STAPHYLOCOCCEMIA 1931–1940. FIVE HUNDRED PATIENTS

BY

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Reprinted from AMERICAN JOURNAL OF CLINICAL PATHOLOGY
Vol. 12, No. 6, June, 1942

Made in the United States of America

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INTRODUCTION

In 1932 we presented a report of 15 patients suffering from staphylococcemia treated with the aid of bacteriophage. An additional series of 100 patients was reported in 1936. In the present series of papers, we purpose to present data in regard to 385 additional patients in our series of staphylococcal sepsis, these patients having been assigned numbers 116 to 500 in chronological order of accession and plan, further, to consider these 385 patients, together with the previous 115, in discussion.

In this paper, we wish to devote particular attention to the criteria on which the selection of patients for the series is based, and to present a chronological list of the 385 patients not previously reported. Some consideration will be given to such factors as the relation of the disease to the season of the year and its sex and age distribution. Particular groups will be selected from the 500 patients for special discussion in subsequent papers. Reference will be made to the influence of bacteriophage therapy upon the course and outcome of the disease, but the more detailed study will be reserved for discussion in the appropriate groups.

SELECTION OF PATIENTS

Admission of patients to this series has been based upon two objective criteria: First, there must have been received by us from the attending physician an invitation to aid in the care of his patient. Second, there must be reasonably convincing evidence that infection of the blood stream with staphylococci actually existed. It should be clear that we did not select the cases. The request for consultation service has been made, in general, only when the attending physician has thought his patient to be in a serious or even desperate condition. Hence there are few, if any, mild cases in the series.

Of the 100 patients reported in 1936 seven did not receive bacteriophage, although it was requested for use in therapy. This small number did not seem adequate to constitute a control group and hence the control relation was not emphasized at that time. In the larger series of 385 patients presented here, there have been, from time to time, those who did not receive bacteriophage therapy although our service was invited. If such patients have been acceptable as cases of genuine staphylococcemia they have been included in the series. As a result, there has accumulated a group accessioned to our series concurrently with, and in the same manner, as the phage-treated patients. The decision in regard to the administration of bacteriophage did not rest with us in any case because we have consistently supplied bacteriophage upon the request of any qualified physician. Whenever we have been consulted, we have recommended its use in all instances of severe infection with staphylococci.

Adequate proof of infection of the blood stream has sometimes presented difficulty. In most instances there were repeatedly positive blood cultures and at least one of these cultures was submitted to us for study. When the patient succumbed we have been willing to accept the case with less reluctance and in such instances the post-mortem demonstration of pyemic lesions containing staphylococci has been accepted as adequate, even in the absence of convincingly positive blood cultures. The evidence of clinically observed metastatic localizations containing staphylococci has been given due weight. However, when the patient has survived, the evidence has been very critically examined and chief weight has been attached to the record of blood cultures. When this evidence has not been reasonably convincing we have excluded the patient from the series.

As might be expected, there were some patients who presented considerable difficulty in the decision to include or exclude them and brief summaries of a few of the records may illustrate these difficulties.

D. S., male aged 44, a diabetic with very large carbuncle on the back of his neck, was admitted to the Post-Graduate Hospital on November 7, 1938. On November 10, under cyclopropane anesthesia, a crucial incision was made in the lesion. Bacteriophage service was requested by the surgeon immediately after the operation. A blood culture taken at this time, 3:58 p.m. November 10, gave a positive growth of *Staphylococcus aureus* in one broth bottle but nothing on the agar plates. Intravenous injections of bacteriophage were given at 4 p.m. and 8 p.m. on November 10 and continued, two or three injections daily, through November 20. Blood cultures taken on November 14 and 16 remained sterile and the patient was discharged in good condition on November 23. The one positive blood culture was taken with care to avoid contamination. However, we have chosen to regard this as merely a transient invasion of the blood stream following surgical trauma to the carbuncle and have therefore excluded this patient from the series of staphylococcemias.

E. S., male aged 14, with an old osteomyelitis of the right hip, underwent a revision operation on December 21, 1938. On December 26 he had a chill with temperature rise to to 103 degrees. A blood culture was taken at this time and gave positive growth of *Staphylococcus aureus* in one broth bottle. Unfortunately no agar plates were poured. Subsequent blood culture was negative. Bacteriophage therapy was begun on December 28 and the patient made a good recovery. Again we have decided to regard this as an example of transient bacteremia and have excluded this patient from the series of staphylococcemias.

No. 490, H. B., male aged 8, bruised his right shoulder about February 19, 1940 and this became painful on February 29. The right humerus was opened on April 2. The record of blood cultures is rather obscure but there is one note of "staphylococci present in 24 hours" on April 3 and another "staphylococci present at 48 hours" on April 4. Apparently these notes relate to the same blood culture taken on April 2, possibly just after the operation. We sent bacteriophage by request on April 3 but it was not used. The patient was treated with sulfathiazole with success and was discharged on June 10, 1940. This also would seem to have been an example of transient bacteremia following operation. However, because the patient recovered without bacteriophage we have not wished to take the responsibility of excluding him from the series and he has therefore been included.

No. 493, A. M., female aged 11, presented a laceration of the right great toe on May 13, 1940, with adjacent swelling. This was incised on May 14, following which the inflammation spread rapidly. She was admitted to hospital on May 20 with a temperature of 105.4 degrees. Blood cultures taken on May 21 and 22 developed colonies of *Staphylococcus aureus*, 8 and 10, respectively, per cc. of blood. Subsequent blood cultures taken on May 27, 29, June 1, 4 and 5 remained negative. Sulfathiazole was given intravenously, beginning May 23. On June 2 both legs were incised and on June 4 more extensive incision was

made in the right leg and a transfusion was given. Following this operation the temperature rose to 107 and the pulse rate to 160. Bacteriophage was requested and supplied on this day. However, it was first used on June 7 and then in doses of 2 cc. twice daily. On June 20 osteotomy and sequestrectomy were performed on both tibiae and a transfusion was given. The condition of the patient was "very poor" at this time. Bacteriophage, 10 cc., was given by intravenous drip on June 23 with production of chill, pallor, cyanosis and temperature rise of 2.6 degrees to 104.8. It was again administered intravenously on June 24, apparently 2 cc., and again there was chill and rise in temperature to 104.6. On July 2 both incisions were packed with vaseline gauze and the legs encased in plaster. The patient was discharged improved on July 25. Apparently no blood culture was taken after June 5. The record does not permit one to conclude that bacteriophage played any part in overcoming the infection of the blood stream. However, there were two evidently valid positive blood cultures in May, and hence the case is included in the staphylococcemia series.

No. 232, J. Q., female aged 2 months, was admitted to hospital on October 7, 1936. Blood cultures taken October 8, 15, 17 and 23 were positive for *Staphylococcus aureus*. Those taken on October 29, November 7 and 29 remained negative. There was otitis media and also stubborn generalized furunculosis. The child was given numerous transfusions and many of the lesions were incised from time to time. The temperature ranged from 99 to 105.4 in the period October 7 to 24. Then it assumed a lower level, between 98 and 103, until October 30; then a still lower level, 98 to 100.4, until discharge. Bacteriophage was requested by letter on November 6 and in this letter it was stated that the patient had repeatedly positive blood cultures of hemolytic *Staphylococcus aureus*. Bacteriophage was administered on November 6 at 6 p.m., the dose given being 6 cc., and was continued daily by intramuscular or subcutaneous injection for several days. The record is not entirely satisfactory. However, the baby was discharged home on December 22. It is evident that the infection of the blood stream had disappeared before phage was used and indeed it seems very uncertain that the bacteriophage exercised any effect in this case. We have felt, however, that it could not justly be omitted from the staphylococcemia series because of the record of four positive blood cultures taken during October.

No. 332, V. S., male aged 55, got a splinter in thumb of left hand on February 25, 1938, which he removed on February 27. On March 1 he was admitted to hospital with ascending lymphangitis of the forearm. Blood cultures taken March 3 and 4 developed colonies of *Staphylococcus aureus*, 10 per cc. of the patient's blood in the latter. A metastatic abscess appeared in the left popliteal space. Prontylin was given, fifteen grains three times a day, from March 4 through March 7, and 10 grains from March 8 to 12 inclusive. Blood cultures taken on March 6, 9, and 19 remained negative. Purulent fluid, 40 cc., was aspirated from the left knee on April 20. This was sterile on culture. Bacteriophage was given in a series of intravenous injections from 2:45 p.m. March 19 to 8:15 p.m. March 20 to a total of 302.7 cc., without reaction. However, the temperature which had reached 102.6 on March 17, 101.6 on March 18 and 103.6 on March 20, returned to normal on March 21 and did not exceed 99 degrees at any observation during March 22, 23 and 24. The local condition in the knee also started to improve promptly. The patient was discharged May 25. In this instance the infection of the blood stream appears to have been overcome before the phage was used but the influence of the bacteriophage in control of the active and latent metastatic lesions seems, from the clinical evidence, to have been especially gratifying. The record of two positive blood cultures at the beginning and the presence of the pyemic localization in the knee have persuaded us to include this patient in the staphylococcemia series.

In tabulating the series of cases there has sometimes arisen difficulty in deciding whether to class the patient as an example of death or recovery. It has not seemed proper to accept negative results of blood cultures as proof of recovery

from staphylococcemia even when the patient has had normal temperature. We have, therefore, as a rule, awaited the discharge from hospital "improved" before recording the case as a survival.*

In a very few instances a patient discharged "improved" has subsequently succumbed to an apparent sequel of the staphylococcemia. In those cases where the fatal outcome could be definitely accepted as a sequel of the blood stream infection, the patients have been listed as fatalities. The long interval between time of accession and death of patient as seen in some cases on the chronological list will illustrate this.

The most controversial instance of this sort is represented by the patient No. 371, G. P., aged 24 years. This man was admitted to hospital on October 19, 1938 and blood cultures taken October 20, 24, 26, 28 and November 2 were positive for *Staphylococcus aureus*. Bacteriophage therapy was employed from October 31, 1938 to January 26, 1939. Sulfanilamide, sulfapyridine and neoarsphenamine were also given occasionally. After negative X-ray examination on February 14, he was discharged "improved" on February 15, 1939. Subsequently on May 23, 1939, he was admitted to another hospital where he died on June 5. Post-mortem examination disclosed an osteomyelitis of the skull and a contiguous abscess of the cerebrum. It was impossible to decide whether these were of metastatic origin or the result of extension from the nasal accessory sinuses. Although not quite certain about this case we have classified the patient as an example of recovery from the staphylococcemia.

There are a few others which have occasioned us much concern. These are patients said to have staphylococcus septicemia when our aid has been requested, but for whom we have been unable to obtain an adequate record. For lack of convincing information we have been compelled to omit these from the series. Fortunately these are few indeed. The fact that we have been able to get information in regard to nearly all the sepsis patients speaks well for the scientific interest, ethical principles and essential courtesy of the physicians and the administrative officers of the many hospitals concerned. It is a pleasure to express our appreciation and our thanks to them.

LIST OF PATIENTS

For purpose of identification and reference it seems worth while to present the list of accepted staphylococcemia patients in chronological order based on the date when our service was requested, along with the date when the first positive blood culture was taken and the date of death in fatal cases.

From our previous study of the first 115 patients in the series of 500, it was apparent that there were some rather long periods without a successful case. For example, from January 1 to April 30 in 1931 there was no survival, but actually only two patients received the bacteriophage service for staphylococcemia during

* This criterion of recovery is somewhat different from that of Herrell and Brown who say "By recovery we mean that the blood cultures became negative and the patients were entirely without evidence of infection of the blood stream." (Herrell, Wallace E., and Brown, Alex E.: The treatment of septicemia. Journ. Am. Med. Assn., **116,** 180 (Jan. 18) 1941.)

TABLE 1

SERIAL NUMBER	PATIENT	POSITIVE BLOOD CULTURE	PHAGE CONTACT	DEATH	SERIAL NUMBER	PATIENT	POSITIVE BLOOD CULTURE	PHAGE CONTACT	DEATH
			1934					1936	
116	M 14	Aug. 9	Aug. 14	Aug. 14	181	M 26	Jan. 6	Jan. 19	Recovery
117	F 10	Aug. 16	Aug. 17	Aug. 17	182	F 5	Jan. 31	Feb. 5	Recovery
118	M 7	Sep. ?	Sep. 13	Recovery	183	F 7	Feb. 19	Feb. 22	Recovery
119	M 70	Sep. 15	Sep. 16	Oct. 17	184	F 27	Feb. 9	Feb. 29	Mar. 2
120	M 38	Sep. 13	Sep. 17	Sep. 21	185	M 41	Feb. 29	Mar. 3	Mar. 16
121	M 37	Oct. 8	Oct. 9	Recovery	186	M 22	Jan. 6	Mar. 10	Jun. 18
122	M 31	Oct. 2	Oct. 9	Recovery	187	M 11	Mar. 13	Mar. 18	Recovery
123	M 37	Sep. 10	Oct. 11	Recovery	188	M 14	Jan. ?	Mar. 21	Recovery
124	F 9	Oct. 6	Oct. 15	Nov. 9	189	F 50	Mar. 24	Mar. 25	Mar. 26
125	F 27	Oct. 18	Oct. 20	Oct. 21	190	F 28	Mar. 27	Mar. 29	Recovery
126	M 37	Oct. 24	Oct. 26	Oct. 27	191	F 10	Mar. 31	Mar. 31	Apr. 1
127	M 27	Oct. 24	Oct. 27	Oct. 27	192	M 16	Apr. 4	Apr. 11	Recovery
128	M 15	Oct. 22	Nov. 3	Recovery	193	F 26	Apr. 8	Apr. 13	Apr. 20
129	M 8	Oct. 30	Nov. 4	Nov. 12	194	M 28	Apr. 16	Apr. 19	Recovery
130	M 50	Nov. 16	Nov. 17	Nov. 21	195	M 57	Apr. 20	Apr. 23	Apr. 25
131	M 4	Dec. 5	Dec. 6	Recovery	196	F 15	Apr. 24	Apr. 25	May 2
132	F 60	Dec. 5	Dec. 7	Dec. 8	197	F 45	Apr. 25	Apr. 25	Recovery
133	M 13	Dec. 23	Dec. 24	Recovery	198	F 5	Apr. 24	Apr. 29	Recovery
134	F 28	Dec. 25	Dec. 28	Dec. 29	199	M 17	May 6	May 7	May 11
					200	M 37	May 11	May 12	Recovery
			1935						
135	M 77	Jan. 4	Jan. 6	Jan. 7	201	M 37	May 16	May 17	May 17
136	M 14	Jan. 4	Jan. 8	Jan. 27	202	M 6	May 14	May 18	Recovery
137	M 9	Jan. 9	Jan. 11	Jan. 12	203	M 55	May 21	May 23	Jul. 24
138	F 52	Jan. 12	Jan. 12	Recovery	204	M 14	May 21	May 23	May 31
139	M 16	Jan. 12	Jan. 14	Recovery	205	F 8	May 24	May 29	Recovery
140	F 37	Jan. 26	Jan. 25	Feb. 18	206	M 38	May 28	May 30	Recovery
141	M 9	Jan. 26	Jan. 29	Recovery	207	M 17	Jun. 3	Jun. 6	Recovery
142	M 11	Feb. 8	Feb. 11	Feb. 14	208	M 50	Jun. 18	Jun. 24	Recovery
143	M 40	Jan. 17	Feb. 11	Recovery	209	M 40	Jun. 23	Jun. 24	Jun. 26
144	F 14	Feb. 9	Feb. 13	Mar. 1	210	M 16	Jun. ?	Jun. 25	Recovery
145	M 40	Feb. 21	Feb. 22	Feb. 24	211	F 50	Jun. 23	Jun. 25	Jul. 1
146	M 12	Feb. 12	Mar. 1	Apr. 17	212	M 74	Jul. 9	Jul. 9	Jul. 10
147	F 27	Feb. 27	Mar. 4	Mar. 5	213	M 35	Jul. 18	Jul. 20	Jul. 26
148	M 3	Mar. 26	Mar. 27	Apr. 15	214	M 45	Jul. 23	Jul. 21	Jul. 23
149	M 34	Mar. 19	Mar. 27	Recovery	215	F 2	Jul. 19	Jul. 21	Jul. 23
150	M 26	Mar. 20	Apr. 1	May 18	216	F 14	Aug. 3	Aug. 5	Aug. 8
151	F 12	Apr. 1	Apr. 3	Recovery	217	F 4 mo.	Aug. 19	Aug. 21	Sep. 4
152	M 13	Apr. 4	Apr. 10	Apr. 13	218	M 9	Aug. 21	Aug. 23	Aug. 25
153	F 39	Apr. 8	Apr. 12	Apr. 20	219	M 9	Aug. 24	Aug. 25	Aug. 26
154	M 1	Apr. 22	Apr. 24	Recovery	220	M 16	Aug. 30	Aug. 30	Sep. 2
155	F 49	Apr. ?	May 3	May 8	221	M 10	Aug. 26	Sep. 4	Sep. 25
156	M 15	May 1	May 4	May 12	222	M 4	Sep. 3	Sep. 10	Sep. 11
157	F 33	May 5	May 5	May 5	223	M 13	Sep. 11	Sep. 11	Sep. 14
158	M 19	May 11	May 14	Jun. 6	224	F 6	Sep. 11	Sep. 14	Recovery
159	M 34	May ?	May 21	Jun. 20	225	M 7	Sep. 14	Sep. 19	Recovery
160	M 11	Jun. 3	Jun. 5	Jun. 6	226	M 13	Sep. 14	Sep. 19	Sep. 23
161	M 29	Jun. 12	Jun. 12	Jun. 14	227	M 16	Sep. 25	Sep. 25	Sep. 27
162	M 39	Apr. 17	Jun. 17	Jun. 21	228	M 23	Oct. 7	Oct. 9	Recovery
163	F 50	Apr. 12	Jul. 10	Jul. 15	229	M 12	Oct. 7	Oct. 9	Oct. 10
164	M 32	Jul. 17	Jul. 18	Jul. 21	230	M 34	Oct. 19	Oct. 19	Recovery
165	M 14	Jul. 29	Aug. 3	Recovery	231	F 32	Sep. '35	Oct. 26	Sep. '37
166	M 33	Aug. 11	Aug. 8	Recovery	232	F 2 mo.	Oct. 8	Nov. 6	Recovery
167	M 28	Aug. 19	Aug. 22	Aug. 31	233	M 74	Nov. 7	Nov. 9	Recovery
168	M 20	Aug. 15	Aug. 24	Jan. 21/36	234	M 41	Nov. 2	Nov. 9	Nov. 14
169	F 38	Sep. 22	Sep. 23	Recovery	235	F 26	Nov. 8	Nov. 10	Recovery
170	F 50	Oct. 13	Oct. 14	Oct. 15	236	M 74	Nov. 5	Nov. 11	Jan. 28/37
171	M 52	Oct. 30	Oct. 30	Nov. 5	237	F 55	Nov. 24	Nov. 26	Nov. 26
172	M 3 wk.	Oct. 25	Nov. 1	Nov. 25	238	M 9	Nov. 23	Nov. 27	Dec. 6
173	F 19	Oct. 3	Nov. 9	Recovery	239	F 9	Nov. 30	Dec. 4	Recovery
174	M 19	Nov. 8	Nov. 10	Nov. 14	240	M 48	Dec. 4	Dec. 7	Dec. 8
175	M 11	Nov. 18	Nov. 18	Dec. 10	241	M 28	Dec. 9	Dec. 10	Dec. 12
176	M 48	Nov. 14	Nov. 21	Dec. 1	242	M 40	Dec. 21	Dec. 26	Recovery
177	M 28	Nov. 21	Nov. 22	Nov. 25	243	F 32	Dec. 23	Dec. 26	Dec. 29
178	M 30	Dec. 7	Dec. 17	Dec. 20	244	M 12	Dec. 21	Dec. 28	Recovery
179	F 32	Dec. 22	Dec. 24	Dec. 25	245	M 18	Dec. 27	Dec. 29	Dec. 31
180	F 38	Dec. 23	Dec. 27	Dec. 29					

TABLE 1—*Continued*

SERIAL NUMBER	PATIENT	POSITIVE BLOOD CULTURE	PHAGE CONTACT	DEATH	SERIAL NUMBER	PATIENT	POSITIVE BLOOD CULTURE	PHAGE CONTACT	DEATH
			1937					1938	
246	M 16	Dec. 18	Jan. 7	Jan. 17	312	M 50	Dec. 10	Jan. 6	Feb. 3
247	M 48	Jan. 7	Jan. 9	Jan. 10	313	M 51	Dec. 31	Jan. 6	Jan. 8
248	M 6	Jan. 9	Jan. 10	Jan. 11	314	M 10 mo.	Jan. 8	Jan. 8	Jan. 9
249	M 12	Jan. 15	Jan. 16	Jan. 18	315	F 10	Dec. 28	Jan. 10	Jan. 16
250	F 30	Jan. 18	Jan. 19	Jan. 19	316	M 8	Jan. 7	Jan. 11	Recovery
251	F 43	Jan. ?	Jan. 20	Jan. 20	317	F 7	Jan. 12	Jan. 13	Jan. 30
252	M 42	Jan. 24	Jan. 25	Jan. 25	318	F 24	Jan. 5	Jan. 17	Jan. 23
253	F 22	Feb. ?	Feb. 3	Feb. 5	319	M 25	Jan. 17	Jan. 19	Jan. 20
254	F 44	Feb. 3	Feb. 4	Feb. 5	320	M 10	Jan. 16	Jan. 19	Jan. 22
255	M 34	Feb. 1	Feb. 6	Recovery	321	F 3	Jan. 17	Jan. 22	Recovery
256	M 28	Feb. 6	Feb. 6	Feb. 21	322	F 37	Jan. 20	Jan. 24	Feb. 3
257	M 56	Feb. 3	Feb. 7	Recovery	323	M 55	Jan. 27	Jan. 30	Jan. 31
258	M 53	Feb. 5	Feb. 13	Feb. 20	324	M 35	Jan. 27	Jan. 31	Mar. 22
259	M 39	Feb. 9	Feb. 16	Feb. 21	325	F 26	Feb. 3	Feb. 7	Recovery
260	M 14	Nov. '36	Feb. 26	Recovery	326	M 10	Feb. 6	Feb. 9	Feb. 16
261	F 17	Feb. ?	Feb. 26	Mar. 18	327	F 65	Feb. 7	Feb. 17	Apr. 9
262	F 59	Mar. 4	Mar. 9	Mar. 20	328	M 61	Feb. 22	Mar. 2	Mar. 11
263	M 40	Feb. 23	Mar. 11	Mar. 20	329	M 30	Feb. 28	Mar. 3	Mar. 12
264	M 46	Jan. 26	Mar. 12	Mar. 20	330	M 30	Mar. 2	Mar. 9	Recovery
265	F 32	Mar. 8	Mar. 29	Recovery	331	F 56	Mar. 15	Mar. 16	Mar. 16
266	M 68	Apr. 13	Apr. 14	Apr. 15	332	M 55	Mar. 3	Mar. 18	Recovery
267	F 11	Apr. 10	Apr. 14	Apr. 16	333	M 62	Mar. 21	Mar. 27	Mar. 31
268	M 48	Apr. 15	Apr. 17	Apr. 18	334	M 9	Mar. 29	Mar. 30	Recovery
269	M 18	May 3	May 5	May 9	335	F 15	Apr. 7	Apr. 8	Recovery
270	M 20	May 3	May 8	Recovery	336	F 47	Apr. 6	Apr. 8	Apr. 11
271	F 30	May 20	May 28	Recovery	337	M 39	Apr. 23	Apr. 25	Apr. 26
272	F 35	May 27	Jun. 7	Jun. 12	338	F 45	Apr. 29	Apr. 28	Recovery
273	F 25	Jun. 12	Jun. 18	Jul. 11	339	F 63	Apr. ?	Apr. 30	May 2
274	M 22	Jun. 26	Jun. 28	Jun. 28	340	M 19	May 1	May 3	May 6
275	M 65	Jun. 21	Jun. 29	Jul. 12	341	M 52	Mar. 18	May 4	May 23
276	M 9	Jul. 11	Jul. 12	Recovery	342	M 2 mo.	May 6	May 5	May 11
277	M 16	Jul. 7	Jul. 14	Recovery	343	M 14	May 2	May 6	May 9
278	M 13	Jul. 11	Jul. 16	Jul. 18	344	F 22	May 9	May 11	May 15
279	F 30	Jun. 30	Jul. 22	Recovery	345	F 27	May 17	May 19	May 20
280	M 13	Jul. 26	Aug. 4	Recovery	346	M 55	Jun. 8	Jun. 13	Jun. 13
281	M 12	Jul. 23	Aug. 5	Aug. 8	347	M 68	Jun. 8	Jun. 14	Jul. 3
282	M 8	Aug. 10	Aug. 13	Recovery	348	F 13	Jul. 6	Jul. 7	Jul. 10
283	F 21	Aug. 12	Aug. 16	Aug. 20	349	F 26	Jul. 8	Jul. 10	Oct. 9
284	M 42	Aug. 16	Aug. 17	Aug. 20	350	F 25	Jun. 27	Jul. 14	Jul. 23
285	F 45	Aug. 14	Aug. 18	Sep. 2	351	M 40	Jul. 22	Jul. 27	Aug. 11
286	M 10	Aug. 23	Aug. 27	Sep. 2	352	M 45	Jul. 18	Jul. 28	Aug. 9
287	M 34	Aug. 29	Sep. 6	Sep. 16	353	M 8	Aug. 6	Aug. 7	Recovery
288	M 10	Sep. 10	Sep. 15	Sep. 24	354	M 21	Aug. 12	Aug. 12	Aug. 13
289	F 64	Sep. 17	Sep. 18	Sep. 20	355	F 25	Aug. 12	Aug. 15	Aug. 19
290	M 14	Oct. 4	Oct. 5	Oct. 6	356	M 66	Aug. 17	Aug. 20	Aug. 25
291	F 32	Oct. 5	Oct. 10	Dec. 16	357	M 12	Aug. 18	Aug. 24	Aug. 26
292	F 12	Oct. 7	Oct. 11	Oct. 20	358	M 8	Aug. 18	Aug. 24	Recovery
293	M 13	Oct. 8	Oct. 11	Oct. 13	359	M 34	Aug. 29	Aug. 31	Sep. 25
294	F 26	Oct. 11	Oct. 16	Apr. 2/38	360	F 21	Aug. 22	Sep. 2	Sep. 11
295	M 58	Oct. 16	Oct. 18	Oct. 22	361	F 34	Sep. 2	Sep. 5	Recovery
296	M 11	Oct. 13	Oct. 18	Recovery	362	M 15	Sep. 1	Sep. 6	Recovery
297	F 31	Oct. 24	Oct. 25	Oct. 27	363	F 4	Sep. 2	Sep. 7	Sep. 10
298	M 16	Oct. 28	Oct. 29	Recovery	364	M 33	Aug. 22	Sep. 12	Recovery
299	F 41	Nov. 5	Nov. 7	Recoevry	365	M 17	Sep. 15	Sep. 17	Nov. 6
300	M 12	Nov. 6	Nov. 8	Recovery	366	F 15	Aug. 29	Sep. 25	Oct. 16
301	M 8	Nov. 14	Nov. 19	Recovery	367	M 9	Oct. 3	Oct. 8	Oct. 16
302	F 15	Nov. 17	Nov. 24	Nov. 28	368	F 4	Oct. 17	Oct. 18	Recovery
303	F 63	Nov. 29	Nov. 29	Nov. 30	369	M 34	Oct. 18	Oct. 22	Recovery
304	M 12	Nov. 27	Nov. 30	Recovery	370	M 8	Oct. 19	Oct. 25	Recovery
305	M 15	Nov. 30	Dec. 1	Dec. 3	371	M 24	Oct. 20	Oct. 31	Recovery
306	M 12	Nov. 29	Dec. 3	Recovery	372	M 16	Nov. 14	Nov. 13	Recovery
307	M 1 mo.	Dec. 1	Dec. 3	Dec. 9	373	M 50	Nov. 11	Nov. 18	Nov. 19
308	M 36	Sep. 20	Dec. 6	Recovery	374	F 23	Nov. 18	Nov. 21	Nov. 23
309	M 24	Dec. 15	Dec. 24	Dec. 26	375	M 40	Nov. 14	Nov. 25	Recovery
310	M 4	Dec. 24	Dec. 29	Jan. 3	376	F 24	Nov. 25	Nov. 26	Nov. 26
311	M 48	Dec. 26	Dec. 31	Jan. 1	377	M 29	Nov. 24	Nov. 26	Recovery

TABLE 1—*Continued*

SERIAL NUMBER	PATIENT	POSITIVE BLOOD CULTURE	PHAGE CONTACT	DEATH
			1938	
378	M 37	Dec. 7	Dec. 9	Recovery
379	M 30	Dec. 7	Dec. 12	Recovery
380	M 61	Dec. 6	Dec. 13	Dec. 22
381	M 36	Dec. 23	Dec. 27	Dec. 31
			1939	
382	F 5	Dec. 30	Jan. 3	Jan. 9
383	M 13	Jan. 12	Jan. 13	Jan. 14
384	M 34	Dec. 28	Jan. 14	Feb. 7
385	M 9	Jan. 13	Jan. 15	Recovery
386	M 1	Jan. 11	Jan. 16	Recovery
387	M 73	Jan. 22	Jan. 24	Mar. 27
388	F 20	Jan. 27	Jan. 28	Jan. 28
389	M 70	Jan. 29	Jan. 30	Feb. 1
390	F 8	Jan. 30	Jan. 30	Feb. 6
391	F 16	Jan. ?	Feb. 1	Recovery
392	M 40	Jan. 26	Feb. 10	Feb. 15
393	M 20	Feb. 6	Feb. 11	Recovery
394	M 15	Feb. 7	Feb. 15	Feb. 21
395	M 19	Feb. 17	Feb. 20	Recovery
396	M 14	Feb. 16	Feb. 21	Feb. 22
397	F 45	Feb. 19	Feb. 21	Feb. 22
398	F 66	Feb. 21	Feb. 25	Recovery
399	M 39	Feb. 24	Feb. 28	Mar. 16
400	M 59	Mar. 1	Mar. 4	Mar. 8
401	M 50	Mar. 4	Mar. 4	Mar. 5
402	M 19	Mar. 8	Mar. 9	Recovery
403	M 11	Mar. 13	Mar. 15	Mar. 19
404	M 26	Feb. 14	Mar. 16	Recovery
405	F 55	Mar. 12	Mar. 23	Mar. 30
406	M 60	Mar. 22	Mar. 24	Recovery
407	M 31	Mar. 26	Mar. 27	Apr. 4
408	F 32	Apr. 2	Apr. 4	Apr. 11
409	M 51	Apr. 5	Apr. 7	Recovery
410	M 15	Apr. 6	Apr. 13	Jun. 28
411	M 14	May 12	May 13	May 22
412	F 6	May 10	May 17	May 19
413	F 8	May 19	May 20	Recovery
414	M 8	May 22	May 24	Recovery
415	M 53	May 23	May 26	May 29
416	F 27	May 29	May 31	Recovery
417	F 34	Jun. 5	Jun. 5	Jun. 11
418	M 35	Jun. 6	Jun. 7	Jun. 8
419	M 7 mo.	Jun. 7	Jun. 8	Jun. 9
420	M 11	Jun. 4	Jun. 8	Recovery
421	F 5	Jun. 8	Jun. 9	Recovery
422	F 65	Jun. 6	Jun. 10	Jun. 12
423	F 14	Jun. 8	Jun. 14	Aug. 1
424	F 59	Jun. 16	Jun. 19	Jun. 22
425	M 62	Jun. 22	Jun. 24	Jun. 26
426	F 13	Jun. 25	Jun. 29	Recovery
427	M 9	Jul. 5	Jul. 6	Recovery
428	M 14	Jun. 20	Jul. 7	Aug. 21
429	M 13	Jul. 6	Jul. 12	Recovery
430	F 37	Jul. ?	Jul. 14	Jul. 18
431	M 9	Jul. 13	Jul. 15	Recovery
432	F 24	Jul. 20	Jul. 22	Jul. 23
433	M 15	Jul. 22	Jul. 23	Aug. 3
434	F 17	Jul. 30	Jul. 31	Jul. 31
435	M 8	Jul. 31	Aug. 1	Recovery
436	M 8	Jul. 28	Aug. 3	Recovery
437	M 23	Aug. 8	Aug. 8	Recovery
438	M 5	Aug. 9	Aug. 10	Recovery
439	M 14	Aug. 10	Aug. 11	Recovery
440	M 10	Aug. 14	Aug. 18	Aug. 22
441	F 6	Aug. ?	Aug. 19	Aug. 20
442	M 10	Aug. 19	1939 Aug. 19	Recovery
443	F 16	Jun. 25	Aug. 21	Recovery
444	M 60	Aug. 21	Aug. 24	Aug. 26
445	F 17	Aug. 21	Aug. 24	Aug. 26
446	M 42	Aug. 23	Aug. 29	Aug. 31
447	F 3	Aug. 28	Aug. 30	Sep. 4
448	F 20	Aug. 27	Aug. 30	Recovery
449	M 11	Aug. 30	Sep. 1	Sep. 2
450	M 51	Sep. 2	Sep. 4	Sep. 5
451	M 52	Aug. 31	Sep. 7	Sep. 17
452	M 9	Aug. 30	Sep. 7	Sep. 11
453	F 55	Sep. 7	Sep. 8	Recovery
454	F 3	Sep. 6	Sep. 8	Jan. 25/40
455	M 20	Sep. 13	Sep. 12	Recovery
456	M 32	Sep. 9	Sep. 14	Sep. 17
457	M 5	Sep. 14	Sep. 15	Sep. 22
458	F 8	Sep. 18	Sep. 22	Recovery
459	M 51	Sep. 28	Sep. 27	Oct. 17
460	M 49	Sep. 28	Sep. 30	Oct. 1
461	F 12	Sep. 28	Oct. 2	Oct. 3
462	F 27	Oct. 2	Oct. 5	Oct. 12
463	F 13	Sep. 26	Oct. 5	Recovery
464	M 12	Sep. 25	Oct. 6	Oct. 8
465	F 7	Oct. 4	Oct. 10	Recovery
466	M 54	Oct. 7	Oct. 19	Nov. 17
467	M 23	Oct. 20	Oct. 25	Recovery
468	M 60	Oct. 24	Oct. 26	Oct. 26
469	M 3	Oct. 25	Oct. 26	Nov. 3
470	M 26	Oct. 26	Oct. 27	Oct. 28
471	M 46	Oct. 28	Oct. 28	Nov. 30
472	M 15	Sep. 29	Oct. 31	Sep. 4/40
473	M 14	Nov. 8	Nov. 11	Nov. 20
474	M 14	Nov. 18	Nov. 22	Recovery
475	M 16	Nov. 27	Dec. 1	Dec. 4
476	M 29	Dec. 1	Dec. 4	Dec. 10
477	F 17	Dec. 11	Dec. 16	Recovery
			1940	
478	M 11	Jan. 2	Jan. 3	Jan. 11
479	M 56	Jan. 4	Jan. 8	Recovery
480	M 13	Jan. 10	Jan. 12	Recovery
481	M 16	Oct. '39	Jan. 17	Recovery
482	M 9	Jan. 16	Jan. 18	Jan. 23
483	F 15	Jan. 18	Jan. 22	Recovery
484	M 10	Jan. 20	Jan. 23	Recovery
485	M 44	Jan. 26	Jan. 30	Apr. 4
486	F 52	Feb. 14	Feb. 15	Mar. 20
487	F 5	Feb. 13	Feb. 20	Mar. 17
488	M 40	Mar. 5	Mar. 16	Mar. 16
489	F 59	Mar. 22	Mar. 30	May 11
490	M 8	Apr. 1	Apr. 3	Recovery
491	F 68	Apr. 4	Apr. 5	Apr. 6
492	F 5	May 23	Jun. 3	Jun. 5
493	F 11	May 21	Jun. 4	Recovery
494	F 27	Jun. 5	Jun. 5	Recovery
495	M 68	Jun. 4	Jun. 11	Recovery
496	M 13	Jul. 6	Jul. 8	Recovery
497	M 4	Jul. 10	Jul. 17	Recovery
498	F 10	Jul. 29	Jul. 31	Aug. 10
499	F 43	Jul. 29	Aug. 1	Recovery
500	M 16	Aug. 27	Aug. 29	Sep. 3

this period of four months. In 1932 from February to July, inclusive, a period of six months, there were 12 patients without a survival. From December 1, 1932 to May 31, 1933, a period of six months, there were 16 patients, all of whom died. From the above chronological list, it can be seen that there were similar shorter periods of ill success in May, June and July, 1935 (10 patients with 10 deaths) and again in May, June and July 1938 (13 patients with 13 deaths). In glancing at the table one recognizes also several periods when the recoveries were exceptionally numerous. During the last two years, beginning with September, 1938, there have been 141 patients with 59 (41.8 per cent) survivals and the last part of the table, covering the period January 1 to August 29, 1940 is especially remarkable, showing 23 patients with 11 deaths and 12 (52.2 per cent) survivals.

SEASONAL RELATION

The possible influence of season upon the morbidity and mortality of staphylococcemia was briefly mentioned in our paper of 1936. Studying the distribution of the 500 patients according to month, based on the date of the first positive blood culture, it is evident that there is no notable seasonal relationship in regard to incidence. There is the definite indication of a higher rate of survival of those with first positive blood culture during the fall months of September, October and November (41 per cent) followed by the lowest rate of survival during the winter months of December, January and February (26 per cent). The differences are not great enough, however, to allow definite recognition of marked seasonal variation.

AGE AND SEX

The distribution of the entire 500 patients with staphylococcemia according to age and sex is shown in figure 1. This is a disease which attacks the newborn as well as the aged. There are more males, a total of 322, possibly because of greater exposure to external wounds and less meticulous care of the skin. The predominance of males is especially evident in the age period 8 to 16 years, inclusive, suggesting an influence of rough play and active athletic effort. In this age period of high morbidity the recovery rate is fairly high.

The number of males and females in each age decade with the number of survivors in each group is shown in table 2. Evidently the prognosis in staphylococcemia is less favorable after the age of 40 in both sexes. Males in the first decade of life seem to have the best chance of overcoming the disease.

SUSCEPTIBILITY OF THE STAPHYLOCOCCUS TO LYSIS BY PHAGE

In the vast majority of instances the staphylococcus of sufficient virulence to be present in a genuine blood culture has been found to be easily susceptible to lysis by our stock preparation of staphylococcus bacteriophage. Of the 416 cases of this series in which we received cultures from the blood and in regard to which complete data are available, 366 cultures (89 per cent) were completely lyzed by the stock preparation of bacteriophages. Since complete lysis by our stock bacteriophages is so frequent in staphylococci obtained from the blood

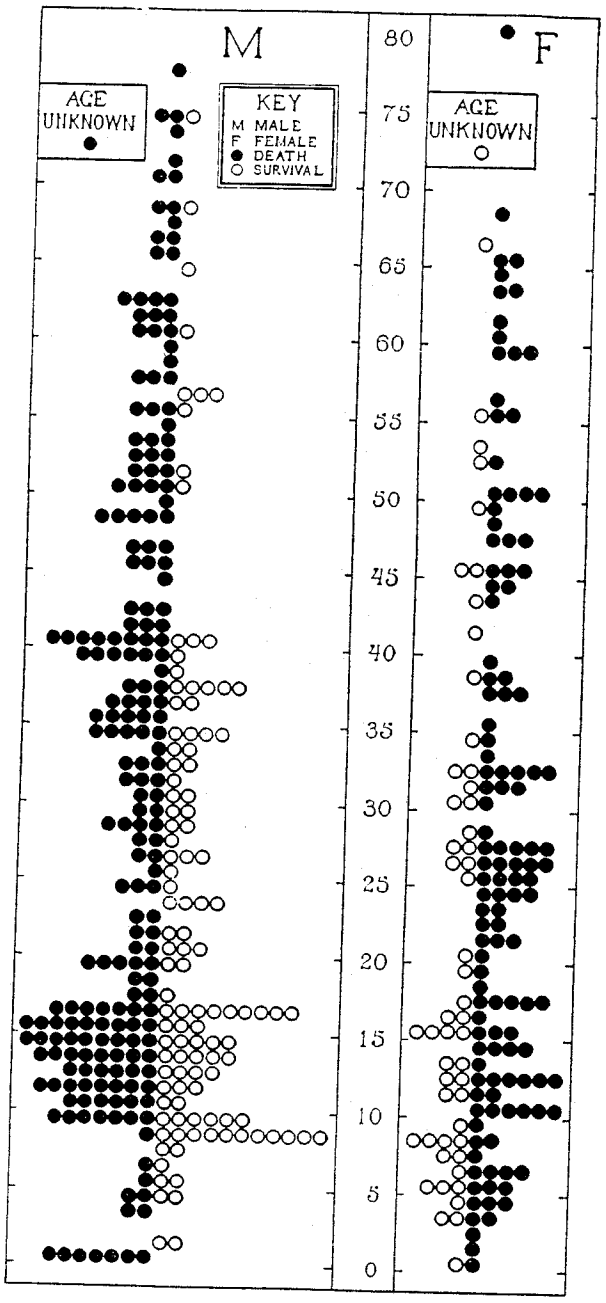

FIG. 1

stream, we have come to question very critically the validity of a pretended blood culture of staphylococcus which persists in its resistance to the lytic agent.

In contrast to this are the results of studies of lysozyme,[1] which may be com-

pared with bacteriophage in respect to its ability to cause the dissolution of bacteria. It has been found that this enzyme is most active against the non-pathogenic staphylococci, showing little effect on the virulent types.

It might be well to point out here that although the stock preparations of bacteriophage give such satisfactory lysis *in vitro*, it does not follow that they are as effective *in vivo* as the specific bacteriophages, prepared with the organism isolated from the patient in question. It has been repeatedly shown in this series of cases that the stock bacteriophages which are employed in staphylococcemia cases from the time our services are invited until the specific preparation is avail-

TABLE 2

PATIENTS AND SURVIVORS IN EACH AGE DECADE

DECADE	MALES			FEMALES		
	Patients	Survivors	Per cent	Patients	Survivors	Per cent
Ninth	0	0		1	0	0
Eighth	8	1	13	0	0	
Seventh	20	3	15	9	1	11
Sixth	28	6	21	14	3	21
Fifth	30	3	10	16	5	31
Fourth	53	20	38	25	7	28
Third	39	19	49	34	7	21
Second	96	34	35	44	14	32
First	47	26	55	34	15	44
Unknown	1	0	0	1	1	100
Total	322	112	35	178	53	29

TABLE 3

STAPHYLOCOCCEMIA IN VARIOUS HOSPITALS

	HOSPITAL													
	A	B	C	D	E	F	G	H	I	J	K	L	M	N
Patients	10	6	5	9	6	9	44	14	24	12	8	11	6	9
Survivors	7	4	3	5	3	4	12	3	5	2	1	1	0	0
Per cent	70	66	60	55	50	44	27	21	21	17	13	9	0	0

able, seem to have a less favorable effect on the course of the disease than the phage which has been produced by lysis of the specific organism.

OTHER CONSIDERATIONS

Our series of 500 patients includes those cared for in 169 different hospitals in various parts of the United States. In various instances there have been many patients from this series in one hospital. Thus there is presented the opportunity to contrast results. Some of the hospitals having a number of patients are listed in Table 3 with the percentage of survivals.

It is perhaps significant that one young physician who had, as an undergraduate, done some volunteer work in our laboratory, served his internship of two years at Hospital F in the east and then a residency of two years in Hospital A in the middle west. Many of the 19 patients from these two hospitals were seen by this physician and the phage therapy carried out or supervised by him. One may contrast the results in Hospitals A and F with the record of other large hospitals such as K, L, M and N. It is also of interest to contrast Hospital D with Hospital L, both charity hospitals in the metropolitan area of New York. In fact, we have come to feel that bacteriophage therapy of staphylococcemia is practically hopeless in some of these large hospitals, possibly because the program of therapy requires more time and effort than is available for treatment of the individual patient.

In a previous paper[2] of this series we have dealt in detail with the technic of treatment of staphylococcemia with bacteriophage. It will be sufficient here to stress certain important factors. Of greatest importance in determining the outcome of treatment may be mentioned the condition of the heart, lungs, brain and kidneys at the start of bacteriophage therapy; the skill, care and diligence exercised in the application of this agent and the wisdom exercised in using or withholding accessory therapeutic measures such as incisions, administration of narcotics, bactericidal and bacteriostatic drugs, transfusions, adequate nutrition and general support. Delay in starting the treatment often permits irreparable damage so that the situation becomes hopeless. An alert clinical sense, quick to recognize the signs and symptoms of staphylococcemia, coupled with technical skill and a willing enthusiasm to undertake and carry through the rather exacting and laborious program of therapy would seem to be the most significant factor in determining a high rate of recovery in this disease.

GROUPING OF THE PATIENTS

In this paper we have attempted to set forth the criteria for admission of a patient to our staphylococcemia series, to record the patients in chronological order and to show their distribution by sex and age in respect to death and survival. We have also contrasted results obtained in different larger hospitals. We have not attempted here to estimate the influence of bacteriophage therapy and one can gain only the general impression that about one third of the patients have survived, 165 out of the 500 in the series. In order to learn about the possible influence of therapeutic measures an intimate study of individual patients will be required, which can best be accomplished by selecting special groups. On the basis of anatomical division, we plan later to consider such groups as meningitis, septic thrombosis of the cavernous sinus, various locations of osteomyelitis, endocarditis, pericarditis and renal abscess. One might also break up the series into groups by calendar years so as to contrast the changing methods in therapy of staphylococcemia from the radical surgery of 1930 through the periods of therapy by toxoid, stannoxyl, antitoxic serum, sulfanilamide, sulfapyridine and sulfamethylthiazole to the sulfathiazole of 1940, all of which have been used from time to time for patients in this series.

More profitable, however, seems to be the classification of the patients into (1) those who received no bacteriophage therapy and thus constitute a concurrent control group, (2) those who recovered from the staphylococcemia prior to the administration of bacteriophage, constituting a group receiving phage during the stage of metastatic lesions, (3) those who died within three days after phage therapy was initiated, constituting a group of fulminant and terminal cases, (4) those who died later than three days after initiation of phage therapy, constituting a group of therapeutic failures and (5) those surviving after phage therapy.

In the concurrent control group there were 30 patients who did not receive bacteriophage into their bodies although the service had been requested. Five of these, aged 4, 8, 14, 16 and 17 have survived. There were 25 patients whose blood cultures became negative before bacteriophage therapy was started, with only 7 deaths. These may well be contrasted with similar patients from the

TABLE 4

STAPHYLOCOCCEMIA PATIENTS—GROUP SUMMARY

TIME PERIOD	NO BACTERIOPHAGE		PHAGE AFTER NEGATIVE BLOOD CULTURE		WITH BACTERIOPHAGE THERAPY			TOTAL
	Died	Survived	Died	Survived	Died within 3 days	Died after 3 days	Survived	
Before Aug. 13, 1934	6	1	0	2	32	45	29	115
Aug. 13, to Dec. 31, 1934	1	1	0	3	6	5	3	19
Year 1935	1	0	1	0	12	21	11	46
Year 1936	3	0	0	5	17	18	22	65
Year 1937	4	0	2	4	19	22	15	66
Year 1938	5	0	1	1	20	22	21	70
Year 1939	5	2	3	2	28	25	31	96
Year 1940	0	1	0	1	3	8	10	23
Total	25	5	7	18	137	166	142	500

control group who recovered, for a time at least, from the blood stream invasion, but subsequently succumbed to the infection. It would seem that the bacteriophage has a peculiar value in the prolonged protective treatment of those patients who may have overcome their infection of the blood stream, either spontaneously or with the aid of therapeutic chemicals or with the aid of bacteriophage. In the fulminant and terminal group there were 137 patients, many of them treated for considerable periods by various methods until bacteriophage was finally requested as a measure of desperation. Those who died later than three days after initiation of phage therapy numbered 166. This group affords opportunity to observe considerable variety of technical procedures in the use of therapeutic agents and to evaluate the results, in particular to learn what not to do. Finally, those who survived after actually receiving bacteriophage therapy numbered 142. Among these there were examples which illustrate a wise choice of therapeutic program in dealing with the disease. We believe, however, that still

better results are possible at present. These might be achieved through prompt diagnosis and early use of adequate bacteriophage and sulfathiazole in combined therapy, supported by small fractional transfusions. The sulfathiazole should then be discontinued after about 10 days, but the intravenous bacteriophage continued over a prolonged period of time.

SUMMARY

1. An additional 385 patients with staphylococcemia are listed bringing the total up to 500 in our series of patients with infection of the blood stream by staphylococci.

2. Staphylococcal infection occurs at all seasons with little variation. There is an apparent rise in the recovery rate during the fall months.

3. Staphylococcemia occurs from infancy to old age, in both sexes. In our series there are more males (322) than females (178), and this excess of males is especially evident in the age period from 8 to 16 years, inclusive. The prognosis of the disease is distinctly less favorable after the age of 40.

4. The staphylococci isolated from the blood stream are generally quite susceptible to the action of bacteriophages now available in the laboratory, as shown by *in vitro* tests.

5. An alert clinical sense, quick to recognize the signs and symptoms of staphylococcemia, coupled with skill and willing enthusiasm to carry through the rather exacting program of bacteriophage therapy, together with good judgment in the use of accessory therapeutic measures, would appear to be of greatest significance in determining a high rate of recovery.

6. Patients survive staphylococcemia when cared for in various ways, such as expectant treatment, chemotherapy, and conservative or radical surgery, but the frequency of survival is not great in genuine infection of the blood stream with staphylococci and the survivors are often left with undesirable sequelae. In the present series there are 5 (17 per cent) survivors among the 30 concurrent control patients who did not receive bacteriophage therapy.

7. There were 25 patients in this series who received bacteriophage during the metastatic stage of the disease, only after the blood-stream infection had been overcome. Of these patients, 18 have survived.

8. Of the remaining 445 patients there were 137 who died before the end of the third day after bacteriophage treatment was started. These are rather arbitrarily assigned to the group of moribund patients.

9. The remaining 308 patients who received bacteriophage into their bodies earlier then three days preceding exitus constitute the group in which bacteriophage therapy was tried with more or less reasonable chance of success. Of these, 142 patients (46 per cent) survived. They will be considered in subsequent sections.

10. The total number of patients in this series who received bacteriophage therapy was 470 of whom 160 (34 per cent) survived.

11. The use of bacteriophage in conjunction with other agents, particularly

sulfathiazole and fractional transfusions, offers a more favorable outlook in the severe forms of infection with staphylococci.

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