THE BACTERIOLYSANT THERAPY OF BACILLARY DYSENTERY IN CHILDREN *

THERAPEUTIC APPLICATION OF BACTERIOLYSANTS; D'HERELLE'S
PHENOMENON

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It has been demonstrated by d'Herelle and others¹ that if a small portion of feces from a dysenteric convalescent or even from a normal person is inoculated in a flask of bouillon, and this mixed culture is passed through a Berkfeld filter, the resulting sterile filtrate, when added to young cultures of dysentery and other bacilli, will kill and dissolve the organisms. If a portion of this dissolved culture is, in turn, added to another young dysentery culture, the organisms will again be killed and dissolved. This phenomenon can in this way be reproduced for innumerable successive generations. The names bacteriophage, bacteriolysant and lytic agent have been given to these filtrates. When they are injected intravenously and subcutaneously into rabbits and other animals, no harmful effects are produced. These animals develop antibodies for the organisms against which the filtrates are active. It was obvious to many observers that these filtrates which would kill and dissolve dysentery bacilli in vitro, which were non-pathogenic and would immunize animals, should be tried therapeutically in clinical cases of dysentery. However, the question arises as to whether the administration of an antidysentery bacteriophage to dysentery patients might not possibly be harmful. The intestinal lesions of dysentery are probably caused by an endotoxin, and it would seem logical to assume that if dysentery bacilli in the intestinal tract were killed and dissolved as the result of the administration of a bacteriophage, a large amount of endotoxin would be liberated. Nevertheless Kabeshima and others¹ have demonstrated that injections of an antidysentery bacteriophage into rabbits infected with dysentery bacilli are harmless. I have injected large amounts of these filtrates into a rabbit and am convinced that they are innocuous. Inasmuch as Flexner dysentery in children is one of our worst diseases, and as

* Received for publication Feb. 23, 1922.

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1. A summary of the literature and a complete bibliography is given in Davison, W. C., Bibliographic review of bacteriolysants (d'Herelle's phenomenon), Abstr. Bacteriol., Baltimore, 1922 (in press).

serotherapy² and our present treatment are ineffectual in reducing the high mortality, I felt justified in cautiously proceeding with bacteriolysant therapy during the summer of 1921.

Bacteriolytic filtrates active against one or more strains of Flexner bacilli were obtained by d'Herelle's method. The bacteriolytic activity of these filtrates was tested in eight instances against the organism isolated from the patients' stools and in seven the filtrates were found to be active. The method of obtaining these filtrates and testing their activity is described elsewhere.³

These filtrates were administered to twelve infants, aged from 2 months to 4 years, suffering from bacillary dysentery (Flexner). Clinically these children represented typical cases of this disease.⁴ *B. dysenteriae* (Flexner), and by that I refer to the whole group of mannite fermenting dysentery bacilli,⁵ were isolated from the stools of ten of the twelve patients. The individual dose of the bacteriolysant was from 5 to 198 c.c. and was given from one to ten times. The interval between doses was from four to twenty-four hours. The total amounts administered to any one child varied from 5 to 1,381 c.c. Seven children drank the filtrates from a cup or a nursing bottle (the taste is very similar to that of broth); in five cases the filtrates were introduced by rectum with a high enema tube; to two patients they were given by gastric gavage together with the feedings of protein milk. In two infants, in addition to rectal administration, the filtrates were introduced into the stomach through a constant drip nasal tube together with the saline that was being used to maintain the body fluid.

Nine of these twelve patients had severe infections and seven of them died, a mortality of 78 per cent. Three had moderate infections and none died, making a total mortality for the twelve cases of 58 per cent. These figures are practically identical with those we have previously published² for severe and moderate dysenteric infections in children, both untreated cases and those treated with subcutaneous and intramuscular injections of antidysenteric serum. In no instance did the patient seem any the worse for the treatment. One patient's stools decreased in number after rectal treatments with a filtrate but inasmuch as the bacteriolytic filtrate used, though active against another strain of the Flexner bacillus, had but slight lytic action on the organisms isolated from this patient's stools, it may be concluded that the improve-

2. Josephs, H. W., and Davison, W. C.: The Serotherapy of Bacillary Dysentery in Children, *J. A. M. A.* **77**:1863 (Dec. 10) 1921.

3. Davison, W. C.: Observations on the Nature of Bacteriophages, Bacteriolysants, Lytic Agents, d'Herelle's Phenomenon, *Proc. Soc. Am. Bacteriologists*, Dec. 29, 1921; *J. Bacteriol.*, 1922 (in press).

4. Davison, W. C.: Bacillary Dysentery in Children, *Bull. Johns Hopkins Hosp.* **21**:225, 1920.

5. Davison, W. C.: Divisions of the So-called Flexner Group of Dysentery Bacilli, *J. Exper. M.* **32**:651, 1920.

RESULTS OF ADMINISTRATION OF DYSENTERY *BACILLUS BACTERIOLYSANT*

Case No.	Age	Race	Stool Culture	Degree of Severity of Infection	Method of Administration of Bacteriolysant	Days After Onset on Which First Dose of Bacteriolysant Was Given	Number of Doses of Bacteriolysant Given	Interval Between Doses, Hours	Amount of Each Dose, C.c.	Total Amount of Bacteriolysant Given, C.c.	Lytic Activity of Bacteriolysant Against Dysentery Bacillus isolated from Patient's Stool	Duration of Disease, Days	Final Outcome of Patient	Effect of Bacteriolysant
29271	2 mos.	White	B. dysenteriae (Flexner)	Severe	Rectal injection	11	2	8	34-35	80	Slight	17	Recovered	No effect
29556	15 mos.	White	Negative	Severe	By mouth (bottle)	16	2	24	36-60	96	Not tested	20	Died	No effect
29627	12 mos.	White	B. dysenteriae (Flexner)	Severe	By mouth (gavage)	13	3	8-12	80-100	280	Strong	15	Died	No effect
29717	12 mos.	Colored	B. dysenteriae (Flexner)	Severe	By mouth (bottle and gavage)	20	3	4-16	45	135	Not tested	21	Died	No effect
29010	6 mos.	Colored	B. dysenteriae (Flexner)	Severe	Rectal injection and nasal drip	13	4	6-12	55-126	323	Strong	14	Died	No effect
29565	14 mos.	White	B. dysenteriae (Flexner)	Severe	By mouth (bottle)	26	4	7-12	30-60	195	Strong	39	Died	No effect
29272	2 mos.	White	Negative	Severe	Rectal injection	11	6	8-17	25-40	170	Not tested	13	Died	No effect
29413	7 mos.	White	B. dysenteriae (Flexner)	Severe	Rectal injection	6	6	5-24	25-50	250	Slight	24	Recovered	Apparent benefit
29569	3 mos.	White	B. dysenteriae (Flexner)	Severe	Rectal injection and by mouth and by mouth (bottle)	8	10	6-24	55-198	1,381	Strong	18	Died	No effect
29456	9 mos.	White	B. dysenteriae (Flexner)	Moderate	By mouth (bottle)	16	1		40	40	Not tested	21	Recovered	No effect
29622	2½ yrs.	White	B. dysenteriae (Flexner)	Moderate	By mouth (cup)	16	1		72	72	Strong	?	Recovered	No effect
29700	4 yrs.	White	B. dysenteriae (Flexner)	Moderate	By mouth (cup)	1	1		5	5	Negative	9	Recovered	No effect

ment was due to the cleaning of the lower colon by the rectal irrigation rather than to the bacteriolytic action of the filtrate. In none of the other children was there any apparent effect on the course or duration of the disease. No systematic study was made to determine the effect of the treatment on the rate of disappearance of the dysentery bacilli from the stool. In Case 29,569, *B. dysenteriae* (Flexner) were isolated from the stools twenty-four hours after the last of ten doses of bacteriolysant. The total amount of filtrate given this patient was 1,381 c.c. It is interesting to note that the bacteriolysants used in this case lysed the dysentery bacilli isolated after the treatment in higher dilutions than the organism isolated shortly after the onset of the disease, so that is fair to assume that this patient did not die because his organisms became resistant to the filtrates.

The failure of bacteriolysant therapy in this series may possibly be explained on the ground that the treatment in the majority of the cases was commenced late in the disease. The only two patients treated within the first week after the onset of the disease recovered. However, this criticism is met by the large amounts of filtrate used, coupled with the fact that two-thirds of the deaths from bacillary dysentery in children, whether treated or not, occur within the first twelve days² and that patients surviving that period have a much better chance of recovery.

D'Herelle,¹ on the other hand, has reported striking cures from bacteriophagic therapy in seven adults suffering from dysentery as well as in animals afflicted with various infections. Larger series alone will demonstrate the practical value of bacteriolysants.

CONCLUSION

As far as can be judged from this limited series of cases of bacillary dysentery in children, in which bacteriolytic filtrates in amounts of from 5 to 1,381 c.c. were administered, bacteriolysant therapy did not influence the mortality or the course of the disease.