

RECOVERY OF A TYPHOID BACILLUS-CARRIER DURING VACCINE TREATMENT *

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Medical literature during the past five years has contained numerous reports of chronic typhoid bacillus-carriers, but there has been very little discussion of the treatment of these patients. The reason for this paucity appears to be that treatment has been unsatisfactory, and in but few cases has the infection been eradicated.

Dehler¹ has cured by cholecystostomy two patients who discharged the bacilli in the feces, but the bacilli did not disappear from the stools of a paratyphoid carrier on whom Forster² did cholecystostomy for gallstones. Grimme³ reported the recovery of an intestinal typhoid carrier on whom cholecystectomy was done. Park⁴ failed to eradicate the infection in "Typhoid Mary," an intestinal carrier, by the use of intestinal antiseptics and hexamethylenamin; the latter drug was given in doses of 100 to 150 grains daily. Park cites Lentz, who stated that he could not get rid of the bacilli by any treatment. Albert⁵ reported the disappearance of bacilli from the urine of a carrier treated with hexamethylenamin, but no details were given and no statement made as to permanent recovery. Niepraschk⁶ had success with hexamethylenamin and boric acid (triborate of hexamethylentetramin) in the treatment of a urinary carrier after he had failed with hexamethylenamin alone and in combination with resorcin. He gave this preparation in doses of 1.5 gm. four times daily. Hammond⁷ failed to cure an intestinal carrier to whom he gave hexamethylenamin for months.

Litterer⁸ treated by vaccination a patient with a discharging typhoid bone lesion. He estimated that there were a half million bacilli in a

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1. Dehler: *München. med. Wchnschr.*, 1907, liv, No. 43.

2. Forster: *Verhandl. d. deutsch. path. Gesellsch.*, 1907, p. 163.

3. Grimme: *München. med. Wchnschr.*, 1908, lv, No. 1.

4. Park, W. H.: *Jour. Am. Med. Assn.*, 1908, li, 981.

5. Albert, H.: *Jour. Am. Med. Assn.*, 1908, li, 982. Discussion of Dr. Park's paper.

6. Niepraschk: *Ztschr. f. Hyg. u. Infektionskrankh.*, 1909, lxiv, 454.

7. Hammond, F. S.: *Jour. Am. Med. Assn.*, 1909, lii, 48.

8. Litterer, W. L.: *Jour. Am. Med. Assn.*, 1908, li, 982. Discussion of Dr. Park's paper.

platinum loopful of the pus. He thought, justifiably, that the patient should be regarded as a chronic typhoid bacillus-carrier. Under vaccine treatment the patient showed great improvement, but was not entirely cured at the time of the report. He has recently informed us that this patient and another similar carrier were both cured by vaccination in three and two months, respectively.

Irwin and Houston⁹ have successfully treated a urinary carrier by vaccination after failure with hexamethylenamin. The bacilli disappeared after the third dose and four subsequent examinations covering a period of two months were negative. Six vaccinations were given, the doses increasing from 50 to 1,000 million. Meader¹⁰ treated successfully by vaccination a patient who discharged bacilli in her feces. The patient had had typhoid fever thirty years previously and had been exposed to infection five years previously. Before vaccination was begun, treatment was attempted with hexamethylenamin; 15 grains three times daily for two weeks were given, and then 75 grains daily. The large doses had to be discontinued after three or four days because of painful micturition. No diminution in the number of typhoid bacilli discharged in the feces could be detected. An attempt was then made to plant *B. coli* in the lower bowel in the hope that it would overgrow the typhoid organisms. Four doses, each about a pint, of a bouillon culture, were given per rectum. The typhoid organisms persisted in the stools and treatment with lactic acid bacillus tablets was tried; this also failed. Autogenous vaccines were then given at intervals of from one to two weeks. Six vaccinations were given, the doses increasing from 25 to 1,000 million, after which the stool cultures were negative on three separate examinations. Meader studied the bactericidal and agglutinating power of the blood during vaccination. The former rapidly rose, reaching its greatest power after 400 million bacilli were injected; it then fell rapidly, and seven days after 1,000 million bacilli were injected the bactericidal power had fallen to a point practically the same as when immunization work began. An interesting observation was that during the period of declining bactericidal power the agglutinating power became evident in dilutions of from 1 to 500 in one hour. The first stool examination that was found negative was seven days after the above phenomenon. No examination was made for twenty-three days previously, so it is difficult to correlate the disappearance of the bacilli with the serum phenomena. Meader seems inclined to think that the high bactericidal power of the serum was immediately correlated with the disappearance of the bacilli, but the stool was positive for bacilli only three days before the examination that showed the highest point of bactericidal power, and ten days after the previous

9. Irwin, S. T., and Houston, T.: *Lancet*, London, Jan. 30, 1909.

10. Meader, F. M.: *Bull. Johns Hopkins Hosp.*, 1910, xxi, 280.

TABULATED DATA

Date.	Vaccin. Millions of Bacilli	Stool Cultures	Urine Cultures	Colonies per Loopful	Loopfuls of Urine Used	Agglutination Tests					
						Stock Culture			Urine Culture		
						Dilution Serum	Reaction	Time (hrs.)	Dilution Serum	Reaction	Time (hrs.)
9/22/10	—	—
10/4/10	—
10/7/10	—	+	+†	1-40	±	1	1-40	+	1
10/10/10	25
10/11/10	—
10/15/10	+	+†	1-50	±	1	1-40	±	1
10/19/10	50
10/26/10	+	+†	1-50	—	1	1-50	+	1
10/28/10	100
11/4/10	+	+†	1-50 1-100	+	1 6
11/6/10	150
11/16/10	200	..	+	+†	1-50 1-200	+	1 2
11/26/10	250	..	+	92	3	1-100 1-250	+	1 2
2/6/10	400	..	+	18	3	1-500	+	3
12/9/10	+	45	3	1-50 1-200 1-300	+	1 2 2
12/17/10	+	32	3	1-150 1-1000	+	1 6	1-150 1-300 1-400	— ± ±	1 6 6
1/3/11	+	5	3	1-150 1-200	+	6 6	1-150 1-200	— ±	6 6
1/10/11	1000	1-50	+	1
1/21/11	+	2	3	1-150	±	1	1-150 1-200	± ±	1 1
2/1/11	1500
2/11/11	?	...	3	1-400	+	5	1-400	+	5
2/15/11	—	0	3	1-1000	+	6	1-1000	+	6
2/20/11	—	0	0.2 c.c.
2/28/11	—	0	0.2 c.c.
3/1/11	1-1000	+	6	1-600 1-1000	± ±	6 6
3/24/11	—	0	2 c.c. §	1-200 1-400 1-800	+	1 4 19
5/2/11	—	0	10 c.c. §

* Forty typhoid-like colonies per loopful of urine. A transplant from one colony proved it to be *B. fecalis alkaliogenes*. Colonies of *B. coli* were also present. We thought it probable that all the colonies were contaminations and decided to make other cultures from a more carefully obtained urine.
† Numerous. § Bouillon inoculated and plates made from bouillon cultures.

examination. The bacilli disappeared some time during a period of twenty-three days that covered the maximum point and the rapid decline of bactericidal power and the rise and fall of agglutinating power. Our experience with our own case leads us to suggest that the phenomena were coincidences, and that the disappearance of bacilli was due to the healing of a chronic lesion under the influence of vaccination — that the healing was completed coincidentally with the serum phenomena.

Cummins, Fawcus and Kennedy¹¹ treated six typhoid carriers and one paratyphoid A carrier. Two of these were urinary carriers and five intestinal. They used implantation of *B. bulgaricus*; they tried intestinal and urinary antiseptics, including hexamethylenamin (urotropin) alone and together with another diuretic; they attempted to influence the infection by acidifying the urine by means of the administration of sodium benzoate and acid phosphate of soda; they exposed the gall-bladder and kidneys to *x*-rays; and they vaccinated three patients with stock and autogenous vaccines.

One intestinal carrier recovered during the administration of *B. bulgaricus* in large doses, but others were not improved by it. An intermittent intestinal carrier ceased to discharge bacilli on two occasions after exposure of the gall-bladder to the *x*-rays, and the bacilli were not found in his stools when he was discharged from observation. It was thought, however, that this absence of bacilli might be due to a natural intermission rather than to cure by treatment. Bacilli in the feces and urine respectively of two other patients decreased in numbers after *x*-ray treatment, but increased again when treatment was discontinued. Antiseptics reduced the number of bacilli but when antiseptics were discontinued the number rapidly rose. Vaccination was carried out on three patients, one an intestinal carrier, two urinary carriers. It failed in all three cases to eradicate the infection.

The authors are sure, therefore, of the recovery of only one patient during treatment, an intestinal carrier treated with lactic acid bacilli (*B. bulgaricus*). They think that a combination of vaccination with hexamethylenamin in urinary carriers, and of vaccination with *x*-rays in gall-bladder intestinal carriers may prove to be effectual.

Stone¹² has reported one typhoid carrier treated by vaccination. His patient was a urinary carrier, and recovered during treatment with autogenous vaccines. Six doses, increasing from 100 to 400 million, were given, and stool cultures were negative after the sixth dose.

To sum up, three chronic intestinal typhoid carriers have recovered after operations on the gall-bladder. One urinary carrier has recovered

11. Cummins, S. L.: Fawcus, H. B., and Kennedy, J. C.: Treatment of Typhoid Carriers, Jour. Roy. Army Med. Corps, Lond., 1910, xiv, 351.

12. Stone, W. J.: Jour. Am. Med. Assn., 1910, iv, 1708.

during the administration of hexamethylenamin in combination with boric acid (triborate of hexamethylentetramin). One intestinal carrier recovered when lactic acid bacilli (*B. bulgaricus*) were implanted in the alimentary tract. One intestinal carrier apparently recovered after repeated exposures of the gall-bladder to *x*-rays. One intestinal carrier, two urinary carriers, and two carriers discharging bacilli from bone lesions have recovered during vaccination with autogenous vaccines. We shall add to the number one urinary carrier that recovered likewise during vaccination with autogenous vaccine. Altogether then, there have been only twelve recoveries of typhoid carriers as far as we have been able to find; six recoveries of intestinal carriers, four of urinary carriers and two of carriers with bone lesions. Including our own patient, six have recovered during treatment with autogenous vaccines.

CASE REPORT

Our patient was a little American girl, white, aged 4½ years. She had had an attack of fever, that was probably a mild initial attack of typhoid, in July, 1910, during which she was not under our care. She was admitted to Colon Hospital (No. 26,236) Aug. 3, 1910. She had a typical uneventful rather mild attack of typhoid fever, during which her serum in 1 to 50 dilution agglutinated the stock culture of *B. typhosus* in one hour. During the last fourteen days of convalescence she was given for prophylactic reasons 3 grains of hexamethylenamin three times daily—rather large doses for a small child. She was discharged from the hospital Sept. 3, 1910.

On September 18, the child's mother was admitted to the hospital with continued fever, the onset having been about three days previously, or twelve days after the child's return home. *B. typhosus* was isolated by blood culture. The course of illness was typical of a rather severe attack of typhoid fever.

On September 19, the child's father was admitted with a mild remittent fever that persisted ten days, maximum 101.5 F. The onset of his attack was September 16, or thirteen days after the child's return home. A blood-culture, made after six days of fever and four days before the temperature remained normal, was negative. Although the patient had never had typhoid fever, two agglutination tests by Bass¹³ macroscopic method were positive. There appeared a few quite definite rose spots. The spleen was not palpable. In the light of these facts and of subsequent events, it is quite certain that this was a mild attack of typhoid fever.

These two cases led us at once to suspect that the child was discharging typhoid bacilli in her urine or feces, and that she had infected her father and mother. Four examinations of her stools were all negative for *B. typhosus*. On the first attempt we failed, also, to obtain *B. typhosus* from the urine, but the second culture, Oct. 7, 1910, was positive, and the organisms were isolated ten times thereafter without a failure until they finally disappeared, Feb. 15, 1911, about six months after the attack of typhoid fever was over. Five successive negative examinations, covering a period of about three months, were then made.

Vaccination with autogenous vaccines was begun on Oct. 10, 1910, and nine doses, increasing from 25 to 1,500 million, were given, the last on Feb. 1, 1911, after which typhoid bacilli could no longer be isolated from the urine. The bacilli gradually decreased in numbers as vaccination proceeded. The first vaccine used (seven doses) was sterilized at 60 C. for one hour; the second vaccine (two doses), at 53 C. for one hour. The vaccinations gave slight local reactions

13. Bass, C. C.: THE ARCHIVES INT. MED., 1910, vi, 717.

only until the last injection of 1,500 million bacilli, when a mild general reaction occurred. The injection was given about 10 a. m., February 1, and at 8 p. m. the patient's temperature was 102. By noon the next day, the temperature had reached normal. During the entire time the patient seemed in perfect health.

Numerous agglutination tests were made before, during and following the vaccination period. Before vaccination the patient's serum in a 1-to-40 dilution gave a positive reaction in one hour against a suspension in salt solution of a twenty-four-hour agar culture of her own organisms, and an incomplete reaction against the bacilli of a stock culture. Three days after the first vaccination the reaction against both strains was incomplete. Seven days after the second vaccination, a 1-to-50 dilution of serum agglutinated the urine culture in one hour, but the reaction was negative in one hour against the stock culture, which, however, was agglutinated in six hours by dilutions of serum up to 1 to 200. After the seventh vaccination (400 million bacilli), the serum in a 1-to-150 dilution agglutinated the stock culture in one hour, and in six hours the stock culture was agglutinated by a 1-to-1,000 dilution. At this time a 1-to-150 dilution of the serum failed to agglutinate the urine culture, and in six hours the maximum dilution that caused agglutination was 1 to 300. Vaccination was then suspended for thirty-five days, during which the agglutinating power of the serum decreased. After twenty-eight days a 1-to-150 dilution of the serum agglutinated both strains in six hours, but in the same time a 1-to-200 dilution gave an incomplete reaction against the stock culture and was negative against the urine culture. Vaccination was resumed Jan. 10, 1911, and on Jan. 21 a 1-to-150 dilution of serum agglutinated in one hour the urine culture, but gave an incomplete reaction against the stock culture. On Feb. 1, 1911, the last vaccination (1,500 million bacilli) was given, and on February 15 the serum in a dilution of 1 to 1,000 agglutinated both organisms in six hours. On March 1, a 1-to-1,000 dilution still agglutinated the stock culture in six hours, but the reaction was incomplete against the urine culture. On March 24, nearly two months after the last vaccination, the serum in a 1-to-200 dilution agglutinated the stock culture in one hour, and a 1-to-400 dilution, in four hours.

Between the dates of Dec. 6, 1910, and Jan. 10, 1911 (see table), no vaccinations were given, and the agglutinating power of the serum against both the urine culture and the stock culture decreased. On December 17, a 1-to-1,000 dilution of serum was positive in six hours against the stock culture, but a 1-to-300 dilution was the maximum dilution positive against the urine culture. On January 3, a 1-to-200 dilution gave in six hours an incomplete reaction against the stock culture and a negative result against the urine culture. During the period of this decreasing agglutinating power of the serum, the number of bacilli in the urine not only failed to increase, but actually decreased from 32 per loopful of urine on December 17 to 5 per loopful on January 3.

At the time of the observations no records were made of the numbers of colonies on the plates, but our impression is that during the first two months the number remained approximately the same. On November 26, there were 92 colonies per loopful of urine, and, with one exception, the number decreased gradually thereafter—92, (18), 45, 32, 5, 2, 0.

Nov. 26, 1910	92 colonies per loopful
Dec. 9, 1910 (13 days' interval).....	45 colonies per loopful
Dec. 17, 1910 (8 days' interval).....	32 colonies per loopful
Jan. 3, 1911 (17 days' interval).....	5 colonies per loopful
Jan. 21, 1911 (18 days' interval).....	2 colonies per loopful
Feb. 11, 1911 (21 days' interval).....	0 colonies per loopful

If the time intervals are all changed to two weeks and the number of bacilli are calculated for each examination according to the rate of decrease for each period, the following results are obtained: 92, 42, 20, 4, 2, 0. In other words, the decrease in the number of bacilli proceeded with almost mathematical precision, the number being reduced one-half every two weeks, excepting during the

third interval, when reduction was more rapid. A part of this reduction was not associated with an increasing agglutinating power of the blood serum, but with a decreasing power; nor did the reduction cease when the agglutinating power rose again with subsequent vaccination. The phenomena suggest strongly that antibodies produced by vaccination were not acting on bacilli in the urine, but that a chronic typhoid lesion that was discharging typhoid bacilli in the urine slowly healed under the influence of vaccination, probably as the result of the action of antibodies in the lymph or exudate on the bacilli in the lesion. That there were not antibodies sufficient even to inhibit growth in the urine was shown by inoculating the sterile urine, just after the disappearance of typhoid bacilli, with typhoid organisms from both the stock and urine cultures. Both organisms grew well, in spite of the fact that the agglutinating power of the blood serum at this time was 1 to 1,000 in six hours.

Our experience leads us to suggest, therefore, that the eradication of the infection of chronic typhoid carriers by vaccination is brought about by the gradual healing of a chronic lesion under the influence of antibodies produced by the vaccination. If the bacilli grow in secretions and excretions only, it does not seem that vaccination would be effectual. Hexamethylenamin or lactic acid bacilli might be effectual in such cases. The only other treatment that our patient received was four 5-grain doses of hexamethylenamin on December 6 and 7. The previous examination of urine, November 26, had shown 92 bacilli per loopful. This result had discouraged us, and we brought the patient to the hospital to give a trial to hexamethylenamin treatment. We obtained a specimen of urine and began hexamethylenamin treatment before the plates were incubated. On the following day, we found the number of colonies so reduced that we discontinued hexamethylenamin and resumed vaccine treatment. That the four doses of hexamethylenamin had no permanent effect on the bacilli was shown by the fact that the number of organisms was 45 per loopful two days after the drug was given.

There may be a question as to whether or not our patient should be considered a chronic typhoid carrier. According to the classification of Frosch,¹⁴ she should be considered one. Frosch divided carriers into two groups: "those who excrete bacilli for less than three months, and those who excrete them for three months and longer. The latter class constitute the chronic bacilli carriers, the *Dauerausscheidern* of the Germans" (Simonds). Our patient carried typhoid bacilli for about six months after the temperature of her typhoid attack remained normal, and, accepting Frosch's classification, she may be considered fairly as having been a chronic typhoid bacillus carrier.

The possibility cannot be denied that the lesion that discharged bacilli may have undergone spontaneous healing without regard to vaccination. We prefer to say, therefore, that our patient recovered during vaccination, rather than that she was cured by the treatment. In the light of what is known of chronic typhoid carriers and of the chronicity of post-typhoid lesions, however, it does not seem probable that recovery was spontaneous.

One other objection might be made. Some typhoid carriers, both urinary and intestinal, discharge the bacilli intermittently. It may be suggested with reason that the disappearance of bacilli in our case may have been due to an intermission. This is possible. But the bacilli were

14. Frosch: *Klin. Jahrb.*, 1908, xix, 537. Cited by Simonds, J. P.: *Am. Jour. Med. Sc.*, Aug., 1910, cxi, 247.

present on eleven successive examinations covering a period of more than three months, they gradually decreased in numbers and finally disappeared, and they have been absent on five successive examinations covering a period of almost three months. The first urine examination made was negative for typhoid bacilli, but the result was probably due to faulty technic, for we had just begun making bacteriological examinations of stools and urines. It seems probable to us, therefore, that our patient was a continuous chronic typhoid carrier, and that she made a permanent recovery during treatment with autogenous vaccines.

BACTERIOLOGICAL CONSIDERATIONS

Isolation.—The method of isolation of typhoid bacilli from the urine was that of Endo.¹⁵ Endo's medium is a heavy agar to which is added basic fuchsin, lactose and sufficient sodium sulphite to decolorize the fuchsin. The red dye, fuchsin ($C_{20}H_{19}N_3HCl$), is an acid salt of rosanilin, a colorless leukobase. The acid component of the red rosanilin salt is easily reduced by sodium sulphite. When lactose-fermenting organisms grow on the above medium, the acid formed combines with the decolorized rosanilin and the colonies are stained red. The heavy agar medium is exactly like "ordinary" agar, excepting that 20 gm. of agar-agar per 1,000 c.c. are used instead of 15 gm. To 1,000 c.c. of the agar medium are added: lactose, 10 gm.; basic fuchsin, 1.8 c.c. of a 10 per cent. solution in alcohol; sodium sulphite, 25 to 40 c.c. of a 10 per cent. aqueous solution. The sodium sulphite should be added until the red color has changed to a faint pink. The agar medium can be prepared in bulk to be kept in stock, but the fuchsin, lactose and sodium sulphite should be added just before pouring into the plates. One hundred cubic centimeters of the medium will make about four or five plates, which should be 12 to 15 cm. in diameter. The plates are exposed to the air (covered with clean paper), for one hour, during which they harden and dry. One loopful or more of the material to be examined is then placed on the surface of the first plate, and with a sterile bent glass rod it is spread widely over the surface; the rod is then stroked over the surface of the second plate; then the third, and so on. The plates are covered, wrapped in paper to exclude light, and incubated for twenty-four hours. The colonies of the lactose-fermenting organisms are then red, while the colonies of non-lactose-fermenting organisms are colorless. The method thus furnishes an easy way of isolating typhoid, paratyphoid and dysentery bacilli. The organism that causes difficulty most frequently is *B. fecalis alkaligenes*.

15. Endo: *Centralbl. f. Bakteriol.*, 1904, xxxv, 109. A transcription of Endo's article was kindly given us by Dr. S. T. Darling, chief of the Board of Health Laboratory, Ancon, Canal Zone.

Identification.—The organisms that we isolated from the urine were small, actively motile, Gram-negative bacilli. They formed small, 1 to 2 mm. diameter, translucent colonies with a bluish refractility on agar plates. Litmus milk was slightly acidified by them and remained acid. There was an invisible growth on potato. No indol was formed in Dunham's peptone medium. Bouillon showed a general turbidity without pellicle or sediment. There was no gas formation in any of the semi-solid litmus sugar media; acid formed in dextrose, mannite, galactose and dextrin; there was no change in lactose, saccharose or dulcete. The organisms were agglutinated by the serum of a typhoid patient (the child's mother) in a 1-to-50 dilution in one hour. After the child was vaccinated with her own organisms, her serum agglutinated a stock culture of typhoid bacilli in a 1-to-200 dilution in one hour and in a 1-to-1,000 dilution in six hours.

SUMMARY

1. The literature of the treatment of typhoid bacillus-carriers is reviewed. Eleven recoveries, excluding our case, have occurred. Five of these patients recovered during vaccination with autogenous vaccines.

2. Our patient was a white child, female, aged 4½ years. Shortly after her attack of typhoid fever, her father and mother were infected. Typhoid organisms in pure culture were isolated from the child's urine. Hexamethylenamin had been administered to the patient during two weeks of convalescence from the typhoid attack.

3. Practically the only treatment given was vaccination with autogenous vaccines. Nine doses were given, increasing from 25 to 1,500 million. The bacilli decreased gradually and disappeared after the ninth vaccination. Eleven successive urine cultures were positive for *B. typhosus* and then five successive cultures were negative.

4. The total duration of the bacilluria, from the time of normal temperature, was about six months. The patient appeared to be a continuous carrier.

5. It seems that the disappearance of the bacilli was not an intermission but a true recovery, brought about by the gradual healing of a chronic lesion under the influence of vaccination.

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