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or emotion, were prominent and in whom no source of reflex stimulation was found. However, in some of those patients with possible sources of a vagovagal reflex, factors of nervous origin were evident, especially in those with duodenal ulcer.

Hurst commented on the effect of fatigue and of nervous factors. The effect of nervous influences was in some instances pronounced, and in more cases than the 3 so designated the patients could easily have been classed with what Huston calls the "spasmodic aptitude," or what Eppinger and Hess refer to as the "vagotonic type." One of our patients was a temperamental musician whose disease was classified here as duodenal ulcer. Even during times when the ulcer was quiescent, he would develop severe symptoms of hiatus hernia through worry or emotional excitement. His symptoms were relieved by atropine. Another patient, a physician, was unable to sleep unless in a semi-reclining position when the hernia was present but would be perfectly free from symptoms with adequate rest and relief from so-called nervous strain.

It will be seen from the table that among 48 cases there were 27 in which there was some possible source of vagovagal reflex. In 5 patients such a source was associated with hiatal hernia. This is unquestionably a larger proportion of reflex stimulation than would be found in 48 patients of similar age sampled at random.

There were only 3 patients with significant secondary anemias, and in 2 of these the hernia was incarcerated. In all 3 there was evidence of blood in the stools.

Thirty of the patients came under observation because of gastrointestinal symptoms. Sixteen came under observation because of symptoms of angina pectoris, and 2 because of paroxysmal auricular fibrillation which came on when the hernia occurred. In 1 of the latter stooping over was a factor, and in the other, emotional strain and fatigue. Four of those with anginal symptoms died suddenly of what was diagnosed as coronary occlusion. In only 1 of these cases was the patient seen at the time of death and the diagnosis confirmed at autopsy.

Three patients were operated on for cholelithiasis and obtained relief. In the cases in which obesity was a determining factor in the occurrence of the hernia, the patient invariably experienced relief on following a diet and obtaining a reduction of weight.

The result of treatment is difficult to evaluate without a separate analysis of each case, which is not within the scope of this paper. All patients were treated medicinally and placed on liberal ulcer management, with phenobarbital and atropine or belladonna, or some drug with an atropine-like action. All experienced some degree of relief, from very little to complete, depending on the underlying factor which determined the hernia.

**Difference of Practice Among Scientific Men.**—There is a difference of practice among scientific men with regard to publishing speculations suggested by their results. Nothing is easier than to let one's imagination spin fantasies on the basis of slight evidence. Fancies may or may not later prove true. As a rule it has seemed to me wiser to advise beginners to confine their report to the facts which have been obtained in the course of investigation and to withhold intimations possibilities derived from these facts until there has been further study.—Connon, Walter B.: The Way of an Investigator, New York, W. W. Norton & Co., Inc., 1945.

**TREATMENT OF TYPHOID FEVER WITH TYPE SPECIFIC BACTERIOPHAGE**

**Preliminary Report**

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Bacteriophage has been used for the past ten years in the treatment of patients with typhoid fever in the Communicable Disease Unit of the Los Angeles County General Hospital. During the first four years of this period unselected stock bacteriophage was utilized for therapy. All the patients so treated reacted with a chill and fever, to be described in more detail later. Therapeutically, some seemed to derive no benefit whatever, while others proceeded with an obviously or at least an apparently modified course, and some achieved truly startling bacteriologic and clinical recovery. Results in these latter patients were so spectacular that they caused us to continue the study despite the discouragement of many failures and indifferent successes, for they seemed to indicate an unknown factor which might, when discovered, lead to more uniformly good results. Bower published a preliminary report of the problem at this stage.

The search for this unknown factor led to a consideration of the bacteriophage itself. The present concept of the nature of these virus-like agents is that the bacteriophages are parasites of bacteria. The host-parasite relationship in this case may or may not result in lysis of the bacteria involved. The number of bacteriophages is legion, and there are detectable differences in their ability to attack certain genera and species of bacteria. As the spectrum of attack becomes convergent the bacteriophage in question is frequently spoken of as being specific. As a result of the work of Craigie and Yen it is now known that a given immunologic type of bacteriophage active on Vi antigen containing Eberthella typhosa organisms can be adapted to differentiate types of this organism. Such an adapted phage not only is highly specific, but it also shows or exhibits the ability of lysing the corresponding type of bacterium when the bacteriophage is present in extremely high dilutions. Several workers have demonstrated that experimentally induced typhoid infection in mice is capable of resolution by the parenteral use of typhoid bacteriophage (Fisk and Ward). During recent years it has been shown that the treatment of experimental typhoid infections in mice with type specific bacteriophage results in apparent multiplication of phage in vivo. A similar state has been shown to exist in other instances.

From the Department of Communicable Diseases, Los Angeles County General Hospital.

Read before the Section on Pediatrics at the Ninety-Fifth Annual Session of the American Medical Association, San Francisco, July 4, 1946.

1. Dr. Thomas McCleave of Berkeley, Calif., brought his early work to our attention. This served as an initial stimulus for our work.


These considerations led to the second phase of our study, during which patients were treated only with type specific bacteriophage proved to be especially potent in lysing their own organisms. This change we feel has been responsible for an improvement in the results of treatment. In the course of this regimen each patient's organisms were obtained from a culture of his own blood, and high potency bacteriophage specific for his type of E. typhosa organisms was prepared. This, incidentally, is not invariably possible, because some strains of the organism do not type. Early in the study 1 cc. of the bacteriophage material was injected directly into the vein; later it was found the reaction could be reduced and in some measure controlled by the dilution of this 1 cc. in a 5 per cent dextrose solution.

The patients in this report received their type specific bacteriophage material in 500 cc. of a dextrose solution administered by the intravenous drip method over a period of four to seven hours. The first clinical observation after treatment was started was a moderate chill which lasted approximately thirty minutes. After the chill the temperature began to mount and reached a peak of 105 to 107 F. within three to six hours after treatment began. The temperature returned to normal within nine and one-half to twenty-four hours after the commencement of treatment and in most instances remained normal thereafter. In none of the cases here reported did clinical shock occur during the rapid rise and fall of temperature, although we did see this syndrome frequently with the earlier method of administration. All patients had been properly prepared before treatment and were watched closely during it. Transfusions, parenteral fluids and the like were given as needed.

We have now treated 56 patients with type specific bacteriophage. Of this group, 3, or a little more than 5 per cent, died. The survivors without exception showed a profound change in the course of their infections, regardless of the stage of the disease in which they were treated. About 10 per cent had a clinical and bacteriologic relapse; these patients were amenable to repeated treatment. Cultures of blood from all the others became immediately and permanently negative. Thus, the majority of these patients may be said to have achieved a cure by crisis according to the criteria: (1) blood cultures negative twenty-four hours after treatment and continuously negative thereafter; (2) absence of fever after treatment, and (3) immediate clinical improvement.

One of the most spectacular objective accomplishments of this form of treatment was the rapidity with which the patient returned to his normal mental outlook. Within twenty-four to forty-eight hours after bacteriophage therapy, the patient who had been comatose and in the "typhoid state" or who had demonstrated the characteristic whining, querulous, obstreperous manner amazed everyone by his cheerful, grateful, cooperative attitude. A state of euphoria existed. Also, patients whose anorexia before treatment was so great as to make forced feedings necessary, afterward usually asked for food, weakly at first and later, vociferously.

The following cases of typhoid fever are here presented in brief. They represent a cross section of the patients treated with type specific bacteriophage. All temperatures recorded are rectal.

CASE 1.—C. E. B., a white boy aged 7, had typhoid fever due to type C organisms.

This child entered the hospital on Oct. 20, 1945 with the history of three weeks of abdominal soreness, general malaise and fever. His appetite had been poor; however, there had been no nausea, vomiting or diarrhea. There was a steady loss of weight and progressive weakness.

On examination one was impressed by the pallor and emaciation of the child. He would whimper and whine when he was touched or moved; otherwise he was quiet and appeared lethargic. The mouth was dry and dirty. The skin was hot and dry and presented rose-like spots on the abdomen and lower part of the chest. The spots disappeared within a week. Cultures of material from the blood, stool, urine and rose spots remained negative day after day until Nov. 7, 1945 when E. typhosa (type C) grew out in the culture of blood. Several blood transfusions were given.

On Nov. 15, 1945 a solution of 1 cc. of type C bacteriophage in 500 cc. of 5 per cent dextrose was given by the intravenous drip method. A mild chill lasting thirty-five minutes occurred...
one and a half hours after phage was started. The bacteriophage took five and a quarter hours to run in. The temperature peak of 106.8°F. was reached in four and a quarter hours after therapy began. It reached normal in nine and a half hours and then fell to 96 F. where it remained for nine hours. At no time was the child in shock. Twenty-four hours after phage the most notable improvement, other than the normal temperature, was the remarkable change in the disposition and attitude of the child. There was no more complaining. He was interested in his surroundings for the first time since entry. The temperature remained normal from this time forth; recovery was rapid. Cultures of blood, stool and urine remained negative. The patient was discharged as completely recovered on Dec. 10, 1945.

Case 2.—P. A., a Mexican woman aged 19, had typhoid fever due to type C organisms.

This patient entered the hospital on Dec. 27, 1945, having delivered on this date a viable eight month infant, with the diagnosis of typhoid fever established. She had contracted the disease in Mexico where, a month or so before, she had been caring for a grandmother who had the disease.

Examination revealed a thin, poorly developed woman whose temperature was 103 F., pulse rate 120 and blood pressure 102 systolic and 70 diastolic. The throat was injected; the spleen was not palpated; the uterus was firm and contracted; there were no rose spots. The Widal reaction test made on the patient’s serum on Dec. 27, 1945 was positive in a dilution of 1:320 and, on Jan. 6, 1946 in a dilution of 1:1280. The blood on culture was positive for E. typhosa.

On Jan. 6, 1946, 1 cc. of bacteriophage (type C) was given intravenously in 500 cc. of a 5 per cent dextrose solution which required four hours for administration. Within an hour and a half the patient began to chill; at the end of four hours the temperature was 105 F. At the end of eight hours the temperature was 95 F., where it remained for twelve hours. Thereafter it was normal until the discharge of the patient on Jan. 27, 1946. Blood, stool and urine yielded negative cultures after the completion of treatment.

Case 3.—E. C. L., a white man aged 39 had typhoid fever due to type F organisms.

This patient was sent to the Communicable Disease Unit from another hospital where two days previously he had had a cholecystectomy. The history revealed that for one month the patient had complained of malaise, listlessness and general debility. One week before entry to the other hospital there had been a slight sore throat and a mild, nonproductive nocturnal cough. During this period the patient became febrile, and his temperature ranged between 102 and 105 F. On Sept. 10, 1945 he had three chills. On September 11 nausea and vomiting developed, and the next day there was abdominal fulness and severe pain in the lower abdomen. On September 13 an exploratory laparotomy was performed. A normal appendix was found, but the gallbladder was moderately gangrenous. On incision of the mucosa of the gallbladder ulcers were found; examination of the terminal ileum revealed similar ulcerations. Cultures of bile produced typhoid organisms. Unpiped spring water at a trailer camp was the probable source of infection.

On entry here (Sept. 17, 1945) the patient was extremely toxic, moderately dehydrated and lethargic. The temperature was 100 F., the pulse rate was 84, and the respiratory rate was 20. The mouth and throat were dry; there were a few fine, moist rales over the base of the right lung; the abdomen was moderately distended and tender and had a linear incision in the right upper quadrant with a rubber drain protruding from its lower end. No rose spots were seen.

The patient became progressively worse; the temperature varied between 102 and 105 F. The abdominal wound became necrotic and separated so that intestinal tisue presented itself. Cultures of blood as well as those from the incisional drainage were positive for E. typhosa. The reaction of the patient’s serum to the Widal test was positive in dilutions of 1:2560. Cultures of urine and stool were negative and remained so throughout the illness.

On Oct. 3, 1945, 1 cc. of type F phage was given in 500 cc. of a 5 per cent dextrose solution which took six and a half hours to administer. Within two hours a chill began which continued for thirty minutes. The temperature reached a peak of 106 F. in five hours and fell to normal in five more hours. From this time on the temperature remained normal. There was no evidence of shock; the blood pressure was maintained at 110 systolic and 80 diastolic. The subjective and objective clinical improvement apparent within forty-eight hours was spectacular. Cultures of blood as well as of incisional drainage became negative immediately. By October 15 the abdominal incision was healed. On October 25 the patient became ambulatory, and on Oct. 31, 1945 he was discharged.

Case 4.—C. C., a white man aged 31, had typhoid fever due to type F organisms.

He was admitted Sept. 19, 1945 with a history of fever, chills, general malaise, weakness, nausea which had persisted for two weeks and a nonproductive cough for the past two days.
On entry the patient had a temperature of 104 F., a pulse rate of 104 and a respiratory rate of 24. Rose spots were found on the chest; the throat was injected; the lungs were clear, and the spleen was not felt. Blood cultures of blood through the portal vein were positive for E. typhosa type F, and the reaction of the patient's serum to the Widal test was positive in a dilution of 1:320. On Sept. 27, 1945, a solution of 1 cc. of type F phage in 500 cc. of 5 per cent dextrose was given intravenously over a period of four and a half hours. The temperature's peak of 106.4 F. was reached at this time, and the temperature turned to normal seventeen hours after the peak. Clinical improvement was immediate and gratifying. The disposition of the patient changed from a fault-finding nature to a cheerful, optimistic one. Cultures of blood remained negative. A culture of urine was positive for E. typhosa once (Oct. 13, 1945), and cultures from the stool were positive twice (October 10, 13) but were negative thereafter. The patient was discharged on Oct. 26, 1945.

Case 5.—C. H., a Mexican man aged 25, had typhoid fever caused by type C organisms. He was admitted to the hospital Aug. 30, 1945. His history disclosed that he had come from Mexico twenty-four days before and had had chills, fever, diarrhea and abdominal pain for at least eight days, together with pain in the left side of the chest and a slight cough for five days. He had had E. typhosa in a culture of his blood and a positive Widal reaction in a 1:1280 dilution of his serum before admission.

He was a poorly nourished, acutely ill, decidedly toxic man with dry skin, evidence of pneumonia in the upper lobe of the left lung and slight generalized abdominal tenderness. No rose spots were seen. From the time of entry the patient's life was despaired of because of repeated large hemorhages from the bowel and nose. These occurred for the first time on Aug. 31, 1945 and daily thereafter until Sept. 12, 1945. For this reason, the patient received nothing by mouth but was given dextrose by the continuous drip method, repeated transfusions of blood and vitamin K.

On Sept. 8, 1945 type C phage was available, and 1 cc. was given in 500 cc. of a 5 per cent dextrose solution over a five and a half hour period. A chill occurred one hour after treatment was started and lasted thirty-five minutes. There was a steady rise of temperature from 102 to 107 F. in a three hour period. At the termination of phage administration the temperature was 105 F., where it remained for seven hours; a normal level was reached fifteen hours after treatment began. Blood pressure was maintained at about 78 systolic and 32 diastolic throughout. Within three hours after treatment began the patient lost approximately 300 cc. of blood by rectum. Replacement of the blood was made by transfusion. Cultures of blood remained negative for the typhoid bacillus. The temperature remained normal, and bleeding ceased on Sept. 12, 1945. Because cultures of urine were positive on three occasions, the patient remained in the hospital until Oct. 31, 1945. Prior to that date, however, all cultures had become negative.

Case 6.—O. L. S., a Negro woman aged 29 had typhoid fever due to type A organisms. She was admitted Oct. 9, 1945 from another service in the hospital with a report of a blood culture positive for E. typhosa. The patient had been febrile for one week; in addition there had been nausea, vomiting and diarrhea.

The patient was a thin, extremely dehydrated, stuporous, distended woman with sordes, dry skin, dulness over the lower lobe of the left lung and a moderately distended and tender abdomen. The liver and spleen were palpable and tender.

Daily cultures of blood remained positive for E. typhosa, type A. One cubic centimeter of type A phage was administered in 500 cc. of a 5 per cent dextrose solution over a period of four hours, on Oct. 15, 1945. A mild chill occurred in an hour and a half and lasted thirty minutes. The temperature peak of 106.2 F. was reached in four hours, and the temperature returned to normal in nine and one-half hours after treatment began. It remained normal from this time forward. The patient was comfortable during the period of treatment, and although the blood pressure changed from 112 systolic and 72 diastolic to 98 systolic and 60 diastolic there was no evidence of shock. The most spectacular objective change was in her personality. From stupor she went to cheerful loquacity; whereas before it had been difficult to convince her that she was ill, it now became difficult to satisfy her enormous appetite.

Summary

Type specific bacteriophage was used intravenously in the treatment of 16 patients with typhoid fever. Three patients had complications before treatment began, but recovery occurred. The mortality for the series was 5 per cent.

Conclusion

Treatment by means of type specific bacteriophage offers a promising and safe procedure against typhoid fever. Patients must have careful general care according to their particular needs. Type specific bacteriophage is the accepted form of therapy against the disease in the Communicable Disease Unit of the Los Angeles County General Hospital for all patients whose Eberthella typhosa organisms can be typed.

Abstract of Discussion

Dr. William A. Reilly, San Francisco: The important point to this paper is that the phage is type specific. I think every one should realize that. Otherwise, as Dr. Hamilton has told me, it is hardly worth while to talk about the use of phage in typhoid; but this is a new departure and I think it will be admitted that Dr. Hamilton's results are spectacular and certainly worth while if some one else would check into this and try to repeat it on some of their patients in other parts of the country. Derrill, and Frederick Gay and Kruger and others who worked on phage in typhoid have stated that it is not helpful to any great extent except for occasional cases. This is an important contribution in the sense that we have heard about streptomycin. In mouse typhoid it is very successful, but that is altogether a different picture than in man. There are a few cases reported of obliteration of fever and organisms from the body but, by far and large, the reports today on human beings have been disappointing. As one looks at these temperature charts one cannot fail to be impressed with the sudden critical drop in temperature and the concomitant improvement in the patient, as it were, waking up and wanting to eat and being very cooperative thereafter. Ninety per cent of these patients have been freed from many of the clinical manifestations of typhoid, and thereafter most of them have been freed from the organisms in their blood or stool.

There is a great need for controlling typhoid all over the world. In Palermo the civilians told me that every year they have a thousand cases of typhoid in a population of 4,000 and think nothing of it. During the war typhoid was present all over the place, including our own army. There is a great place for the future development of something specifically curative for typhoid.

Dr. Wilton L. Halfverson, San Francisco: Any of you who have had the opportunity of working with the staff in contagious disease hospitals in Los Angeles on this program realize the great interest that we have in it. The spectacular nature of the recovery of these patients is something we don't forget when we see the patient go through the episode. Dr. Hamilton and Dr. Reilly later indicated that the death rate has decreased. I took occasion to check our figures here in California for the last twenty years, and reported cases that we have had show a case mortality rate better than 14 per cent. These patients who came into the hospital were probably sicker than the ordinary run of patients. Therefore one would expect a proportionally higher fatality rate. I would like to emphasize that it isn't easy to prepare or to secure the bacteriophage. There must be a very close tie-up between the laboratory and the hospital ward; a prompt securing of blood cultures and then immediately, of course, developing the bacteriophage in the laboratory and making it available as soon as possible. The authors have indicated that this takes time. Type specificity in this field is extremely
helpful to the epidemiologist in tracing infections in epidemic serials. In California since 1939 we have traced six epidemics in which type specificity or the typing of the organism found in the patient was definitely of assistance in determining the source of the infection. One of these occurred just a year or two ago. I am happy to have had the opportunity to be associated with the staff of the contagious disease hospital in California. I believe this is a contribution which will be of great importance to us in typhoid.

THE USE OF RESIDUAL HEARING
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For many years deafness has been recognized as an exceedingly important public health problem in this country, yet concerted action on the part of health agencies toward the prevention and amelioration of this affliction has been productive of tangible results only within the past decade. While much has been said and written concerning the prevalence of hearing impairment and the extreme importance of bringing together some sincere and intelligent persons from the ranks of the medical sciences to study this problem and to find its solution, practical programs of action were not adopted until the beginning of World War II. The challenge was finally met by medical officers, public-spirited physicians and laymen, who through unity of thought and agreement formulated policies for a factual, nonemotional approach to the various phases of this affliction and established practical programs of service to those with impairment of hearing. Always in the past, the one great stumbling block has been the lack of satisfactory methods of treatment. For more than a century the leading apostles of public health and medicine in this country directed opinion to the real issues of prevention but admitted their inability to tackle the job of treatment step by step and to find a solution for the difficult problem of cure. Every time the insuperable barrier of lacking a precise knowledge of what to do for the hard of hearing patient was encountered, workers in this field veered sharply away from therapeutic considerations and returned to the original pronouncement so nobly, yet so futilely advocated—prevention.

I am a faithful advocate of a program of prevention in any and all fields of medicine. The medical profession must never fail to concern itself incisively with methods of preventing human suffering and affliction and to this end must strive for inerogue logic in dealing with this important phase of disease. However, most physicians will agree, I believe, that none of the present plans for the prevention of impaired hearing is ideal or perhaps even good. While some of them appear to operate successfully and possess accepted values, not many of them have been taken for granted by the members of the medical profession. I have never been convinced of the truth of the often published statement that 75 to 80 per cent of all cases of impaired hearing are preventable, and that this large proportion of its victims could have avoided their affliction had it been identified early and had proper methods of prevention been instituted. How can one prevent a degeneration of the auditory nerves which often occurs as the result of severe toxic diseases? By what method can one avoid otosclerosis? How are physicians to keep the eustachian tubes of children in working order and the middle ears free from infection during the course of diseases which infect the upper respiratory tract, particularly measles, scarlet fever, mumps and whooping cough? The latter diseases, in which manifestations on the part of the nose and throat invariably appear which endanger the ears, are everyday hazards to which children are exposed in spite of the most diligent enforcement of preventive measures. Prevention is an admirable policy, one that must remain the fiat of the medical profession, yet physicians must recognize its limitations. The point where prevention terminates and therapeutic procedures begin must be clearly discerned if practitioners are to achieve a solidarity of purpose and action that will function for the best interest of the person who is hard of hearing.

The statistical data pertaining to the incidence of hearing impairment in this country are exceedingly unsatisfactory and unreliable. There are specific reports on the occurrence of disease among animals and the increase and decrease of livestock in this country annually, but data on the various types and numbers of physically handicapped children are not obtainable. The scattered reports concerning the prevalence of impaired hearing among school children vary widely in different publications and are not based on acceptable sources of information and accurate compilation. My skepticism of the reliability of these data and my thirty years experience in a large clinic where many aural cases are seen daily lead me to express succinctly my disbelief of the frequently published statement that 75 to 80 per cent of all cases of deafness in the United States are preventable.

When the profession finally realized that it had reached an impasse in the road of progress in this important phase of medicine and that it was obliged to offer something more to the public than elaborate programs of prevention and expansive statistical compilations, scientific men in the field of audiology began to study therapeutic measures that gave promise of restoring serviceable hearing to persons with impaired auditory function. Physicians and workers in the acoustics sciences began to make important observations in the treatment of deafness. These gave rise to theories which by careful experimentation in some instances were reduced to scientific facts. Today, some of these facts are being incorporated into practical usage. Certain methods of treatment appear to operate successfully and to possess values which seem to be understood and accepted. Outwardly, they appear safe and secure in the armamentarium of treatment for the hard of hearing. While there is much confusion and lack of understanding in the realm of therapeutics today, experimental studies and practical applications give hope of achieving a meeting of minds and a conformity of thought on these issues. I confidently believe that physicians have wisely directed the attention of research workers to the real problems of deafness and that they are rapidly formulating a program of therapy, which will establish a solidarity of purpose and action that will function admirably for the rehabilitation of persons with a loss of serviceable hearing.

Physicians recognize one form of impaired hearing, more frequently observed in children than in adults, which is due to some disturbance in the sound conduction mechanism of the ear, the external auditory canal, the tympanic membrane, the middle ear or the eustachian tubes. This form of auditory impairment is frequently due to an anomaly of pressure within