

PROTEIN THERAPY IN TYPHOID AND PARATYPHOID FEVER.

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PROTEIN THERAPY IN TYPHOID AND PARATYPHOID FEVER. *

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The "intravenous vaccine" or foreign protein therapy was only introduced nine years ago but it has been used in a great variety of conditions. Since then much experimental work has been done. As evidence of the extent of this work a book was recently published on protein therapy¹ which contains a bibliography of over twelve hundred articles all of which have been written since 1915.

In the "Journal of the American Medical Association" for the past two years were found over sixty articles and abstracts dealing with this subject, perhaps the greater number coming from European journals. From China the only reports are from Dr. Cadbury² who has used it quite extensively in Canton, and there are some references to its use in the Peking Union Medical College Hospital. It is also probably being used to a considerable extent in other hospitals and in private practice in China.

The types of cases in which protein therapy is used and recommended are most varied. Some of the diseases treated and with reported good results are: acute and chronic arthritis; chronic osteomyelitis with discharging sinuses; puerperal and pelvic infections; gonorrheal urethritis; chancroid; buboes; acute and chronic enteritis; dysenteries; keratitis; acute iritis; optic neuritis; conjunctivitis; corneal ulcer; skin diseases, such as psoriasis, leucoderma, eczema, erythema and lupus; myalgias; neuralgias; typhoid fever; typhus fever; chorea; influenza, and other conditions.

In the Hunan-Yale Hospital we have used foreign protein for the past three years in a variety of conditions, chiefly acute and chronic arthritis and some febrile conditions, with special attention to its effect on our cases of typhoid fever.

Typhoid fever is endemic in Changsha, but during the summer and early fall it is almost epidemic, and it is very depressing to

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have a ward full of patients very sick with this disease and be so helpless to effect a cure. During 1922 we had ninety-eight cases with a mortality of seventeen per cent.

The treatment of typhoid fever is largely a question of maintaining the nutrition of the patient and, as far as possible, by careful nursing to avoid complications. We have very little in the line of active therapeutic agents at our disposal that have any effect on the course of the disease.

Miller, in his monograph on typhoid fever in "Oxford Medicine", mentions protein therapy as a rather dangerous method, to be used with great caution. He states that the results in general in typhoid can be classified as (1) about 20 per cent show recovery with a drop in temperature by crisis; (2) in about 20 per cent the disease is shortened with drop by lysis; (3) in about 20 per cent the temperature changes to a swinging type without affecting the course; (4) about 40 per cent show no effect. Miller states further that protein therapy if on further study it shows a lower mortality and is free from danger will be valuable, as it definitely shortens the course in a considerable percentage of cases.

During the past two and one-half years we have treated forty-eight cases of typhoid fever and para-typhoid fever with foreign protein. As it was felt the method was dangerous, involving at least some risk to the patient, and that there was danger of ascribing a normal recovery as being due to this special treatment, precautions were taken only to give the vaccine, (1) after the patient had been a few days in the hospital in order to observe the course of the temperature, so as to be sure there was no tendency of the temperature to drop normally; (2) when the case was uncomplicated; and (3) it was not given in cases evidently hopelessly sick. This means that only selected cases were treated, so that comparison of figures with the untreated is of no value in the study of the relative percentage of mortality or of complications; only by a study of the individual cases have we been able to come to any conclusion.

The procedure after selection of the case was to inject intravenously T.A.B. vaccine, properly diluted in normal saline, so that the patient received about 50,000,000 organisms. This is the form in which most of the therapy has been carried out. Lately, following suggestions of work recorded in foreign journals, we have used intramuscular injections of milk. Doses of 5-10 c.c.

of milk which has been sterilized are given into the gluteal muscle, using the same precautions to avoid entering a vein as in intramuscular mercury injections. In order to avoid possible anaphylactic symptoms, 1 c.c. is first given followed in one hour by the balance of the dose.

In the average case, in about one hour after the intravenous injection, or four to twelve hours after the intramuscular injection, there is a reaction with a chill and rise of temperature to around $39^{\circ}\text{C}.$ — $40^{\circ}\text{C}.$ The temperature gradually declines during the next twenty-four hours and there is generally a definite improvement in the subjective feelings of the patient, irrespective of the future course of the temperature.

The degree of reaction has varied much. Twenty-five patients are noted as having had severe reactions resembling a severe malarial chill. Ten are noted as having moderate reactions, eight had none, and the remainder were not recorded. Accompanying the chill there is the usual drop in the leucocyte count, followed by a leucocytosis, although this has not been marked in our cases. In only five cases was the blood count followed during and after the reaction. In these the leucocytosis varied from 9,000 to 16,000.

Theoretically, the benefit is derived from the reaction, a stimulation of leucocytosis and of the body defenses, or an "activation of protoplasm", as one author puts it. As a rule the best results have followed when the chills have been severe, but many severe reactions were followed by no change in the course of the disease, and some have improved after little or no demonstrable reaction.

RESULTS.

As may be seen by Table 1, there was considerable variation in the response to this form of treatment. In thirteen of the cases there was a rapid drop in the temperature curve, resembling the crisis of pneumonia. Nine patients were given a second dose and in three of them a crisis followed. Following are presented some typical cases of this series with the charts showing the effect of treatment. In all cases the subjective improvement was as great as the objective.

TABLE I. EFFECT OF PROTEIN THERAPY IN 48 CASES OF TYPHOID FEVER AND PARA-TYPHOID FEVER.

Series Number	Name	Hospital Number	Diagnosis	Age	Day of Disease Treatment Given	Duration of Fever after Treatment	Condition at Time of Discharge	Result of Treatment
1	Ching ...金	1250	Typh.	18	15	2	Cured	Crisis
2	Chiu ...邱	1310	"	37	10	*	Unimpr.	None
3	Huang ...黃	1359	"	38	11	2	Cured	Crisis
4	Pen ...彭	302	"	43	37	1	Cured	Crisis
5	Fuh ...傅	1498	"	14	11	19		
6	Yang ...楊	1586	"	15	25	25	Cured	Break
7	Hsu ...許	1703	"	22	20	1	Cured	None
8	Hsiao ...蕭	1504	"	16	19	3*	Impr.	Crisis
9	Cheng ...鄭	783	"	40	20	3	Cured	Break
10	Yang ...楊	1756	"	14	9	8		Lysis
11	Hsiao ...蕭	1452	"	20	9	*	Impr.	None
12	Liu... ...劉	1419	Para.-t.A.	20	11	*	Impr.	None
13	Li ...李	1301	"	54	32	1	Died	None
14	Chen ...陳	1088	"	18	10	15	Cured	Crisis
15	Fan ...	691	"	18	44	5		None
16	Hsieh ...謝	692	"	19	15	36	Impr.	Lysis
17	Lung ...龍	578	"	21	26	1	Cured	Crisis
18	Li ...黎	622	"	20	26	1	Died	None
19	Hsiung ...熊	1145	"	36	26	1	Impr.	Crisis
20	Chang ...張	571	Typh.	17	14	*	Impr.	None
21	Liu... ...劉	791	"	32	38	1	Died	None
22	Hsieh ...謝	734	"	23	13	*	Cured	Crisis
23	Tso ...祖	848	"	42	18	*	Died	Break
24	Kiang ...江	875	"	23	12	18	Impr.	None
25	Chang ...	362	"	26	31	35		None
26	...熊	438	"	42	24	*	Impr.	Lysis
27	Liu... ...劉	393	"	21	30	1	Unimpr.	None
28	Liu... ...劉	323	"	15	20	3	Cured	Crisis
29	Tang ...唐	290	"	20	9	24	Cured	Lysis
30	Li ...李	202	"	25	13	6		None
31	Chang ...張	148	"	21	16	3	Cured	Crisis
32	Li ...李	190	"	20	19	11	Cured	Lysis
33	Wu ...伍	1516	"	40	20	26	Cured	None
34	Huang ...黃	1569	"	30	27	38	Impr.	None
35	Li ...李	1451	"	25	11	6	Cured	Crisis
36	Wu ...吳	1407	"	21	41	5	Impr.	None
							Cured	Lysis

TABLE I.—(Continued.)

Series Number	Name	Hospital Number	Diagnosis	Age	Day of Disease Treatment Given	Duration of Fever after Treatment	Condition at Time of Discharge	Result of Treatment
37	Wu... ...伍	1379	Typh.	17	22	12	Cured	None
38	Liu... ...劉	821	"	20	19	23		
					8		Cured	None
39	Fan ...范	763	"	31	47	3	Impr.	Lysis
40	Yi ...易	834	"	16	6	*	Died	None
41	Liu... ...劉	856	"	38	23	27		
					*		Died	None
42	Kuo ...郭	1513	"	15	36	3	Cured	Lysis
43	D. G. F....	529	Para.-B.	26	21	2	Cured	Crisis
44	Li ...李	600	Typh.	14	23	20	Cured	None
45	Tseng ...曾	601	"	30	14	6	Impr.	Lysis
46	Tang ...唐	734	"	20	15	5	Cured	Lysis
47	Yuen ...袁	718	"	18	25	2	Cured	Crisis
48	A. C. S....	726	Para.-B.	34	16	24		
					4		Cured	Lysis

* Discharged before the temperature reached normal.

Case No. 1.—Ching, 金, a probationer nurse of this hospital, 19 years of age, was admitted September 5, 1922, with typhoid fever. He was given 50,000,000 T. A. B. vaccine on the 16th day of his illness. Had a recovery by crisis and an uneventful convalescence. (Fig. 1.)

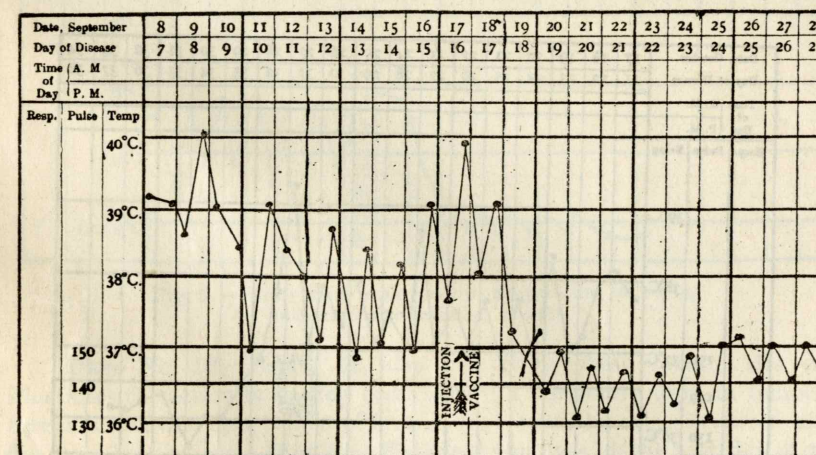


Fig. 1.—Typhoid fever: crisis on 17th day following intravenous injection of T.A.B. vaccine.

Case No. 7.—Hsu, 許, student, aged 22, with typhoid fever, was treated on the 19th day of his illness. Recovery was by crisis and temperature was normal during the remainder of his stay. (Fig. 2.)

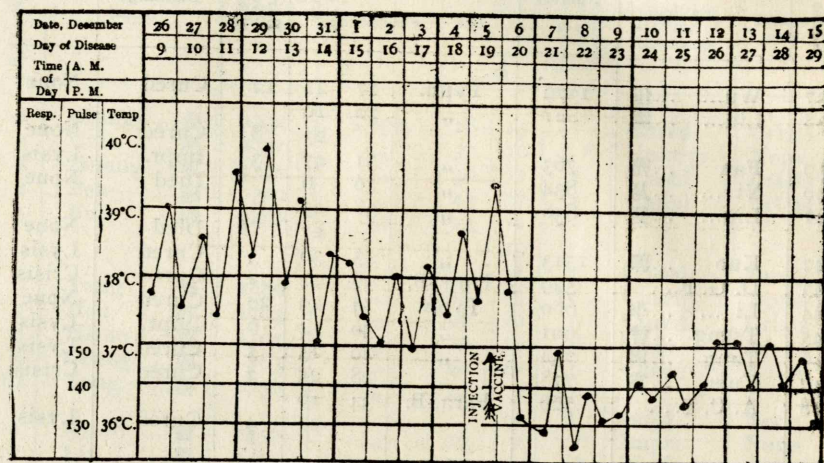


Fig. 2.—Typhoid fever: crisis on 20th day following foreign protein therapy.

Case No. 13.—Li, 李, a woman of 54 was admitted with typhoid fever on October 14, 1922, in the third week of the disease. She was given 50,000,000 T. A. B. vaccine intravenously on the 31st day. Crisis followed a severe chill and temperature remained subnormal during the five days she stayed in the ward. (Fig. 3.)

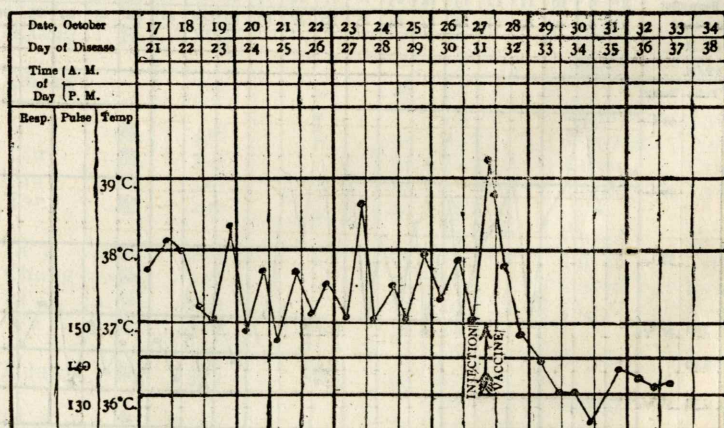


Fig. 3.—Typhoid fever: result of intravenous dose of vaccine on 31st day.

Case No. 18.—Li, 黎, a student of 20, with paratyphoid fever, admitted on the 21st day and treated on the 26th day of his illness. Had a recovery by crisis. He left the hospital two days later insisting he was cured. (Fig. 4.)

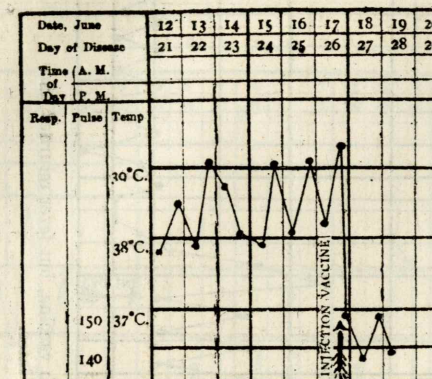


Fig. 4.—Typhoid fever: crisis following foreign protein therapy.

Case No. 43.—D. G. F. a foreigner, with paratyphoid fever, 26 years of age, was admitted on the eighth day of the disease and treated on the 21st day with 10 c. c. of milk intragluteally. He had a good reaction with a drop by crisis and an uneventful convalescence. (Fig. 5.)

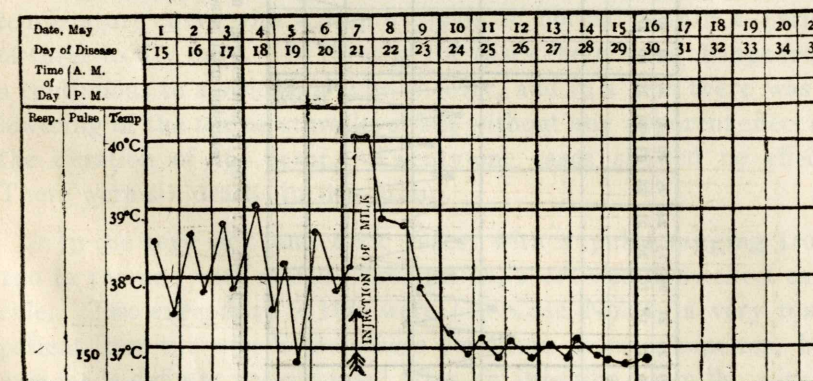
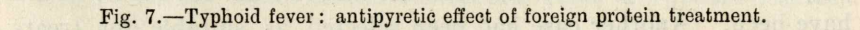


Fig. 5.—Paratyphoid fever: fall in temperature following intramuscular injection of milk.

Case No. 16.—Hsieh, 謝, also had paratyphoid fever. His case illustrates the action in the few cases where a temporary drop in temperature was followed by a return of fever, but recovery by crisis occurred after the second treatment. (Fig. 6.) First injection was on the 21st day of the disease. After a return of symptoms, the second treatment on the 46th day was followed by a crisis and rapid recovery.



Date, May	Day of Disease	Temp. (A. M.)	Temp. (P. M.)	Temp.
Day	Day	Day	Day	Day
		40°C.	39°C.	38°C.
				150 37°C.
				140



In eleven cases there was a definite change in the course of the temperature curve with a drop by lysis to normal within a period of three to five days. In three of the cases there was a change from a continuous to a swinging type of fever, and in a few there was a lowering of the temperature level but without any apparent effect on the duration of the fever. Twenty-one cases showed no effect. There were six deaths in this group.

In the very sick and toxic cases, with a pulse ranging from 100 to 120 and with marked prostration, there was little effect as a rule. Two exceptions to this were (1) Case No.46, a very toxic patient from the poor-house whose condition seemed hopeless, but who made definite improvement after an injection of milk, with a recovery by lysis; and (2) Case No.45, where the illness was complicated by intestinal hemorrhages and bilateral parotitis, and the patient seemed to be pulled through by protein therapy.

Dr. W. W. Cadbury, in 1922, reported ten cases of typhoid fever treated by intravenous vaccine injections, in which seven were cured by crisis, one by lysis; there was no effect in two very malignant cases.

Analysis of the stages of the disease at which the treatment was instituted shows that little effect was noted when treatment was given in the first week. About an equal number of good results were obtained in the later stages, although there was a higher percentage of recoveries between three and six weeks. The paratyphoid cases seem to respond better than the patients with typhoid.

COMPLICATIONS.

In the whole series of our cases of typhoid fever and paratyphoid fever, and in the other cases treated by this method, we have not seen any ill-effects directly as a result of the treatment. The chill is unpleasant and in some cases was accompanied by a degree of cyanosis and mild shock but the treatment has always been followed by subjective improvement.

In connection with the administration of the remedy we have had some narrow escapes. Once an interne was caught just as he was about to inject two and one-half billion organisms instead of the proper dose of fifty millions. No one knows what the result would have been. Another case had been selected as suitable for treatment, but the injection was postponed for a day for some incidental reason. That night the patient had an intestinal hemorrhage and died within 24 hours. If the vaccine had been given it surely would have been blamed as the cause of death.

COMMENT.

The cases are too few to permit any generalization but the results, as far as we have gone, fall rather closely into the percentage groups as given by Miller. In the others, no harm has been done. It seems that we must look further for the treatment of the very toxic or malignant cases of typhoid fever. We have tried emetin in a number (fifteen) with no effect whatever on the temperature curve. The use of serum of convalescent cases of typhoid fever has been suggested, but we have had no experience with it and apparently its clinical and experimental use has been disappointing.³

SUMMARY

1. Foreign protein therapy has been tried in a series of 48 cases of typhoid and paratyphoid fever in the Hunan-Yale Hospital, Changsha.

2. Intravenous injections of typhoid vaccine and intramuscular injections of milk were used.

3. The following results were obtained: in 27 per cent the course of the disease was interrupted and recovery occurred by crisis. In 23 per cent there was a drop in temperature and recovery by lysis. In 6 per cent there was a break in the temperature, but without shortening its course. In 44 per cent the course of the disease was not affected.

4. The very toxic cases, as a rule, showed little response to this treatment.

5. No ill effects from the treatment were seen.

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