during sulfanilamide therapy was obtained in twelve cases (10.4 per cent), during serum therapy in six cases (15 per cent) and in eight control cases (8.5 per cent. Nine of the twelve patients in whom extensions developed during sulfanilamide therapy eventually recovered. The patients were also followed to determine the completeness of resolution. The consolidation cleared up in all but one of the patients classed as recovered. This patient still had evidence of unresolved pneumonia five months after sulfanilamide therapy had been discontinued. The effect of sulfanil-

amide on the sputum will be reported by Dr. Arthur W. Frisch in a separate communication.

Effect of Sulfanilamide on Complications.—The incidence of empyema was 1.7 per cent in the sulfanilamide group, 10 per cent for the serum-treated patients and

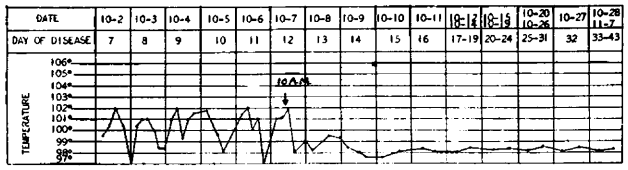

Chart 3.—Temperature in case 3.

TABLE 6 (case 3).—*Crisis Following the Use of Sulfanilamide, Type XIV Pneumonia and Bacteremia*

Patient a Negro aged 27; admission October 1 and discharge Nov. 7, 1937; delayed resolution.

Day of Disease	Oral Dose Sulfanilamide, Grains	Blood Level in Mg. per 100 Cc.	Blood Picture Hb.	R.B.C.	W.B.C.	NF-F%	Blood Culture	Miscellany
7	...	...	12.6	4.45	33,000	84-14	XIV	X-ray, consolidation R.U.L.; sputum, type XIV
9	...	...	12.0	4.17	29,000	80-14	XIV	
10	...	...	....	....	.....	.....	XIV	X-ray, consolidation right lung
11	...	...	....	....	.....	.....	XIV	Very toxic
12	140	13	11.4	4.1	36,600	84-14	.....	Crisis after sulfanilamide
13	80	7	11.8	....	35,600	45-50	.....	Marked cyanosis
14	60	6.6	....	....	.....	.....	Neg.	
15	20	...	....	....	.....	.....	.....	Symptom free
16	...	...	11.6	....	24,300	65-24	.....	
17-19	...	...	10.8	3.6	23,400	51-39	.....	Icteric index 10; massive consolidation still present
20-24	...	...	11.8	4.6	17,000	36-55	.....	X-ray, consolidation and atelectasis
25-31	...	...	10.2	4.19	13,500	23-51	.....	Diathermy, right side of chest
32	...	...	....	....	.....	.....	.....	X-ray, considerable resolution
34-34	...	...	11.4	4.35	9,200	33-59	.....	Complete resolution

2.1 per cent for the controls. More frequent than empyema were small pleural effusions, which did not become purulent and eventually disappeared without surgical intervention. The incidence of these in the three groups was 4.3 per cent, 7.5 per cent and 5.3 per cent respectively. None of the patients in this series had lung abscess or pericarditis.

Effect of Sulfanilamide on Mortality.—The mortality rate for the 115 patients treated with sulfanilamide was 15.7 per cent and for the ninety-four controls was 30.8 per cent. The death rate in fifty-seven cases of types I, II, V, VII and VIII pneumonia treated with sulfanilamide was 10.5 per cent, whereas it was 27.5 per cent in forty cases of the same types treated with serum. While these figures are favorable to sulfanilamide, they are inconclusive because of the small number of cases, unevenly balanced as to type as well as to the following factors: The age distribution favored sulfanilamide. Likewise, the proportion of patients with leukopenia was lower in the sulfanilamide group. These factors were partly balanced by the longer average duration before treatment and the higher incidence of alcoholism, particularly delirium tremens, in the sulfanilamide group. The average extent of the consolidation was nearly equal in the sulfanilamide and control groups and considerably less in the serum group. The incidence of bacteremia was highest in the serum group and lowest in the controls.

The mortality for pneumonia complicated by bacteremia is given in table 5. The mortality rate was 33⅓ per cent for the patients treated with sulfanilamide, 50 per cent for those treated with serum and 86.6 per cent for the controls.

The results with type II pneumonia were particularly encouraging. Among eighteen patients treated with sulfanilamide there were 16.6 per cent of deaths, as compared with a mortality of 42.9 per cent for fourteen patients treated with serum. The results with the other types are given in table 1 and will not be discussed further because of the small number of cases of each type.

TOXIC MANIFESTATIONS

Cyanosis.—This developed in practically every patient treated with sulfanilamide. There was no apparent correlation between the depth of the cyanosis and the outcome in the case. Many patients with deep cyanosis made satisfactory recoveries. It has been shown that sulfanilamide cyanosis is usually due to blood pigmenta-

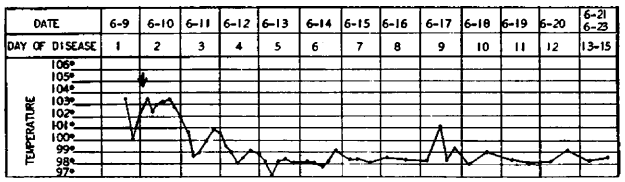

Chart 4.—Temperature in case 4.

TABLE 7 (case 4).—*Abortive Course of Type II Pneumonia and Bacteremia Following Sulfanilamide Therapy*

Patient a white man aged 47; onset 3 a. m. June 9, admission June 9 and discharge June 23, 1938; chronic alcoholism.

Day of Disease	Sulfanilamide, Dose in Grains	Blood Level in Mg. per 100 Cc.	Blood Picture Hb.	R.B.C.	W.B.C.	NF-F%	Blood Culture	Sputum	Miscellany
1	0	....	10.0	....	19,600	15-74	Pos.	II	
2	240	10.3	9.5	3.45	17,300	46-43	.....	II	X-ray, consolidation R.L.L.
3	120	11.1	9.5	....	15,100	66-27	Neg.	..	Kline test pos., Kahn test pos.
4	120	....	....	....	.....	.....	.....	..	
5	60	13.1	10.5	3.66	9,900	50-38	.....	..	
6	0	....	....	....	.....	.....	.....	..	X-ray, consolidation with small pleural effusion
9	0	....	11.0	3.6	8,400	30-47	.....	..	
12	0	....	11.0	....	4,100	12-55	.....	..	
13-15	0	....	....	....	.....	.....	.....	..	Consolidation resolving, fluid disappearing

tion, less commonly to methemoglobinemia and rarely to sulfhemoglobinemia.[7] King and Leslie [8] were unable to demonstrate any significant reduction in oxygen saturation of the arterial blood during sulfanilamide therapy in eight cases.

We are planning to repeat these studies on a larger scale with pneumonia, since it must be shown that

7. Marshall, E. K., and Walzl, E. M.: On Cyanosis from Sulfanilamide, Bull. Johns Hopkins Hosp. **61**: 140 (Aug.) 1937. Ottenberg, Reuben, and Fox, C. L.: Explanation for the Cyanosis of Sulfanilamide Therapy, Proc. Soc. Exper. Biol. & Med. **38**: 479 (May) 1938.

8. King, F. H., and Leslie, Alan: Oxygen Saturation of Arterial Blood in the Cyanosis from Sulfanilamide, J. A. M. A. **110**: 2069 (June 18) 1938.

sulfanilamide does not materially reduce arterial oxygen saturation before it can be recommended as a therapeutic agent.

Gastrointestinal Manifestations.—Anorexia and nausea were frequent but seldom severe enough to interfere with the oral administration of the drug.

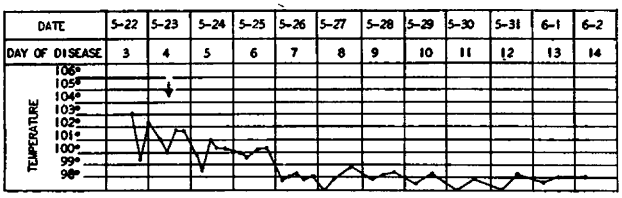

Chart 5.—Temperature in case 5.

TABLE 8 (case 5).—*Recovery from Type V Pneumonia and Bacteremia Following the Use of Sulfanilamide*

Patient a Negro aged 22; onset and admission May 20 and discharge June 2, 1938.

Day of Disease	Sulfanilamide, Dose in Grains	Blood Level in Mg. per 100 Cc.	Blood Picture				Blood Culture	Agglutination	Miscellany
			Hb.	R.B.C.	W.B.C.	NF-F%			
3	0	....	....	....	.....	.....	V	..	
4	160	....	13.0	4.97	21,400	73-13	V	..	X-ray, dense consolidation R.U.L.
5	120	10.1	13.0	....	16,600	68-15	Neg.	..	
6	120	9.0	13.5	5.2	17,500	52-20	Neg.	..	
7	120	10.0	12.0	4.22	13,100	51-30	.....	..	
8	60	9.8	13.5	....	13,100	64-19	.....	..	
9	0	....	....	....	.....	.....	.....	1:20	
12	0	....	13.0	5.32	.....	.....	.....	..	X-ray, resolution nearly complete

Vomiting and diarrhea were rare. Jaundice was present in the six patients in whom hemolytic anemia developed. In one other (chart 2 and table 4) toxic hepatitis developed. Since there was a coincidental extension of the pneumonia, the hepatitis may have been due to the pneumococcic infection.

Cerebral Manifestations.—Lassitude, headache and drowsiness were common toxic manifestations. Delirium developed in fourteen patients treated with sulfanilamide. With nine of these a history of chronic alcoholism was elicited and the clinical picture was typical of delirium tremens. With the other five it could not be definitely determined whether sulfanilamide or the pneumonia itself was responsible for the delirium.

Fever and Rash.—While it was frequently difficult to distinguish between fever due to sulfanilamide and that due to the disease itself, there were seven instances in which the fever continued in spite of apparent clinical improvement. In these cases the temperature tended to reach a peak in the early morning and fell in the afternoon. The fever subsided in all seven cases soon after administration of the drug was stopped. In two of the cases a morbilliform rash accompanied the fever.

Anemia.—In six of the patients treated with sulfanilamide acute hemolytic anemia developed, an incidence of 5.2 per cent. The total fall in hemoglobin content exceeded 4 Gm. per hundred cubic centimeters and the total fall in red cells was in excess of 1,500,000 per cubic millimeter in each case. The anemia developed abruptly in every case, appearing on the second day of sulfanilamide therapy in one case, on the third day in four and on the fifth day in one. In every case the hemoglobin content and red cell count continued to fall for two to three days after the drug therapy was discontinued. One patient had pneumococcic meningitis ten days after the onset of the anemia and died. The other five patients made a complete recovery with the aid of blood transfusions. Four returned for check counts some time after discharge. In one there was no appreciable change in the blood picture two months afterward. In the other three the check blood count was normal.

An example of acute hemolytic anemia developing after 170 grains (11 Gm.) of sulfanilamide is given in chart 6 and table 9 (case 6). The patient had type XIV pneumonia with bacteremia and leukopenia and was considered moribund at the time use of the drug was started. Within two days marked leukocytosis developed and the blood culture become sterile. A complete recovery eventually occurred. A similar abrupt neutrophilic leukocytosis accompanied the hemolytic anemia in four of the five remaining cases. This may prove a valuable warning sign.

In twenty-one additional cases (18.2 per cent) a more gradual and moderate fall in the hemoglobin con-

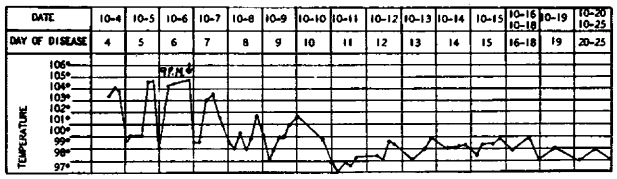

Chart 6.—Temperature in case 6.

TABLE 9 (case 6).—*Acute Hemolytic Anemia Following the Use of Sulfanilamide*

Patient a Negro woman aged 31; onset September 30, admission October 4 and discharge Oct. 25, 1937; tertiary syphilis.

Day of Disease	Oral Dose Sulfanilamide, Grains	Blood Level in Mg. per 100 Cc.	Blood Picture				Blood Culture	Miscellany
			Hb.	R.B.C.	W.B.C.	NF-F%		
4	..	...	....	....	5,700	20-56	.....	X-ray, consolidation R.U.L.
5	..	...	....	....	.....	.....	XIV	Sputum, type XIV
6	90	...	10.6	4.00	5,700	81-15	.....	Very toxic cyanotic, delirious
7	80	7.3	....	....	.....	.....	.....	X-ray, consolidation right lung
8	..	7.5	8.4	....	48,000	64-32	Neg.	Icteric index 50, much less toxic
9	..	...	3.8	....	32,000	55-33	.....	Pulse 150-160, transfusion 600 cc.
10	..	...	8.4	....	29,400	61-34	.....	
11	..	...	7.2	2.58	32,400	50-35	.....	Clinical evidence of resolution
12	..	...	5.6	2.85	29,600	69-24	.....	
13	..	...	5.6	2.35	19,400	49-40	.....	Transfusion, 500 cc.
15	..	...	7.4	2.60	8,100	21-48	.....	X-ray, resolution nearly complete; icteric index 6
19	..	...	9.4	3.30	.....	.....	.....	
20	..	...	....	....	.....	.....	.....	Clinical recovery

tent (between 2 and 4 Gm. per hundred cubic centimeters), with a comparable fall in the number of red cells (between 500,000 and 1,500,000 per cubic millimeter) occurred. In twelve of these the anemia appeared during the administration of sulfanilamide, and in the other nine it developed after the drug therapy was discontinued. Nine of the twenty-one patients had check blood

counts some time after discharge. One, who returned in two weeks, showed no change whereas the other eight, who returned after longer intervals, showed a satisfactory response. Thirty of the sulfanilamide group in whom anemia did not develop while they were in the hospital also returned for check blood counts after discharge. In every instance the blood count was as high as or higher than at discharge.

Acute hemolytic anemia was not observed among the control patients or serum-treated patients. Moderate secondary anemia developed in 11.6 per cent of such patients for whom adequate hematologic records were kept.

Leukocytosis—In none of the patients treated with sulfanilamide did granulocytopenia develop. In all four of the patients with an initial white cell count below 7,000 leukocytosis developed during sulfanilamide therapy, whereas six of the twelve whose initial count was between 7,000 and 10,000 showed a distinct rise after the drug therapy was started. The leukocytosis may have been due either to the infection or to liver extract, which was administered simultaneously to some of the patients, rather than to sulfanilamide. The abrupt leukocytosis which accompanied hemolytic anemia, however, was probably due to sulfanilamide.

COMMENT

While the results with sulfanilamide are encouraging, its place in the treatment of pneumonia has not been definitely determined. The future trend will probably be toward a combination of serotherapy and chemotherapy, particularly with types II and III. Osgood [9] found that a combination of sulfanilamide and serum was more effective against pneumococci in human bone marrow cultures than either preparation alone. We have used the two simultaneously in two cases of type I, in one case of type V and in two cases of type VII pneumonia without a fatality and in five cases of type II with one death.

Concerted efforts are being made to prepare derivatives that are more effective than sulfanilamide against the pneumococcus. Whitby [10] recently reported that sulfapyridine (2-[p-aminobenzene-sulfonamido] pyridine) will protect against minimum lethal doses of 10,000 pneumococci of types I, VII and VIII and against slightly smaller numbers of pneumococci of types II, III and V. Evans and Gaisford [11] reported a mortality rate of 8 per cent for 100 patients treated with this drug as compared with 27 per cent for 100 controls. Their results are unconvincing, however, since they are not analyzed from the standpoint of type, duration before treatment, extent of consolidation and incidence of bacteremia. Good results have been obtained in the laboratory with various sulfones.[12]

SUMMARY

This preliminary report is based on 115 cases of pneumococcic pneumonia treated with uniform doses of sulfanilamide and alternated with forty cases treated with Felton serum and ninety-four controls who received no specific therapy. The results were analyzed from the standpoint of the type of pneumococcus, average age of the patients, duration of the pneumonia before treatment, extent of the consolidation, blood culture, initial white cell count, duration after the onset of treatment, associated diseases and complications. The mortality rate was 15.7 per cent for the entire sulfanilamide group and 30.8 per cent for the controls. The death rate for fifty-seven patients with types I, II, V, VII and VIII pneumonia treated with sulfanilamide was 10.5 per cent, whereas it was 27.5 per cent for forty patients with the same types treated with serum. Of twenty-one patients with pneumococcic bacteremia treated with sulfanilamide seven died, of twelve treated with serum six died and of fifteen controls thirteen died. The most important toxic manifestation was anemia. In 5.2 per cent of the patients treated with sulfanilamide a severe hemolytic anemia developed and in an additional 18.2 per cent moderate secondary anemia developed.

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PNEUMOCOCCIC PNEUMONIAS COMPLICATING PREGNANCY AND THE PUERPERIUM

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It has long been recognized that pneumonia is a serious complication of pregnancy with a considerably higher death rate than for nonpregnant women.[1] Some of the factors pertaining to pregnancy have received limited attention in the past,[2] but data concerning the pneumonias are scarce. From the practical possibilities of reducing mortality, recent developments in the fields of specific serum therapy and of chemotherapy have focused attention on the etiologic agents in infectious diseases, and this has been true particularly in the case of the pneumonias. References to the bacterial incitants of the pneumonias of pregnancy are very scarce and, until the recent reports of Bullowa [3] and of Rogers and Gooch,[4] have been limited to individual case reports.

There is at present a widespread interest among physicians and public health workers in the control of the mortality from pneumonia. Much of this attention is focused on etiologic diagnosis, particularly pneumococcus typing, and on the specific serum treatment of some of the pneumococcic pneumonias. It is appropriate therefore to present a series of 212 cases of "typed" pneumococcic pneumonia complicating preg-

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Owing to lack of space this article has been abbreviated for publication in THE JOURNAL by the omission of tables 1, 3, 4, 7, 10 and 11. The complete article appears in the authors' reprints.

Dr. Alexander W. Winkler assisted in the collection of the data in the earlier part of this study, and Dr. John W. Brown assisted with the more recent cases. Dr. Frederick C. Irving gave us permission to use the data from the Boston Lying-in Hospital, and Dr. K. Jefferson Thompson, former research fellow in obstetrics, carried out the serum treatment of a number of the patients there. The members of the staff of the obstetrics service of the Boston City Hospital cooperated.

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