CLINICAL STUDIES ON THE PATHOPHYSIOLOGY OF BUBONIC AND PNEUMONIC PLAGUE: SOME OBSERVATIONS OF TYPHOID FEVER

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In 22 Vietnamese patients with fever and bubo, Yersinia pestis infection was diagnosed by positive culture or serologic response. All strains of Y. pestis except one isolated from these patients were susceptible to most antimicrobial drugs tested, including trimethoprim. Common clinical features were tachycardia, hypotension, and leukocytosis. One patient died; the others survived while receiving streptomycin, chloramphenicol, trimethoprim-sulfamethoxazole, or combinations of these drugs. Intravascular coagulopathy was demonstrated in 19 (Cont)

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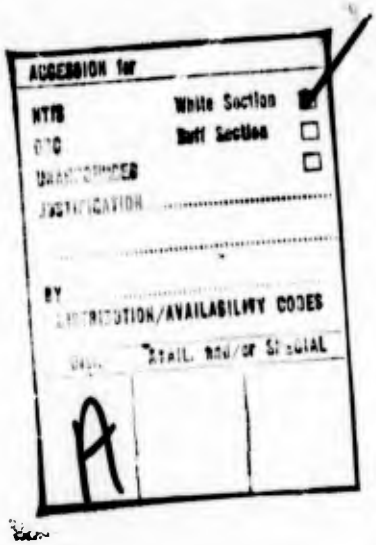
Blood cultures from febrile patients in Saigon yielded Salmonella typhi in eight cases. Four isolates were sensitive to all antibiotics and four isolates were highly resistant to chloramphenicol, tetracycline, streptomycin, and sulphadiazine. While receiving chloramphenicol the patients with drug-resistant S. typhi had prolonged febrile courses, and one patient died. The multiple drug resistance was associated with three distinct Vi-phage types and could be transferred from three of the isolates to recipient Escherichia coli organisms. (Author)



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ABSTRACT

In 22 Vietnamese patients with fever and bubo, Yersinia pestis infection was diagnosed by positive culture or serologic response. All strains of Y. pestis except one isolated from these patients were susceptible to most antimicrobial drugs tested, including trimethoprim. Common clinical features were tachycardia, hypotension, and leukocytosis. One patient died; the others survived while receiving streptomycin, chloramphenicol, trimethoprim-sulfamethoxazole, or combinations of these drugs. Intravascular coagulopathy was demonstrated in 19 patients who had elevated titers of fibrinogen-fibrin degradation products in serum; these titers decreased during convalescence. At the time of discharge, peripheral blood smears of most patients showed eosinophilia.

Blood cultures from febrile patients in Saigon yielded Salmonella typhi in eight cases. Four isolates were sensitive to all antibiotics and four isolates were highly resistant to chloramphenicol, tetracycline, streptomycin, and sulphadiazine. While receiving chloramphenicol the patients with drug-resistant S. typhi had prolonged febrile courses, and one patient died. The multiple drug resistance was associated with three distinct Vi-phage types and could be transferred from three of the isolates to recipient Escherichia coli organisms.

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I.

INTRODUCTION

Throughout history great epidemics of bubonic and pneumonic plague have ravaged many areas of the world and have claimed millions of victims. About 40 per cent of Europe's population succumbed during the Middle Ages and more recently between 1910 and 1930 about 10 million died in India (1). Although most areas of the world today are free of plague, Vietnam yearly reports thousands of cases; in 1970 there were 4,045 cases confirmed and 77 deaths (1).

Whether the low incidence of plague outside Vietnam is due to eradication campaigns and improved sanitation or due to natural biologic cycles is not known. Certainly the potential for new epidemics exists in many less developed countries. Similarly travelers to endemic areas such as Vietnam may carry incubating disease to distant countries and start a new epidemic.

Relatively little is known about the pathophysiology of human plague because this disease occurs largely in areas of the world remote from modern laboratories. The hypothesis that plague exotoxin, which depresses mitochondrial respiration in mouse infections (2), is clinically important as a cardiotoxin has not been supported by studies in patients. There is mounting evidence that plague endotoxin is responsible for purpuric skin lesions and intravascular coagulation observed in a few patients (3,4), but additional clinical data is needed to support this hypothesis.

Although bacterial toxins from Yersinia pestis have been identified the relative importance of their roles in mediating clinical events in man has not been determined. Plague exotoxin produces electrocardiographic changes in susceptible laboratory animals and inhibits mitochondrial enzymes (2). However, tissue levels required for these effects are higher than usually obtained in experimental infection. Thus, it appears unlikely that this toxin is important to man. The role of endotoxin in plague is more certain. Y. pestis possesses an endotoxin that is physiologically and chemically similar to endotoxins found in other Gram-negative bacteria (5,6). The human equivalent of the generalized Shwartzman reaction has been observed in plague patients at autopsy (3) and a clinical study in Vietnam has reported purpura and intravascular coagulation (4). Whether these lesions are attributable to circulating endotoxin and whether fibrin split products are present require answers obtainable by available laboratory assays. More knowledge of toxin mechanisms of tissue damage in plague should lead to improvements in therapy. Although available antibiotics are effective in plague, some patients have such advanced infection that they die despite antibiotic treatment. In such patients new approaches such as antagonists to biochemical effects of plague toxins will be required.

Another Gram-negative bacillus, Salmonella typhi, which causes typhoid fever, is also endemic in Saigon and is responsible for many hospitalizations and deaths annually in Saigon. Although there have been recent reports of antibiotic-resistant S. typhi in Vietnam, chloramphenicol has remained the treatment of choice. Therefore, bacterial isolates were tested for antibiotic sensitivity.

II. Antimicrobial Susceptibilities of Y. pestis Isolates.

Cultures were initially identified as Y. pestis at the Pasteur Institute in Saigon by colonial morphology, gram stain and microscopic morphology, and lysis by bacteriophage. Cultures of 15 patients were successfully transported on Cary-Blair media and reisolated in Baltimore. These 15 isolates were confirmed as Y. pestis by characteristic biochemical reactions and by phage lysis. From patient no. 17 the bubo culture yielded two distinct colony types: a mucoid colony and a smaller dry colony type typical of Y. pestis.

Isolates from all 15 patients (except the mucoid colony type of patient no. 17) were susceptible (by the Kirby-Bauer method) to ampicillin, cephalothin, chloramphenicol, furadantin, gentamicin, kanamycin, streptomycin, and tetracycline. All isolates were resistant to colymycin. The mucoid colony type of patient no. 17 was resistant to ampicillin, furadantin, and kanamycin; although the colony was susceptible to all other drugs tested, the zones of inhibition around all disks were considerably smaller than for the other isolates.

Eleven of these isolates were tested by the agar dilution method for susceptibility to trimethoprim and sulfamethoxazole. For seven isolates the MIC of trimethoprim was 1 µg/ml, while for three isolates the MIC was 3 µg/ml. The mucoid colony type of patient no. 17 was resistant to 3 µg of trimethoprim/ml. The MIC for sulfamethoxazole was 30 µg/ml for all isolates except one (patient no. 20), for which it was 100 µg/ml. Combinations of the drugs (one part trimethoprim to 20 parts sulfamethoxazole by weight) resulted in MICs of 0.1 µg of trimethoprim/ml and 2 µg of sulfamethoxazole/ml for all isolates except the mucoid colony type of patient no. 17, which had MICs of 0.3 µg of trimethoprim/ml and 6 µg of sulfamethoxazole/ml.

III.

Blood Coagulation Studies in Plague.

Twenty-six patients were studied and are summarized in Table I. The first 21 patients were either bacteriologically proven or had diagnostic Fraction I antibody rises. The remaining 5 patients were suspected of having plague because of the clinical presentation.

Platelets were measured by direct counting in a hemacytometer (normal range 150,000-300,000 per mm^3). Fibrinogen levels were assayed by a modification of the thrombin time (normal range 250-400 mg per 100 ml) (7). Fibrinogen degradation products were detected by the tanned red cell hemagglutination inhibition immunoassay (TRCHII) (8).

The TRCHII assay is the most specific test available for disseminated intravascular coagulation (DIC), and a titer of 8 or greater is considered elevated. By this criterion 20 patients had DIC on admission and 12 patients in convalescence. Platelet counts and fibrinogen levels proved to be less sensitive indicators of DIC and were decreased on admission in only 9 and 6 patients respectively as shown in Table I. Despite this high incidence of abnormal coagulation tests, none of the patients showed overt evidence for a bleeding tendency.

IV.

Complement Levels in Plague.

Serum levels of hemolytic complement (C-3) were measured by microtiter assay at Cordis Laboratories, Miami, Florida. Reference sera were run simultaneously with our samples to approximate a normal range; these were in the range 3840-5120 CH50 units per ml.

In 11 patients with proven plague infection, Table II shows that 10 had lower levels than the normal range on admission to the hospital. In 2 patients, including one who died the following day, complement levels were undetectably low. During convalescence, sera was available in 8 patients for re-examination of complement. All were lower than normal. In 5 patients complement levels declined from admission values, while in 3 patients levels were observed to increase or remain unchanged from admission values.

V.

Eosinophilia in Convalescent Plague.

The white blood count in acute plague infection is usually elevated in the range of 20,000 per mm^3 with a preponderance of neutrophilic leukocytes often including juveniles and metamyelocytes. Eosinophils are rarely present in acute plague. However, no one has previously remarked upon the differential white cell counts in convalescing patients.

Table III compares admission and convalescent eosinophil counts in 17 patients with plague in whom convalescent blood smears were obtained. The eosinophil counts were estimated by multiplying the per cent eosinophils by the total white blood cell counts. Absolute eosinophil counts greater than 300 per mm^3 are usually regarded as abnormal. Using this value, only 4 of 17 patients on admission had eosinophilia, while during convalescence 14 of 17 had eosinophilia.

VI.

Blood Coagulation Studies in Typhoid Fever.

During the course of our plague studies in Saigon, it was intended that other febrile illnesses be studied concomitantly to provide control information on other Vietnamese patients. At Cho-Quan Hospital, Ward 11-C, where patients with plague were admitted, typhoid fever was so commonly seen that separate observations on these patients seemed appropriate.

Table IV summarizes the clinical features of 11 patients. Unlike the patients with plague, the hemorrhagic phenomena of melena, purpura, rose spots, or epistaxis were present in most cases. Two of the patients died with significant gastro-intestinal bleeding. Significant titers of fibrinogen degradation products were present in all but 2 of the patients on admission. During convalescence titers remained elevated in most patients. Platelet counts and fibrinogen levels were commonly decreased as shown in Table IV.

VII.

Antibiotic Resistance in Typhoid Fever.

Vietnamese physicians have been aware of chloramphenicol-resistant typhoid fever for about 2 years. This awareness is based on treatment failures in patients and on antibiotic sensitivity testing of isolated bacteria. At Cho-Quan Hospital we also observed some patients who failed to respond to chloramphenicol. Two illustrative cases are described:

A. This 16-year old boy began having fever and vomiting 3 weeks before admission. One week before admission he noted the onset of watery diarrhea several times a day and his continuing fever was accompanied by chills and sweating. One day before admission he developed abdominal pain. The temperature was 105°F, pulse 120 per

minute, respirations 28 per minute, blood pressure 115/75 mm Hg. He had mild, diffuse abdominal tenderness. The spleen was palpable 3 cm below the left costal margin. A macular blanching erythematous rash was present on his anterior trunk and abdomen. The hematocrit was 47%, white blood cell count 4300 per cu mm, and platelets 150,000 per cu mm. A blood culture yielded S. typhi. Initial therapy was intravenous fluids and chloramphenicol 500 mg orally 3 times a day. His hospital course and therapy are summarized in Figure I. Bactrim® (trimethoprim 80 mg, sulfamethoxazole 400 mg) tablets 4 times a day was started on the fourteenth day. He was discharged afebrile on the twenty-first day.

B. Ten days before admission this 15 year old boy developed fever accompanied by watery diarrhea about 4 times a day. Two days before admission he began taking chloramphenicol 750 mg a day. On the day of admission he became delirious and passed a dark red stool. The temperature was 104°F, pulse 152 per minute, respirations 48 per minute, and BP 85/60 mm Hg. He was disoriented and combative. The sclerae were lightly icteric and the liver palpable 6 cm below the right costal margin. The hematocrit was 32°, white blood cell count 4900 per cu mm, and platelets 176,000 per cu mm. A blood culture yielded S. typhi. Lumbar puncture revealed clear fluid under normal pressure with no white blood cells; the culture was negative. He was treated with intravenous chloramphenicol 3 gm per day and intermittent doses of hydrocortisone 100 mg without improvement. On the fifth day the temperature was 102°F; he was stuporous and passed melenic stools. At this time the serum urea nitrogen was 92 mg per 100 ml, creatinine 3.3 mg per 100 ml, bilirubin 1.4 mg per 100 ml (Direct 1.2) SGOT 610 milli-international units (M-IU) per ml, SGPT 56 M-IU per 100 ml, and alkaline phosphatase 66 M-IU per 100 ml. He was transfused but became comatose and died on the sixth hospital day.

From 8 patients blood cultures yielded S. typhi. By the Kirby-Bauer method at the NCDC, Atlanta, Georgia 4 of the isolates were found to be resistant to chlormaphenicol, tetracycline, streptomycin, and sulfadiazine. Table V shows the results of tube-dilution sensitivity testing, phage-typing, and mating studies for transfer of antibiotic resistance (R-factors) to E. coli. The 4 resistant strains were comprised of 3 distinct Vi-phage types. Three of the resistant strains transferred a full resistance pattern to recipient E. coli strains.

VIII.

CONCLUSIONS

Previous studies had shown that disseminated intravascular coagulation (DIC) could occur in plague infections (3,4). These studies emphasized the generalized Shwartzman phenomenon as evidenced

by renal glomerular thrombi at autopsy (3) and skin biopsies of purpura showing fibrin thrombi (4). However, blood studies for DIC had previously included only platelets, fibrinogens, partial thromboplastin times, and ethanol gelation tests (4), all of which may be abnormal in situations other than DIC. The availability of the highly specific TRCHII for fibrinogen-fibrin degradation products and the elevated titers frequently found in this study allows us to conclude that DIC is commonly present in acute plague despite the rarity of clinical evidence for hemorrhagic diathesis.

Serum complement levels were found reduced in most patients studied. However, the significance of these reductions is hard to judge at this time because of the small numbers of patients studied and the lack of controls in normal Vietnamese subjects. In other acute bacterial infections serum complement levels have been noted to be rarely reduced (9), but studies of Gram-negative sepsis showed a mean complement level lower than normal (10), and another study of bacterial shock showed lower levels in shock than in normotensive infected patients (11).

Eosinophilia was frequently seen in these convalescing plague patients but was rare during the acute stage. Without knowledge of their eosinophil counts prior to infection, it is not possible to know whether during convalescence patients re-acquired eosinophilia or develop it de novo as a result of the plague infection and its treatment. Experimental studies in eosinophilic animals show that acute pyelonephritis with E. coli will abolish eosinophilia (12); eosinopenia likewise could be produced by injections of typhoid vaccine, which contains endotoxin. In our patients a similar mechanism may have occurred. It is also possible that plague infection or antibiotic treatment provoked migration of intestinal helminths, either by the stress of fever or disturbance of normal bowel flora by antibiotics.

Patients with typhoid fever in this study had a high incidence of DIC based on low platelet counts and high titers of fibrinogen-fibrin degradation products. It is interesting to speculate what role DIC played in their bleeding syndromes. The clinical severity and therapeutic failures with chloramphenicol in this series of patients is similar to the experience with drug-resistant typhoid fever in Mexico (13). Although the prevalence of drug-resistance in Vietnam may not be so high as that suggested in our small sample because of selection bias due to outpatient treatment failures, another report from Saigon showed a similarly high frequency of drug resistance in 11 of 35 isolates of S. typhi (14). Thus, drug-resistant typhoid fever appears to be common in Saigon. Because typhoid fever may be fatal before antibiotic sensitivities are available, chloramphenicol should not be used alone in initial therapy. Ampicillin has been shown as effective alternative drug, (15) and trimethoprim-sulfamethoxazole has been

reported as highly effective (16). It is recommended that enteric fever in Vietnam or in travelers recently in Vietnam be initially treated with chloramphenicol combined with ampicillin or trimethoprim-sulfamethoxazole until sensitivity results are available. If an isolate of S. typhi in a particular patient is susceptible to chloramphenicol, then chloramphenicol should be used alone (17).

Epidemiological data on seasonal occurrence and vehicles of transmission are not available. Hospital records and local medical opinion suggest that enteric fever is endemic throughout Vietnam without apparent seasonal variation or identifiable common-source outbreaks. Chloramphenicol-resistant typhoid fever was first reported in Vietnam in 1972, and has been attributed to the indiscriminant use of chloramphenicol (14). However, widespread dispensing of chloramphenicol by pharmacies and physicians has occurred over a much longer period of time, and perhaps other explanations for the appearance of drug resistance need to be sought. The four resistant strains encountered in this study were all highly resistant to tetracycline, streptomycin, and sulphadiazine as well as to chloramphenicol. Three of these four strains transferred their resistance to all four antibiotics to recipient E. coli organisms, and it is suspected that the fourth strain, in which transfer was not demonstrated, contained the identical R factor without a mobilizing transfer factor. This pattern of R-factor-mediated resistance is thus different from S. typhi strains from Chile and Aden reported resistant only to chloramphenicol and non-transferable, and from S. typhi from Kuwait which transferred resistance to chloramphenicol, tetracycline, and ampicillin (18). On the other hand, the strains from the 1972 Mexican typhoid epidemic had the same four-drug resistance pattern as those in this report, and all were R-factor mediated (18).

It is significant that among the four S. typhi strains in this report, all with seemingly identical R factors, there were three distinct Vi-phage typing patterns. Phage-typing data are available for only some of the previously reported chloramphenicol-resistant S. typhi. Two strains from Chile were Vi-phage types A and 46; two strains from Kuwait in 1967 were also Vi-phage type A, and a third was Vi-phage type E1 (18). The three phage types of our resistant strains differed from these; furthermore, the degraded Vi strain is readily distinguishable from the degraded Vi strain of the Mexican epidemic of 1972. In contrast to the situation in Mexico in 1972, our resistant S. typhi strains may represent evidence for the epidemic spread of an R factor rather than of its bacterial hosts, which are already endemic in Vietnam. The same may have been true in Kuwait in 1967 when identical R factors were found in S. typhi strains belonging to two distinct Vi-phage types. Similar multiple drug-resistance episomes have been demonstrated in Shigella dysenteriae 1 from the Central American

pandemic, 2 S. flexneri 2a strains from outbreaks in the United States, as well as in the epidemic S. typhi strains from Mexico (19-21).

The emergence of R-factor-mediated drug resistance in S. typhi in Vietnam presents an opportunity for studying the epidemiology of antibiotic resistance. Whether the same R factor is present in other bacterial species and whether this R factor exists in other parts of the country where chloramphenicol usage is less common remain unknown.

(Part I)

APPENDIX A

Table I. Clinical and Coagulation Data in Plague

Patient No.	Age	Sex	Temperature Rectal °F	Blood Pressure mm Hg	White Blood Cell Count per mm^3
1	6	F	104^9	92/60	22,600
2	12	M	104	-	11,100
3	4	M	105^2	85/65	22,300
4	13	F	103^2	80/60	20,700
5	5	M	104^8	85/50	24,800
6	39	M	100^6	90/60	8,500
7	13	M	100^7	90/60	11,300
8	67	M	104	120/65	12,200
9	8	M	102^2	50/20	25,400
10	50	M	102	100/65	35,000
11	46	M	100	100/60	16,400
12	15	M	102	80/60	22,000
13	49	F	103	90/70	44,600
14	12	M	102^2	80/60	23,100
15	45	M	104	90/60	13,800
16	5	M	104	80/60	12,900
17	9	M	104	100/50	20,400
18	40	M	104^8	70/50	22,600
19	17	M	105^8	70/40	13,100
20	45	F	104	75/50	8,800
21	57	F	102^2	100/80	10,000
22	43	M	100	90/60	5,400
23	10	M	99^8	90/70	17,200
24	10	M	103^5	105/75	6,600
25	49	F	99^5	120/90	10,200
26	16	M	101^8	112/80	11,000

(Part II)

APPENDIX A

Table I. Clinical and Coagulation Data in Plague

	Tests for DIC					
	Admission			Convalescence		
Patient No.	Platelets per mm^3	Fibrinogen mg per 100 ml	Fibrinogen Degradation Products, Titer	Platelets per mm^3	Fibrinogen mg per 100 ml	Fibrinogen Degradation Products, Titer
1	364,000	135	8	-	Died	-
2	190,000	360	8	-	N/A	-
3	222,000	285	16	250,000	170	8
4	298,000	540	64	574,000	340	32
5	301,000	250	32	486,000	145	16
6	114,000	85	16	242,000	99	8
7	78,000	310	8	274,000	170	4
8	198,000	270	8	-	N/A	-
9	200,000	270	128	-	N/A	-
10	82,000	300	32	366,000	500	4
11	152,000	340	8	134,000	285	2
12	74,000	300	8	106,000	600	8
13	64,000	105	256	200,000	210	4
14	178,000	270	32	184,000	270	64
15	62,000	140	32	174,000	150	
16	284,000	300	2	270,000	300	4
17	156,000	300	8	310,000	340	8
18	64,000	540	64	116,000	300	32
19	198,000	190	8	428,000	220	64
20	150,000	340	4	250,000	300	4
21	92,000	270	4	172,000	300	8
22	208,000	540	2	216,000	250	2
23	350,000	180	8	-	N/A	-
24	220,000	270	4	266,000	150	16
25	160,000	300	128	224,000	270	1
26	108,000	250	2	340,000	480	2

APPENDIX B

Table II. Complement Levels in Plague

Patient No.	Hemolytic Complement - CH50 units per ml	
	Admission	Convalescence
1	<10	N/A
2	<10	480
3	320	240
4	3840	< 10
5	240	320
6	20	< 10
7	320	< 10
8	120	N/A
9	240	N/A
10	1280	960
11	1280	1280
Reference Sera:	3840 - 5120 units per ml	

APPENDIX C

Table III. Eosinophilia in Convalescent Plague

Patient No.	Admission		Convalescence	
	Per Cent Eosinophils	Eosinophils/ mm^3	Per Cent Eosinophils	Eosinophils/ mm^3
1	0	0	12	1188
2	0	0	12	1260
3	0	0	6	312
4	0	0	32	3424
5	2	342	1	77
6	0	0	7	368
7	2	440	6	366
8	0	0	0	0
9	0	0	0	0
10	0	0	13	1118
11	2	258	10	915
12	1	204	10	880
13	1	226	4	572
14	0	0	13	780
15	18	972	40	2900
16	0	0	5	333
17	9	918	14	819

APPENDIX D

Table IV. Coagulation Data in Typhoid Fever

Tests for DIC					
Admission			Convalescence		
Platelets per mm^3	Fibrinogen mg per 100 ml	Fibrinogen Degradation Products, Titer	Platelets per mm^3	Fibrinogen mg per 100 ml	Fibrinogen Degradation Products, Titer
176,000	130	32	-	-	-
11,000	135	8	14,000	300	8
148,000	480	8	94,000	600	8
46,000	300	8	460,000	105	16
58,000	160	8	240,000	600	8
150,000	230	16	270,000	150	8
108,000	285	4	266,000	600	4
158,000	300	64	176,000	270	8
38,000	160	16	186,000	300	4
82,000	270	32	-	-	-
162,000	300	4	298,000	200	8

APPENDIX E

Table V. Tube Dilution Susceptibilities, Phage-Types, and Mating Studies in *S. typhi* Isolates

Minimum Inhibitory Concentration µg per ml					
Chloramphenicol	Tetracycline	Sulfadiazine	Streptomycin	Vi-phage Type	Resistance Transferred**
250	250	25,000	125	E7, atypical	None
250	125	25,000	250	E7, atypical	C, T, Su, S
250	125	25,000	500	Degraded Vi	C, T, Su, S
500	125	>25,000	250	Untypable	C, T, Su, S

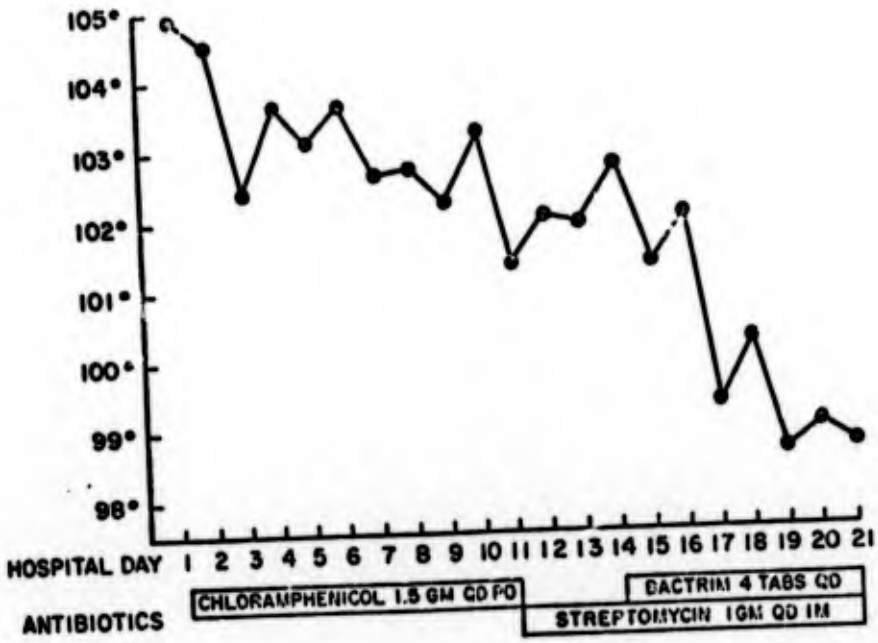

Figure 1. Highest daily rectal temperatures in degrees Fahrenheit during hospital course of Case A.

X,

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