Efficacy of Chloramphenicol Therapy for Typhoid Carriers

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THE VALUE of chloramphenicol in the treatment of typhoid fever has now been well established, but a question remains as to what effect, if any, therapy with chloramphenicol has on the prevention of the chronic typhoid carrier state.

Even before the use of the antibiotics, many attempts were made to find an agent that might be effective in eradicating the focus of typhoid bacilli in the chronic carrier. Search through the literature, to be described shortly, reveals many experiments with many different drugs and combinations of drugs, but these have been unsuccessful, or, if successful, have lacked confirmation. Some investigators reported cures, but in most instances they had reference to temporary or convalescent carriers and not to chronic typhoid carriers. This paper deals only with the chronic typhoid carrier state. Carriers are defined as persons who have not suffered from typhoid fever within the previous 12 months but discharge typhoid bacilli. They may or may not have had a clinically recognized attack of typhoid fever, but they excrete the organism over a period of at least 1 year. Chronic carriers who shed typhoid bacilli at irregular intervals are sometimes called intermittent carriers.

In the absence of a reliable method of terminating the carrier state, particular interest centers in the possibility of preventing its development by the modern methods of treating the acute infection. The study here reported was designed in the summer of 1952 to evaluate the results obtained when cases of typhoid fever were treated with chloramphenicol. Data collected on 1,413 cases from Mississippi and Louisiana suggest that chloramphenicol has no marked effect on the prevention of the typhoid carrier state.

With the rapid reduction in the number of cases of typhoid fever, however, there is a corresponding reduction in the number of carriers. Feemster and co-workers attempted to collect figures on the number of typhoid carriers in the United States, but there was so much variation in the information available from State health departments that the tabulation was not satisfactory (*1*). However, figures are available for Massachusetts, with an estimated prevalence of approximately 25 per 100,000 population (*2*); for New York, 42 per 100,000 population (*3*); and for Mississippi, 228 per 100,000 population (*4*). Typhoid carriers still constitute a sizable and important problem.

The medical, socioeconomic, and psychological importance of the typhoid carrier problem has led many clinicians to seek medical treatments rather than cholecystectomy for the cure of typhoid carriers. Stertenbrink in 1928 reviewed the earlier German literature on this

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subject, analyzing the results achieved with the use of more than a hundred different therapeutic agents (*5*). He concluded that none of the methods was successful or even held promise. With the advent of the sulfonamide derivatives, new tests were devised but these likewise proved disappointing (*6,7*). After Bigger demonstrated the in vitro synergistic action of penicillin and sulfathiazole on *Salmonella typhi*, these drugs were used by several groups of workers in the treatment of chronic typhoid carriers (*8*). Korns and Trussell reported no cures (*9*). Smith and others state that sulfonamides and penicillin are ineffective in therapeutically attainable levels but that the newer antibiotic, chloramphenicol, seems more promising (*10*). However, numerous reports, among them Stryker (*11*) and Nichols (*12*) suggest that treatment of chronic carriers with chloramphenicol results merely in temporary cessation of the shedding of bacilli. A more recent possible exception to the usual experiences is reported by Carnes and associates who state that 6 of 7 carriers were cleared up by preparing them for drug therapy with chloramphenicol by an intensive course of typhoid immunization (*13*).

Materials and Methods

The study reported here was carried out over a period of 3 years, and the data were collected on cases occurring from 1947 through 1952 in Mississippi and Louisiana. The two States are comparable in many respects: As of the 1950 census, the population of Mississippi was 2,178,914 and of Louisiana, 2,683,516; both States have large rural areas; both are in the South Central region and have approximately the same incidence of typhoid fever; and the counties and parishes are well supplied with local health units. The use of chloramphenicol did not become widespread until late 1949. Therefore, while most of the typhoid fever cases in the control group occurred from 1947 to 1949, most of the treated ones occurred from 1950 to 1952.

The study population was divided into four groups according to the treatment received: those receiving no chloramphenicol and referred to as nonspecifically treated; those receiving inadequate total dosage of chloramphenicol; those receiving adequate total dosage initiated before the 15th day from onset of illness; and those receiving adequate total dosage initiated after the 15th day from onset of illness. Only those patients receiving chloramphenicol in dosages of 30 gm. and over were considered adequately treated. In 1950, the drug manufacturer revised the dosage of chloramphenicol (Chloromycetin) to an average of 30 gm. per patient to be given over a period of approximately 14 days. This was the dosage considered "adequate" in this study. Children received proportionate amounts of the drug equivalent to the adult dose on the basis of body weight.

Data were obtained from morbidity reports, hospital records, mortality reports, laboratory reports, epidemiological records in the local health departments, private physicians, pharmacists and reports of field investigations of cases. I investigated all reported cases of typhoid fever in Mississippi during 1950 to 1952 and part of 1949.

All identifying data on typhoid fever cases reported to the two State health departments during the study years 1947 through 1952 were recorded on a master list by year of report and by county or parish. These data included the hospital number and the name of the reporting physician. A list of the cases was then sent to the local health department with a request for the epidemiological record on all cases that had occurred in the county or parish during the study years. After copies were made the original records were returned to the local health departments. As the records were completed they were filed alphabetically, and were then taken to the hospitals where data from the hospital record were transferred to the study record. New records were made on those cases diagnosed by the hospitals as typhoid fever but not reported to the States. I then visited the State laboratories and obtained lists of all cultures reported positive for *S. typhi* during the study years. This information was added to the epidemiological records if it had not already been recorded.

Where information was incomplete, visits were made to the counties and parishes to obtain missing data. In many instances this

necessitated visits to private physicians and to homes of the patients. Pertinent information was transferred to cards for tabulation. Each record was carefully analyzed and evaluated. Reported cases that were considered not to be typhoid fever were omitted from the study. The cases rejected because of insufficient evidence to diagnose them typhoid included probable instances of such diseases as brucellosis, paratyphoid fever, cancer, tuberculosis, amebiasis, pneumonia, murine typhus, histoplasmosis, and tularemia. These were proved later by bacteriological and other diagnostic examinations to be these diseases. Other cases which were undoubtedly typhoid fever were excluded because of inadequate data as to treatment or because of inadequate followup in instances of moving, inability to locate, loss of hospital records, and death. Fifty-three cases in all were rejected.

Diagnostic Criteria

The remaining 1,413 cases presented the usual clinical features of typhoid fever. Furthermore, the diagnosis was proved in more than half of the cases by recovering *S. typhi* from the blood, feces, urine, pus, or spinal fluid. In most of the remaining cases, the diagnosis was based on serologic grounds, plus clinical symptoms and epidemiological evidence, or, in a relatively few cases, on epidemiological association with bacteriologically proved cases. The cases diagnosed on serologic evidence either demonstrated agglutinins in the blood which reached levels of diagnostic significance with anti-O titers of 1:640 and anti-H titers of 1:1280, or higher, or manifested at least a fourfold rise in agglutinin titer. Many of the cases diagnosed on serologic and epidemiological evidence were part of large outbreaks.

All reported typhoid cases were investigated by the local health departments. Specimens of blood, feces, and urine were collected as part of the routine epidemiological investigation of typhoid and suspected typhoid cases and the families of the patients. The Mississippi and Louisiana departments of health require that the cultures of at least two feces specimens and two urine specimens be negative for *S. typhi* on all reported typhoid fever cases before

Table 1. Cases of typhoid fever in Louisiana and Mississippi, 1947–52, by age, race, and sex, with rates per 100,000 population per annum for age and race

State and age (years)	Number of investigated cases [1]									Rate [2]		
	White			Nonwhite			Total					
	Male	Female	Total	Male	Female	Total	Male	Female	Total	White	Nonwhite	Both races
Louisiana												
0–4	27	29	56	37	29	66	64	58	122	4.4	8.8	6.1
5–9	40	35	75	41	39	80	81	74	155	7.2	13.1	9.4
10–19	71	54	125	60	59	119	131	113	244	7.4	12.0	9.1
20–39	102	73	175	46	40	86	148	113	261	5.1	5.9	5.4
40 and over	50	31	81	25	22	47	75	53	128	2.4	3.1	2.6
All ages	290	222	512	209	189	398	499	411	910	4.7	7.5	5.7
Mississippi												
0–4	12	16	28	24	20	44	36	36	72	3.5	4.9	4.2
5–9	29	13	42	35	36	71	64	49	113	6.0	9.6	7.9
10–19	36	27	63	46	36	82	82	63	145	5.0	6.7	5.9
20–39	26	28	54	29	21	50	55	49	104	2.6	3.3	2.9
40 and over	34	16	50	12	7	19	46	23	69	2.2	1.2	1.8
All ages	137	100	237	146	120	266	283	220	503	3.3	4.5	3.8

[1] From State department of health and unreported hospital cases.
[2] Based on population data from 1950 census.

patients are released from isolation and public health supervision. Sheppard-Keidel vacuum bleeding tubes were used to take blood for culture and serology, and standard 10-dram, screwcapped glass bottles containing a preservative were provided for feces and urine specimens. With few exceptions all culture work was done by either the laboratories of the State health departments or in Louisiana by the Charity Hospitals. Materials and methods used for culture and serology in the major laboratories were of approved types and were not changed importantly during the 6 years of the study.

Additional Followup

As part of the followup, a series of feces and urine specimens were obtained during 1953 on all patients whose cultures had been found positive for *S. typhi* intermittently for 2 months or longer during or after convalescence. This followup also included those cases which had not been reported to the State health departments by the hospitals and any cases which in the opinion of the writer, had not been adequately investigated. All told, approximately 780 cases were re-investigated in this manner. As a result of this followup four persons who previously had been discharged following chemotherapy and two negative feces and urine cultures were confirmed as chronic typhoid carriers. By investigating some of the sources of these reopened cases, other chronic carriers were found and were placed under public health supervision. A considerable amount of the "shoe-leather" epidemiology was done by the public health nurses. I also visited and obtained specimens on numerous cases in the study.

Results

Table 1 shows the distribution of all study cases of typhoid fever in Louisiana and Mississippi by age, race, and sex. The table also presents the rates per 100,000 population for the 6-year period 1947 to 1952. In both States the highest rates were found in the groups aged 5–9 and 10–19 years, with those 40 and over showing the lowest rates. The rates were higher among the nonwhites in all age groups.

Table 2. Distribution of typhoid fever cases in Louisiana and Mississippi, 1947–52, by diagnostic criteria and by type of treatment

Treatment	Total cases	Diagnostic criteria											
		Salmonella typhi cultured from—								Serologic evidence [1]		Epidemiological association [2]	
		Blood		Feces		Blood and feces		Total					
		Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Louisiana	910	165	18.1	208	22.9	149	16.4	522	57.4	354	38.9	34	3.7
Chloramphenicol	486	111	22.8	79	16.3	63	13.0	253	52.1	214	44.0	19	3.9
Nonspecific [3]	424	54	12.7	129	30.4	86	20.3	269	63.4	140	33.0	15	3.5
Mississippi	503	145	28.8	89	17.7	81	16.1	315	62.6	151	30.0	37	7.4
Chloramphenicol	313	107	34.2	46	14.7	37	11.8	190	60.7	103	32.9	20	6.4
Nonspecific [3]	190	38	20.0	43	22.6	44	23.2	125	65.8	48	25.3	17	8.9
Both States	1,413	310	21.9	297	21.0	230	16.3	837	59.2	505	35.8	71	5.0
Chloramphenicol	799	218	27.3	125	15.6	100	12.5	443	55.4	317	39.7	39	4.9
Nonspecific [3]	614	92	15.0	172	28.0	130	21.2	394	64.2	188	30.6	32	5.2

[1] Fourfold rise in titer or higher titer positive on single specimen plus epidemiological association with bacteriologically proved cases.
[2] Laboratory diagnosis incomplete but associated with proved cases.
[3] Includes penicillin, sulfonamides, streptomycin, fever pills, and aspirin.

Table 3. Distribution of accepted cases of typhoid fever, by time of collection [1] of first negative fecal specimen and by method of treatment, Louisiana and Mississippi, 1947–52 [2]

Treatment	Total	First negative specimen in week—									
		1		2		3		4–6		After 6 [3]	
		Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Louisiana											
Chloramphenicol	483	68	14. 1	116	24. 0	102	21. 1	132	27. 3	65	13. 5
>30 gm. before day 15 [4]	205	35	17. 2	65	31. 7	46	22. 4	38	18. 5	21	10. 2
>30 gm. after day 15 [5]	73	0	------	3	4. 1	21	28. 8	33	45. 2	16	21. 9
<30 gm. [6]	205	33	16. 1	48	23. 4	35	17. 2	61	29. 7	28	13. 6
Nonspecific [7]	406	36	8. 9	92	22. 7	68	16. 7	122	30. 0	88	21. 7
Mississippi											
Chloramphenicol	307	41	13. 3	76	24. 8	54	17. 6	73	23. 8	63	20. 5
>30 gm. before day 15 [4]	66	11	16. 6	21	31. 8	10	15. 2	10	15. 2	14	21. 2
>30 gm. after day 15 [5]	28	0	------	1	3. 6	6	21. 4	17	60. 7	4	14. 3
<30 gm. [6]	213	30	14. 1	54	25. 4	38	17. 8	46	21. 6	45	21. 1
Nonspecific [7]	184	18	9. 8	31	16. 9	22	11. 9	56	30. 4	57	31. 0
Both States											
Chloramphenicol	790	109	13. 8	192	24. 3	156	19. 7	205	26. 0	128	16. 2
>30 gm. before day 15 [4]	271	46	17. 0	86	31. 7	56	20. 7	48	17. 7	35	12. 9
>30 gm. after day 15 [5]	101	0	------	4	4. 0	27	26. 7	50	49. 5	20	19. 8
<30 gm. [6]	418	63	15. 0	102	24. 4	73	17. 5	107	25. 6	73	17. 5
Nonspecific [7]	590	54	9. 1	123	20. 8	90	15. 3	178	30. 2	145	24. 6

[1] Week after onset.
[2] Includes all cases from which stool specimens were obtained, whether or not bacilli were found in any specimen. "First negative" means first negative specimen after which no positive specimens were obtained.
[3] Includes permanent carriers and persons who remained as temporary carriers for periods ranging up to 8 months.
[4] Total dose with course begun before 15th day of disease.
[5] Total dose but course initiated on or after 15th day of disease.
[6] Inadequate total dose without regard to time of initiation of treatment.
[7] Includes penicillin, sulfonamides, streptomycin, fever pills, and aspirin.

The ratios of male patients to female patients were 1.2:1 in Louisiana and 1.3:1 in Mississippi. Gross attack rates were higher in Louisiana than in Mississippi.

In table 2 the 1,413 cases are distributed by type of treatment and by the criteria upon which the diagnosis was based. Eight hundred and thirty-seven, or 59.2 percent, were diagnosed by isolation of *S. typhi.* Of these, 310, or 37.0 percent, had positive blood cultures; 297, or 35.5 percent, had positive fecal cultures; and 230, or 27.5 percent, were positive for *S. typhi* in both blood and feces. Five hundred and five, or 35.8 percent, were diagnosed on serologic evidence, and only 71, or 5.0 percent were diagnosed on the basis of epidemiological association. A greater percentage of positive specimens were found among nonspecifically treated persons than among chloramphenicol-treated persons (64.2 vs. 55.4), whereas the reverse was true for serologic evidence (30.6 vs. 39.7). The percentages of epidemiological diagnoses were nearly identical (5.2 and 4.9). These differences are similar for each State although Mississippi had 5.2 percent more patients diagnosed by positive culture, slightly fewer diagnosed on serologic evidence, and twice the percentage diagnosed on epidemiological evidence.

Tables 3 and 4 show the relation between treatment and the percentage distribution of cases according to the week after onset in which was collected the first fecal specimen negative for *S. typhi* and not followed by a positive

Table 4. Cumulative percentage distribution of accepted cases of typhoid fever, by time of collection [1] of first negative fecal specimen and by method of treatment, Louisiana and Mississippi, 1947–52 [2]

Treatment	Cumulative percentage of cases with first negative specimen in week—				
	1	2	3	4–6	After 6 [3]
Louisiana					
Chloramphenicol	14. 1	38. 1	59. 2	86. 5	100
>30 gm. before day 15 [4]	17. 2	48. 9	71. 3	89. 8	100
>30 gm. after day 15 [5]	--------	4. 1	32. 9	78. 1	100
<30 gm. [6]	16. 1	39. 5	56. 7	86. 4	100
Nonspecific [7]	8. 9	31. 6	48. 3	78. 3	100
Mississippi					
Chloramphenicol	13. 3	38. 1	55. 7	79. 5	100
>30 gm. before day 15 [4]	16. 6	48. 4	63. 6	78. 8	100
>30 gm. after day 15 [5]	--------	3. 6	25. 0	85. 7	100
<30 gm. [6]	14. 1	39. 5	57. 3	78. 9	100
Nonspecific [7]	9. 8	26. 7	38. 6	69. 0	100
Both States					
Chloramphenicol	13. 8	38. 1	57. 8	83. 8	100
>30 gm. before day 15 [4]	17. 0	48. 7	69. 4	87. 1	100
>30 gm. after day 15 [5]	--------	4. 0	30. 7	80. 2	100
<30 gm. [6]	15. 0	39. 4	56. 9	82. 5	100
Nonspecific [7]	9. 1	29. 9	45. 2	75. 4	100

[1–7] See table 3.

specimen. Since the separate data for the two States are closely similar, attention need be directed only to the combined data for both States. From table 3 it appears that the greatest proportion of reversions occurred during the second week for the group given early adequate treatment, whereas it occurred in the fourth to sixth week for all other groups. Progress in clearing the fecal infection is shown more clearly, perhaps, by the figures for the cumulative percentages in table 4. Excluding the group which received delayed though adequate treatment and in which few isolations were attempted during the early weeks of the disease, the proportion which had permanently reverted was greater at each interval among those given chloramphenicol than among those treated nonspecifically. The most rapid clearing, of course, was in the group treated both early and adequately. In this group nearly half (48.7 percent) became negative during the second week as compared with 29.9 percent of those given only nonspecific treatment.

Twenty chronic carriers, 10 in each State, were found among the 1,413 cases of typhoid fever in Louisiana and Mississippi. Table 5 shows the pooled data of the two States, with distribution of cases by age and sex only. In agreement with long-standing impressions, in all treatment groups carrier rates were higher among persons 20 years old and over than among younger persons. Combining all groups and the data from both States shows that the carrier rates were 0.7 percent for 851 patients under age 20, 1.9 percent for 363 patients aged 20–39 years, and 3.5 percent for 199 patients 40 years old and older. With regard to sex, the overall differences are in opposition to the usual experience but are trivial. The 782 male patients yielded 12 carriers, or 1.5 percent, whereas the 631 female patients yielded 8 carriers, or 1.3 percent. However, in the group with the highest number of carriers, those 40 years of age and older, the expected situation prevailed, with 5.2 percent of the females becoming carriers but only 2.4 percent of the males. Finally, while there were relatively fewer carriers among the specifically treated

patients (8 in an overall total of 799, or 1.0 percent) than among those given no specific treatment (12 out of 614, or 2.0 percent), the difference in rates is not significant. Thus, while the data are compatible with the idea that specific treatment reduces the carrier rate somewhat, they clearly do not prove it.

Table 6 presents the relation of intensity of specific treatment to relapse and death. It is interesting to note that when adequate dosage of chloramphenicol was given early, before the 15th day, the rate of relapse was 5.2 percent, practically the same as for the series with no specific treatment, 5.8 percent. In contrast, the group who had adequate treatment after the 15th day had a relapse rate of 21.5 percent, approximately the same as for the group who had inadequate treatment (21.9 percent). Those adequately treated before the 15th day had the lowest case fatality rate, 1.9 percent, whereas the group given no specific treatment had the highest rate, 8.1 percent. The rates for the series given adequate treatment but after the fifteenth day and for that series given inadequate treatment were essentially the same, 5.0 percent and 5.1 percent respectively.

Discussion

A field study of the type described has some obvious limitations as a method of studying the efficacy of chemotherapeutic agents. Many of the epidemiological record forms used were not really adequate for collecting and recording data pertinent to such a study. For instance, these forms had no specific blocks for recording treatment, name of hospital, admission and discharge dates, clinic or dispensary number, or name of county. The spaces allotted to the environmental history and laboratory data were very inadequate. It would have helped considerably in differential diagnosis to have had a checklist for clinical history, physical findings and course of treatment, with space for history of onset of illness and sequelae. Since adequate supervision cannot be given by the local health departments to patients with communicable diseases who are not hospital-

Table 5. Relation of age, sex, and treatment to the development of the carrier state following typhoid fever in Louisiana and Mississippi, 1947–52

Treatment and age group (years)	Typhoid cases			Typhoid carriers [1]					
	Male	Female	Total	Male		Female		Total	
				Number	Percent	Number	Percent	Number	Percent
Chloramphenicol	442	357	799	7	1.6	1	0.3	8	1.0
>30 gm. before day 15 [2]	163	109	272	3	1.8	1	.9	4	1.5
0–19	85	67	152	1	1.2	0		1	.7
20–39	48	28	76	1	2.1	0		1	1.3
40 and over	30	14	44	1	3.3	1	7.1	2	4.5
>30 gm. after day 15 [3]	55	47	102	0		0		0	
0–19	23	21	44						
20–39	20	15	35						
40 and over	12	11	23						
<30 gm.[4]	224	201	425	4	1.8	0		4	.9
0–19	149	134	283	2	1.3	0		2	.7
20–39	45	50	95						
40 and over	30	17	47	2	6.7	0		2	4.3
Nonspecific [5]	340	274	614	5	1.5	7	2.6	12	2.0
0–19	201	171	372	2	1.0	1	.6	3	.8
20–39	89	68	157	3	3.4	3	4.4	6	3.8
40 and over	50	35	85	0		3	8.6	3	3.5

[1] Persons found to be shedding typhoid bacilli 1 year or longer after onset of illness; deaths not deleted because they had no more than 0.1 percent influence.
[2] Total dose with course begun before 15th day of disease.
[3] Total dose but course initiated on or after 15th day of disease.
[4] Inadequate total dose without regard to time of initiation of treatment.
[5] Includes penicillin, sulfonamides, streptomycin, fever pills, and aspirin.

Table 6. Relation of treatment to relapse and death following typhoid fever in Louisiana and Mississippi, 1947–52

Treatment	Number of cases	Relapses		Deaths	
		Number	Percent	Number	Percent
Chloramphenicol:					
>30 gm. before day 15 [1]	272	14	5. 2	5	1. 9
>30 gm. after day 15 [2]	102	22	21. 5	5	5. 0
<30 gm.[3]	425	93	21. 9	22	5. 1
Nonspecific [4]	614	36	5. 8	50	8. 1

[1] Total dose, with course of treatment begun before 15th day of disease.
[2] Total dose, with course of treatment initiated on or after 15th day of disease.
[3] Inadequate total dose regardless of time of initiation of treatment.
[4] Includes penicillin, sulfonamides, streptomycin, fever pills, and aspirin.

ized, there is some doubt as to the accuracy of the treatment records of such patients. Fortunately, 1,067, or 75.5 percent, of the 1,413 cases under study in the 6-year period, 1947–52, in Louisiana and Mississippi, had been hospitalized. In Louisiana 20 percent more were hospitalized than in Mississippi. These percentages were 82.5 and 62.5 respectively. In both States 638, or 79.9 percent, of the treated patients and 429, or 69.9 percent, of the untreated group were hospitalized.

From table 2 it is evident that of the 1,413 cases included in the study 576, much more than a third, were diagnosed without positive cultures, either blood or fecal, and that positive blood cultures were obtained in only 540 cases, or about 38 percent, of the total. This situation merits some comment and explanation.

During the period of these investigations, I observed repeatedly that, in making a diagnosis of typhoid fever, the practice in many rural areas and in many small private hospitals is to depend only on serologic evidence and clinical symptoms. Fortunately, this applied to only a relatively small part of the study group since many establishments do not admit patients with known or suspected communicable diseases. Many of the cases of typhoid fever in this study were secondary and were picked up by the local health departments while investigating primary or index cases.

Considering the study group as a whole, it might seem that the relative paucity of bacterial isolations, especially from the blood, could be attributed to the specific antibiotic therapy employed in more than half of the cases. Many investigators have reported that the use of chloramphenicol "sterilizes" the blood and intestinal tract very rapidly. Among these, Woodward and others reported blood sterilization but frequent persistence of the agent in feces and urine after initiation of treatment (*14*). Supporting these findings are observations of other investigators based on much larger numbers of cases (*15*, *16*). On the other hand, using blood-clot cultures, Thomas and others (*17*) and Watson (*18*) report numerous isolations from patients undergoing treatment. The present data, when considered with reference to treatment status (table 2), provide no evidence that chloramphenicol influences the frequency with which positive blood cultures are obtained, as the tabulation below indicates:

	Percent of patients with positive blood cultures	
Treatment	*Louisiana*	*Mississippi*
All chloramphenicol	35. 8	46. 0
Nonspecific	33. 0	43. 2

Available evidence indicates that clot cultures are markedly superior to cultures made with whole blood, possibly because the influence of any bloodborne antibiotic and bactericidal serum factors is minimized (*19*). In spite of the general use of clot cultures, isolations of *S. typhi* from the blood in this series (540 or 56.8 percent of the 950 cases with blood culture attempted) were far less than reported by earlier workers (*20*, *21*). As pointed out in most bacteriology texts, for example, Smith and others (*10*), frequency of isolations of *S. typhi* from the blood is closely related to the stage of the disease, maximum recoveries being made at the end of the first week. Thereafter, the bacteria disappear from the blood and specific antibodies increase. In this light possibly the more important factor contributing to the lower rate of recovery in this series was the common delay in obtaining the first specimen for culture and serologic tests.

With respect to positive stool cultures the

situation is somewhat different. That *S. typhi* was not recovered from the feces of 886 or more than four-sevenths of the entire group as a whole was very largely due to failure in many instances to collect stools for test during, or soon after, the acute phase of the illness. However, the data indicate rather clearly that treatment did exert an influence on the detected excretion of typhoid bacilli. As shown in table 2, in Louisiana positive stools were found in 142 of 486 treated patients (29.2 percent) and in 215 of 424 untreated patients (50.7 percent); in Mississippi, the figures were 83 of 313 treated (26.5 percent) and 87 of 190 untreated patients (45.8 percent). Furthermore, as shown in table 4, adequately treated cases tended to become permanently negative earlier (69.4 percent during or before the third week) than the untreated cases (only 45.2 percent by the same time). It should be emphasized, however, that treatment did not eliminate bacilli from the feces with any uniformity. In 81 cases feces were positive during therapy and in 130 after cessation of therapy.

Other factors also probably influenced the data as to fecal excretion of *S. typhi*. In uncontrolled field situations where specimens are collected at irregular intervals, it obviously is difficult to know the precise time when patients cease to excrete typhoid organisms. For purposes of tabulation, I have arbitrarily chosen the time intervals used in table 3 and have entered cases in the table as of the week of collection of the first feces or urine specimen negative for *S. typhi* not followed by a positive culture. Specimens were not submitted from all patients every week nor were they collected on the first day of the stated intervals.

In this study, an effort was made to determine the relation of the persistence of typhoid bacilli in feces to the degree and time of initiation of specified treatment. However, the frequent failure to collect stools for testing during the acute phase of typhoid fever makes it impossible to speak with assurance about the number or proportion of stools positive at any specific stage of the disease. The only definite statements that can be made are that, in any given case, stools taken on or after a certain date were negative and that by a given period after onset in a certain proportion of cases excretion of the bacilli had permanently ceased. These latter figures, obviously, are minimal since, if stools had been collected earlier or more frequently, the assigned date of cessation would have been advanced in many cases.

Of special interest in this study is the excretion of bacilli in the feces beyond 6 weeks from date of onset of typhoid fever. Of the 273 patients not declared permanently negative for *S. typhi* at the end of 6 weeks, 217, or about 16 percent of the total 1,380, were actually found to be excreting the organism at a later time (table 3). Patients determined as having ceased excretion of bacilli numbered 136 in the 6- to 8-week interval, 69 in the third month, 21 during the fourth month, 11 in the fifth month, and 16 during the next 3 months, leaving a total of 20 permanent or chronic carriers, 8 among the chloramphenicol-treated group and 12 among the group receiving nonspecific treatment (table 5). Treatment, incidentally, did not appear to be an important factor in this group. The data in table 3 do suggest that in Mississippi a higher proportion of cases were found excreting the agent after the sixth week than in Louisiana. A partial explanation for this may be that, because of the recognized tendency for treated cases to relapse, it became routine in Mississippi early in 1950 before releasing any patient to obtain recheck specimens about 2 months after onset of typhoid fever.

Although not all of the factors involved in the production of a chronic typhoid carrier are known, at least some are reasonably well indicated. These include age, sex, prior gall bladder disease, and the bacterial strain. With a few specific exceptions, for example, Havens and Dehler (*22*), efforts to analyze large series of typhoid cases have led to the conclusion that both age and sex are important (*23*, *24*). In general, carriers are more common among adults than among children and among women than among men. Frequency of clinically recovered patients who become chronic carriers varies between 2 and 7 percent. The pattern observed in the present series of 1,413 cases is in general agreement with the foregoing analysis. In the group aged 0–19 years, carrier rates of 0.7 to 0.8 percent were observed while in the older age groups rates ranged up to 4.5 percent.

Also, in the group over 40 years of age, 5.2 percent of females but only 2.4 percent of males became carriers. In the entire series, the carrier rate was 1.4 percent. Only in one instance was there a history of prior gall bladder disease although 3 of the 20 carriers recognized in this study later had cholecystectomies. Collins and Finland considered the possibility that strain differences may account for the variations in response to treatment with chloramphenicol (*25*). The belief that only infections with certain phage types result in the chronic carrier state has not been justified by my experience. In this country phage E_1 is the most common type. Of the 6 carriers typed in this study, 2 were E_1. A note of possible interest is that 6 of the 20 newly established carriers in this study lived in the same household with previously known carriers, but only one was related by blood.

In the present study, the crucial question is the possible relation of treatment with chloramphenicol to ultimate evolution of the carrier state. Of the 8 carriers who received chloramphenicol, 4 had been given early adequate treatment and 4 were in the delayed or inadequate treatment group (table 5). Carrier rates for all groups given chloramphenicol and for the group given only nonspecific treatment were 1.0 and 2.0 percent respectively. Although the difference is not significant, it is compatible with the idea that such treatment may reduce the carrier rate to some extent. In support of this idea is the rather clear evidence that in many cases early adequate treatment hastens the time of cessation of excretion of bacteria.

Finally, the study provides data on the relation of treatment to relapse and death. Among the entire group of 1,413 cases there were 165 instances of relapse, or 11.7 percent. These were divided with respect to treatment. Many independent investigators have reported an increasing number of relapses among patients treated with chloramphenicol. Matteucci and others suggest that this evidence would seem to indicate that chloramphenicol therapy of typhoid fever is suppressive rather than curative (*26*). Smadel and his colleagues in 1949, working in Malaya with a series of 44 patients with typhoid fever, observed a striking relation between the duration of chloramphenicol treatment and the incidence of relapses (*27*). They concluded that chloramphenicol should be administered in adequate amounts if relapses are to be avoided. Later Woodward used interrupted treatment in typhoid fever somewhat similar to that used to prevent relapses in the volunteers with scrub typhus (*28*). He reported no relapses among the eight cases given interrupted treatment.

However, in this study, it is quite possible that the actual percentage of relapses was higher than indicated since some of the patients may have had relapses after discharge from the hospital. These patients were not always followed. Furthermore, relapses were seldom recorded on the epidemiological record for nonhospitalized patients. Dubos states that relapses occur in about 10 percent of the cases and the "mortality rate in typhoid fever is about 10 percent" (*29*). He also states that in 60 to 75 percent of the fatal cases death is due to the complications of intestinal hemorrhage or perforation. Smadel and others emphasized that chloramphenicol therapy did not eliminate intestinal hemorrhages or intestinal perforation in typhoid (*27*).

In analyzing the data in this study, it was observed that complications occurred in 38, or 10.2 percent, of the 372 cases treated with 30 grams or more of chloramphenicol, and in 52, or 12.4 percent, of the 418 cases receiving less than 30 grams. In contrast, the control group consisting of 614 cases yielded 188, or 30.6 percent, complications. Some side effects of chloramphenicol were noted, but these were short lived.

Summary

An epidemiological study to investigate the efficacy of chloramphenicol in the prevention of the typhoid carrier state was conducted among 1,413 cases of typhoid fever which occurred during the 6-year period, 1947–52, in Louisiana and Mississippi. The control group comprised 614 cases which occurred largely in the period from 1947–49. In the treated group were 799 cases which occurred during the period 1950–52.

Only 59.2 percent of the cases were diag-

nosed by isolation of *Salmonella typhi;* 35.8 percent were diagnosed on serologic evidence; and 5.0 percent of the diagnoses were based on epidemiological association plus symptoms compatible with those of typhoid fever.

In both States the highest attack rates were found in the group aged 5–9 years and the lowest in those over 40 years old. In all age groups, the rates were higher among nonwhites and males than among whites and females.

Age and sex are apparently important in the development of the typhoid carrier state. The rate of development of the carrier state in the group under 20 years of age was 0.7 percent as compared with 2.5 percent among the group aged 20 and over, a highly significant increase. Among patients 40 years old and over, 5.2 percent of females but only 2.4 percent of males became carriers.

Although early adequate treatment with chloramphenicol appeared to hasten the termination of excretion of *S. typhi* in many cases, evidence that early treatment acted to prevent the chronic carrier state is weak. The carrier rate for all patients treated with chloramphenicol was 1.0 percent and that of the nonspecifically treated group was 2.0 percent.

The study did provide evidence that early adequate treatment was followed by few relapses and few serious complications. Also, with early adequate treatment case fatality was low (1.9 percent) as compared with that in the nonspecifically treated group (8.1 percent).

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Mathematics and Science Teaching

Improving the quality of science and mathematics education in the public schools is more important than increasing the number of students taking such courses, a group of prominent educators and scientists have concluded. A summary of their recommendations, Guidelines for Science and Mathematics, was issued in May 1958 by the Office of Education, Department of Health, Education, and Welfare.

This statement emphasized that mathematics and science teaching should develop the capacity of boys and girls to think for themselves, as well as communicate facts. Some specific guidelines offered by the group were:

- Students should have the opportunity for continuous experiences with science from kindergarten through high school.
- Science and mathematics should be taught as basic sciences. The teaching of them should impart an understanding of the methods of scientific investigations and research.
- Abler students should be offered at least the first year of college work while in high school.
- Continuous training of science and mathematics teachers is required to keep abreast of the changing methods and knowledge.

Additional recommendations concerned curriculum, revision of textbooks, selection of pupils for advanced courses, the use and training of teachers, and other aspects of science and mathematics education.

The guidelines were developed following a conference of educators and scientists held at the Office of Education, Washington, D. C., in February 1958. Its sponsors were the American Association of School Administrators, Council of Chief State School Officers, American Association for the Advancement of Science, National Association of Secondary School Principals, and the Scientific Manpower Commission.