THERAPEUTIC TYPHOID SHOCK

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Nonspecific typhoid shock provides a safe and important method for the production of artificial fever. We have had no unfavorable results and no deaths following its use in several hundred patients. Furthermore, we have found that the fever and chills caused by the intravenous administration of typhoid vaccine have produced satisfactory improvement in properly selected cases. The glands and other cellular tissues of the body participate actively in the febrile reaction which may serve not only to place the pathogenic bacteria in an environment that is unfavorable to viability and reproduction, but the reactions of the cells may serve to enhance the formation of antibodies as well. Some authorities doubt that this twofold reaction can be produced by passive fever induced in the heat cabinet. Likewise, many syphilographers declare that, in the treatment of general paresis, the end results are better after a course of chills induced by malaria than after treatment in the heat cabinet even though, in the latter instance, the temperature may be maintained at 105° to 106.5° F. for as long as six to eight hours. We recognize, too, that in a disease such as erythema nodosum the lesions may disappear with great rapidity when milk protein is given intramuscularly. In this instance, no fever, no chills, and no noticeable general reaction or discomfort occur. This nonspecific effect of protein appears to be active in the reaction to typhoid shock.

There are certain objections to heat therapy produced by use of a cabinet, especially because it is apt to be both expensive and exhausting. While there are many conditions in which this treatment is of great value and should be employed, there are many diseases that will respond to typhoid shock. In such instances, the expense is not great and the procedure is simple. Each method is designed to accomplish certain things. For instance, it is known that the thermal death point of the gonococcus is in the neighborhood of 106.7° F. for two hours in vitro. In patients of robust constitution, it would be inadvisable to treat infections caused by this organism by any other method, but in debilitated subjects, typhoid vaccine can often be employed with considerable benefit.

Knowledge concerning the effects of hyperthermia as a therapeutic procedure is still in a formative stage. Many diseases have been cured or greatly helped by keeping the body at a high temperature for many hours. In our experience, the best results of treatment in the cabinet have been in the gonorrheal diseases. However, this method is used in many other conditions where ordinary therapeutic methods have failed. In a specific case, after a careful clinical and laboratory examination has been completed, a conference is held with the head of the

Physiotherapy Division. We recognize that the artificial fever produced by hyperthermia causes copious sweating with the loss of body fluids and chlorides. This dehydration and demineralization is compensated for, to a considerable extent, by copious draughts of liquids and by the administration of sodium chloride. At all times during the treatment, the patient is under careful medical supervision. Even so, many patients who might improve with artificial fever are not physically able to undergo this ordeal and many of the patients who receive therapeutic typhoid shock in our hospital are from this debilitated group.

The physiologic changes that occur in the body during fever are not well understood. It does appear, however, that many functions of the body are modified for a time, at least, by an elevation of temperature to fever levels. The body metabolism rises about 7 per cent with each degree of increase in temperature, the pulse rate increases, and the pulse pressure enlarges due to a rise in systolic and fall in diastolic pressures. Studies of the capillaries reveal an increased minute volume of blood flow through the peripheral channels. With stimulation of circulatory and glandular processes within the body, there undoubtedly is better mobilization of the mechanisms of tissue defense and better removal of toxic waste substances. At the onset of the chill, the number of leukocytes in the peripheral circulation diminishes. In a very short time, there is a definite rise in the number of polymorphonuclear cells and eosinophils, associated with some decrease in the lymphocytes. The effect of fever on the pathogenic bacteria is probably bacteriostatic. If the temperature is high enough, there may be a decrease in the multiplication and likewise death of many organisms.

Changes in the chemistry of the blood during hyperthermia are not very striking. Among the variations are an increase in the blood uric acid and total nonprotein nitrogen. There is a slight fall of the carbon dioxide and, if sweating is profuse, the blood chlorides may diminish somewhat. It is generally agreed that dehydration is detrimental to the organism if it is permitted to reach the point of depletion of tissue fluids. The maintenance of proper water and salt balance are most important during treatment in a cabinet but it rarely presents any difficult problem during the reactions to typhoid shock. In other words, the metabolic effects as manifested by changes in blood chemistry are much more mild and physical exhaustion rarely occurs by this method.

Hyperthermia induced by typhoid vaccine excels in safety, simplicity, and economy. The treatment can be given either in the home or in the hospital. While it is of considerable advantage to carry out the therapy in a hospital with a private nurse in attendance, an intelligent mother can chart the temperature readings at half hour intervals during the period of high fever. Furthermore, the necessary equipment for

giving the vaccine is very simple—a 10 cc. syringe and needle, a small amount of sterile normal saline solution, and a bottle of typhoid or combined typhoid and paratyphoid vaccine. In contrast to this method, the apparatus for cabinet hyperthermia is rather elaborate and expensive. Likewise, artificial fever cannot be given by infra-red heat or by electromagnetic induction without the constant, watchful care of a well-trained assistant.

The simple method of giving typhoid vaccine as advocated by Howard has been the most satisfactory in our experience. In a modified form, we have employed the following routine:

In an adult, the first dose is 25 million organisms diluted in 10 cc. of normal saline solution at room temperature. The suspension of organisms is injected slowly into a vein of the forearm. While the chill may appear in one-half hour, the reaction may not occur until three hours have passed. The maximum rise of temperature from this initial dose may reach 104° or 105° F., although often it will reach only 103.5° F. In many instances, there is a fall from this high point in an hour and this is followed by a secondary rise of lesser degree, then the fever gradually subsides to normal within 24 to 36 hours. After the temperature has remained within the normal range for 24 hours, a second dose of vaccine, double in amount, is given. Following this dose of 50 million organisms, the chill and febrile response is usually more prompt—within an hour in most instances, and the temperature peak may be somewhat lower than in the first reaction. A secondary rise of fever is seldom experienced and the temperature may reach normal in 8 to 12 hours. Succeeding doses of the vaccine are doubled each time, that is, 100 million for the third dose, 200 million for the fourth, and so on. With the use of this method of administration, it is always important to withhold the injection until the temperature has been normal or nearly normal for 24 hours.

A review of our cases shows that the maximum therapeutic results are reached after six or seven injections. Rarely has it been necessary to produce a greater number of chills although in our earlier studies we did produce as many as 18 reactions without harmful effects. In children from 8 to 15 years of age, the initial dose is approximately 15 million bacilli. These youngsters tolerate the reactions very well. If it is desired to obtain a greater febrile reaction in robust adults, instead of using the method of Howard, a second dose of vaccine of equal strength may be given shortly after the first dose as soon as the temperature begins to rise in the first steep curve. Usually this does not prolong the febrile reaction time beyond that obtained with a single injection. Likewise, the end results seem to be no better.

The curves in charts 1, 2, 3, and 4 illustrate some characteristic

temperature reactions and charts 5 and 6 show temperature curves during hospitalization.

The results of therapeutic typhoid shock may be difficult to evaluate, particularly when other forms of treatment are carried out simultaneously. Likewise, a differentiation must be made between the immediate effects of the artificial fever while the patient is in the hospital and the late results a year or more after the patient has returned to his home. It is evident that well supervised, institutional care will modify the picture a great deal. It is easy for one to become overenthusiastic about any particular form of therapy when the patient is hospitalized and to forget that proper rest, diet, fluids, elimination, physiotherapy, and nursing care may deserve the greater credit for the improvement or the recovery. Likewise, the importance of the psychic effect on the patient must not be discounted. When a man who is suffering with a chronic illness is treated so that he experiences a real chill and fever, he is then certain that at last something is really being done to combat his illness. While this physical experience is good for the patient's emotional state, it should not be permitted to warp one's professional judgment.

Taking all these factors into consideration, we believe that in properly selected cases the use of typhoid shock is of value. The results in a few representative cases are shown in table 1. These

TABLE I

Disease	*Number of Cases*	*Satisfactory Results*		*Unknown Results*	*Unsatisfactory Results*
		Immediate	*Late*		
Acute rheumatic fever (acute endocarditis 1 case)	3	3	2	1	0
Chorea	7	6	4	2	1
Acute encephalitis	5	3	3	0	2
Thrombo-angiitis obliterans	4	2	2	0	2
Chronic rheumatoid arthritis	40	27 (67.5%)	22 (62.8%)	5	13 (32.5%)
Controls—without shock	20	11 (55%)	12 (60%)	0	8 (40%)

are consecutive cases taken from our files and they are considered without prejudice. In the ten cases of acute rheumatic fever and chorea, the immediate results were good in nine instances. Acutely swollen and painful joints subsided after two or three febrile reactions and no bad effects were observed in the one case of active rheumatic endocarditis. The patients with Sydenham's chorea were relieved of

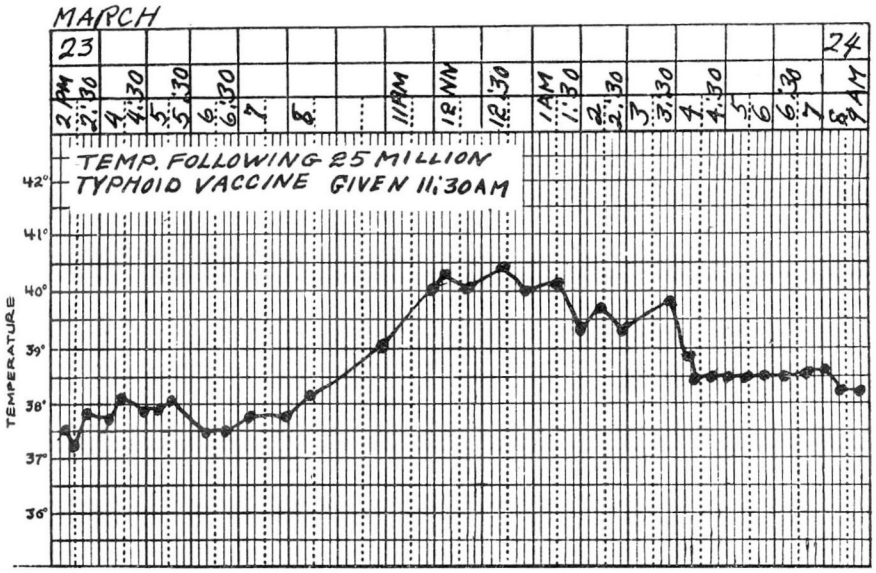

CHART 1: Temperature at half hourly intervals following administration of 25 million typhoid bacilli.

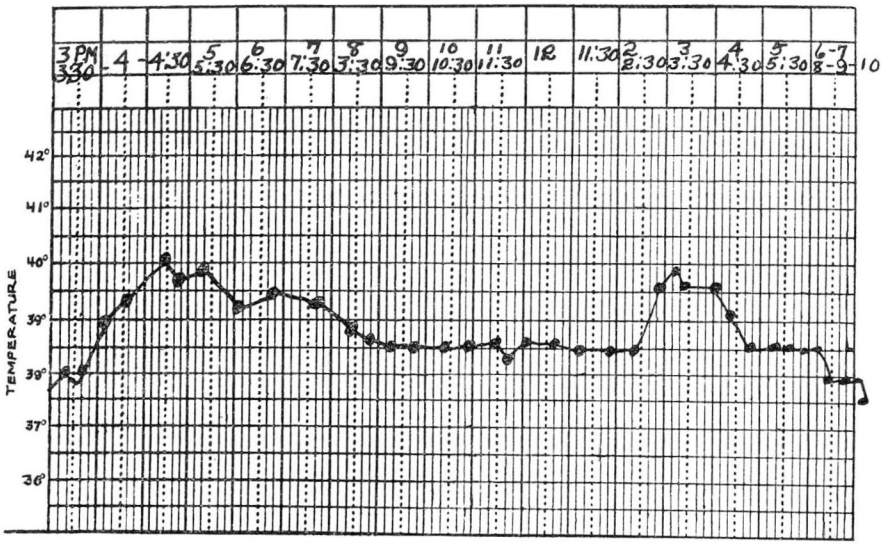

CHART 2: Temperature at half hourly intervals following administration of 50 million typhoid bacilli.

the violent and purposeless muscular movements after the third chill in all but one instance. In this case no improvement was noted either in the early or late observations. Subsequent observations on these nine patients over a period of a year or more showed no recurrence of symptoms although all the patients with arthritis and four of those

with chorea had experienced one or more attacks previous to treatment. It is evident that the period of observation is too short to justify final conclusions, but the immediate results in all except one were most satisfactory.

A group of five patients with acute manifestations of epidemic encephalitis were treated with intravenous typhoid vaccine in the hope that the resulting acute febrile reaction might mobilize intracellular

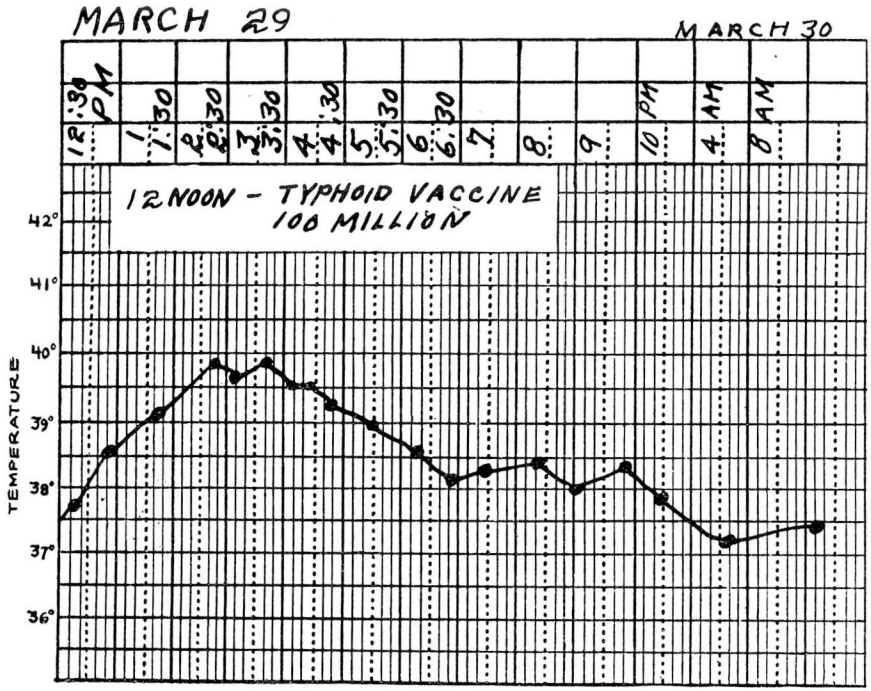

CHART 3: Temperature at half hourly intervals following administration of 100 million typhoid bacilli.

defense to the virus. At the present time the nature of the virus substance is not definitely settled. Whether it is a chemical substance or an ultramicroscopic organism is still a subject for research. Specific vaccines are not available and the value of therapy with salicylates, arsenic, iodides, or other medicinal substances is questionable. When given early in the disease, reactions to protein shock appear to be of definite value. In three of five patients in whom the symptoms had existed for five days, three and one-half weeks, and four months respectively, the immediate improvement following the reaction was very definite. None of these individuals had shown the late manifestations of the disease such as parkinsonism or oculogyric crises. In the two patients who were not helped, advanced parkinsonism had already developed and these symptoms were not affected by treatment.

Our experience with therapeutic typhoid shock in four cases of thrombo-angiitis obliterans was encouraging in two patients and disappointing in two others. If the collateral circulation is susceptible to improvement by vasodilatation, the treatment is of value and can be administered in one course or repeated at intervals of several weeks. It is difficult for one to predict just how good the response will be prior to a therapeutic trial. It is obvious that this measure alone

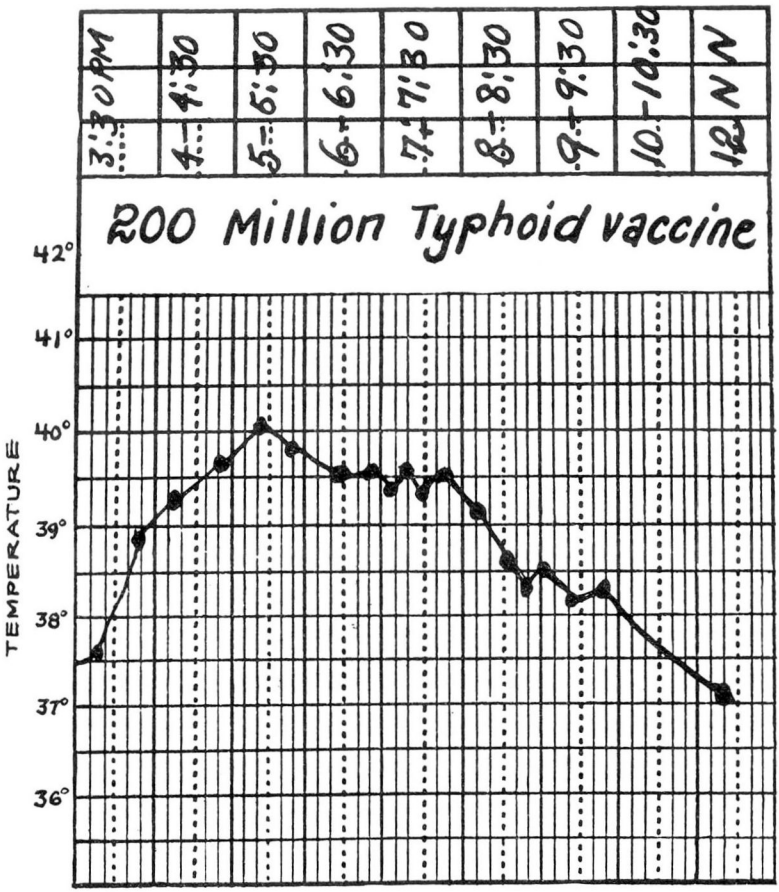

CHART 4: Temperature at half hourly intervals following administration of 200 million typhoid bacilli.

will not cure Buerger's disease. However, when improved peripheral blood flow does occur, there is certain to be an amelioration of pain and some healing of the trophic lesions. It is obvious that no benefit can accrue if the arteries and arterioles are so seriously damaged that there is impairment of blood flow from widespread thrombosis, both in the main and collateral channels. In every case, even if the treatment does not produce therapeutic improvement, it does have con-

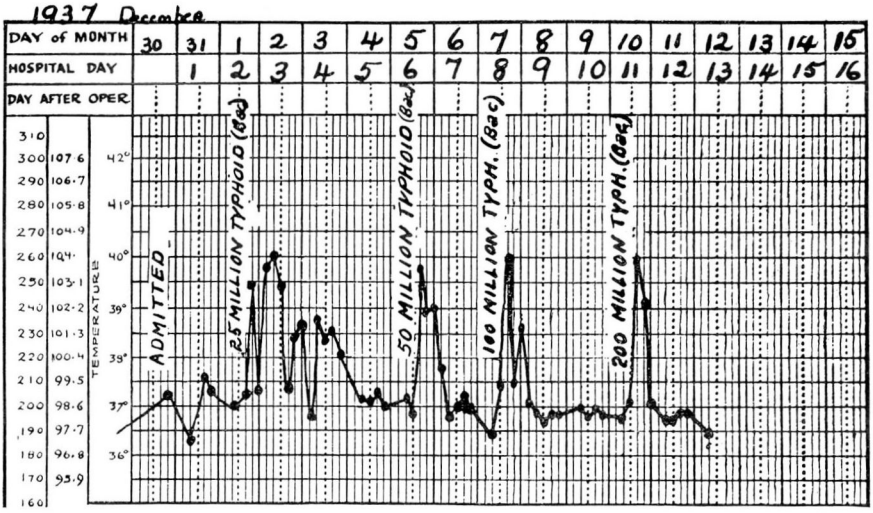

CHART 5: Daily record of temperature during administration of typhoid vaccine.

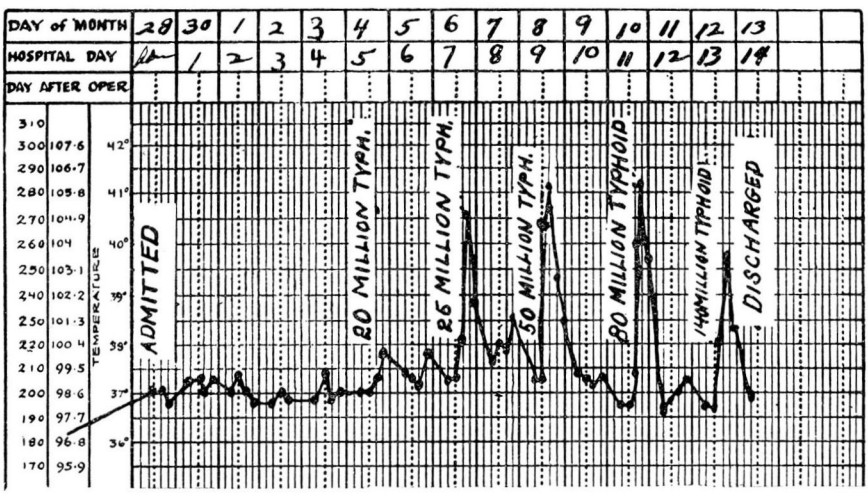

CHART 6: Daily record of temperature during administration of typhoid vaccine.

siderable prognostic value. If the hyperthermia fails, we are certain that the only other treatment of value consists of general tonic measures and hygienic care. Neither fever nor any other form of treatment can protect the patient from the possible necessity of amputation at a later date.

Any attempt to determine the value of nonspecific protein shock in the treatment of chronic rheumatoid arthritis presents many difficulties. If one is familiar with the modern conception of this disease, it will be realized that no single method of therapy, whether it be artificial

fever, streptococcus vaccine, diets, vitamins, glandular products, physiotherapy, removal of infected foci, or any of the magical cures advocated in pharmaceutical pamphlets will restore the patient to normal health. Excellent discussions of this serious and disabling disease will be found in modern monographs and textbooks. A most interesting summary of the problem of chronic arthritis is contained in the "Rheumatism Primer" prepared and printed by the Subcommittee of the American Committee for the Control of Rheumatism. This excellent monograph emphasizes the fact that chronic rheumatoid arthritis is a general disease of the body and not a local disease of the joints. We employed shock therapy in the hope that the cellular reactions would improve the general circulation and metabolism. During the hospital period of a month or more, a careful diagnostic survey was made and when we discovered anemia, a low metabolic rate, foci of infection, faulty diet, poor elimination, gastric achlorhydria, or any other organic or functional abnormality, corrective measures were instituted. In these patients, hyperthermia has served to give considerable relief from pain in the joints and general muscular aching. After a course of chills and fever, the majority of the individuals have been able to rest and sleep better, very often the joint swelling has diminished or disappeared, and the pain has largely subsided. In a series of 40 cases, we found that immediate improvement followed the bouts of fever in 67.5 per cent of the patients. However, in a control series of 20 cases, immediate good results were produced by bed rest, local physiotherapy, and general measures in 55 per cent. These results are not very impressive and certainly do not make a strong case for fever therapy. This is further emphasized by the late follow-up. After a year or more, it was found that 62.8 per cent of those who had taken typhoid shock as well as general treatment had remained improved; while in the control patients who did not receive fever, 60 per cent remained improved. These late results are almost equal and show that any benefit from shock therapy is temporary. However, it has value in its ability to make the patient comfortable and improve his morale. In general, he is more cooperative and desires to know more about his illness when he realizes that an earnest effort is being made to help him get well.

Chills produced by typhoid vaccine have been employed in various special fields of medicine to improve local circulation and stimulate the general metabolism of the cells. In ophthalmology, one or more chills may be used in chronic inflammatory disease of the eye, such as resistant forms of conjunctivitis or as an aid in combatting postoperative infections. Likewise, one or two chills prior to the removal of a foreign body from the eyeball may allay hyperemia due to local irritation. Vitreous exudate seems to undergo absorption more rapidly

after fever reactions and the resulting opacities may be decidedly less than in untreated cases.

Many lesions of the skin respond well to fever therapy. In erythema nodosum, chronic urticaria, resistant secondary lues, tinea sycosis, and even in psoriasis, the improvement is usually rapid. However, it cannot be expected that the underlying condition will be cured by this method alone. It is a good therapeutic adjunct to other forms of medication and may change resistant cases to those that will respond to ordinary measures.

Formerly, we employed typhoid shock in many urological conditions but at present we are using the cabinet hyperthermia as a satisfactory method for the treatment of gonorrheal infections, including acute urethritis, prostatitis, seminal vesiculitis, epididymitis, and above all, gonorrheal arthritis. In these, there is no doubt but that cabinet fever therapy is far superior to any other treatment. It acts as a specific in the cure of the various forms of the diseases noted above.

Patients who are suffering from diabetes, cardiorenal disease, advanced arteriosclerosis, myocardial insufficiency, and angina pectoris should not be given fever therapy without full realization of the possible dangerous consequences of this procedure.

Disease states that are accompanied by febrile reactions can be treated safely by protein shock. While the complete answer to the problem of fever therapy is not at hand, we believe that therapy by typhoid shock, while nonspecific, is of value in many disorders of the body that do not respond to ordinary measures. Likewise, our experience in the use of the method outlined in this paper has been gratifying.