Only 12 of the patients noted improvement after curare was administered, but the lack of permanence in this subjective sense of improvement did not merit continuation of the drug. Furthermore, although 20 of the cases are reported on the charts as showing minor improvements, it must be added that, with the exception of 2 of these cases, there was no definite certainty in the relaxation of the muscle spasm.

From the grouping of the cases according to clinical types, it can be noted that the bulbar and spinal-bulbar cases in general showed the least response to this medication, while the best results, if any, were seen in the spinal paralytic types.

Typical of the patients having bulbar involvement (patient 5), a spinal bulbar poliomyelitis, was a boy aged 8 years who had difficulty in swallowing and an absent cough reflex at the time we gave him the regular dose of curare. Within an hour's time the respiratory effort became more aggravated and cyanosis was quite pronounced, so that the patient was placed in a mechanical respirator. He remained in the respirator for twenty-seven days at South View Hospital and was transferred to a private hospital as a possible permanent respirator patient. This result and the result in case 4 may indicate possible dangers of using curare in any form of bulbar paralysis.

Cases 9 and 34 represent attempts to get improvement with repeated smaller doses of curare. The results show no significant advantage in this procedure.

Although curare has merited a place in anesthesiology and certain types of spastic clinical entities, its use is not warranted during the acute phase of poliomyelitis. Curare may prove to be of more benefit in the residual spastic conditions after the patients have been released from the quarantine period. I am not in a position to comment on its value because I have not investigated its effects in such circumstances.

This series of 34 cases is offered as a conservative observation on the use and effectiveness of curare in poliomyelitis. I hesitate to recommend its routine usage in isolation hospitals for poliomyelitis cases. It surely should not be adopted for home treatment because of the lack of proper supervision and necessary facilities in the event of harmful manifestations.

CONCLUSIONS

1. Curare has been tried in 34 cases of poliomyelitis.

2. Although a few of the patients noted subjective improvement, the findings, objectively, were not encouraging.

3. Bulbar cases did not respond to this treatment, and in 2 cases a rapid downward course necessitated the use of artificial respirators.

4. Curare may be in some instances of temporary benefit, but it is a dangerous drug and is not to be encouraged for the treatment of the acute phase of poliomyelitis.

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Scientists and Politics.—Scientists are being urged to "knock at the door of politics." Scientists probably should do that, if in so doing we do not deviate from the path of science and continue to stick by the facts. If, when "knocking at the door of politics," we follow current political mores, we injure science and render no service to society.—Carlson, A. J.: Is There "A Standard to Which the Wise and the Honest Can Repair?" *Science* **103**:377 (March 29) 1946.

EFFECT OF PARA-AMINOBENZOIC ACID IN TSUTSUGAMUSHI DISEASE

LIEUTENANT NICHOLAS A. TIERNEY (MC), U.S.N.R.

Tsutsugamushi disease, or scrub typhus, is an acute infectious disease caused by Rickettsia orientalis and is transmitted to man by a larval trombiculid mite. This has been one of the severest diseases encountered by the troops in the Pacific and Asiatic theaters of the war. Figures for the case fatality rates according to the U. S. Army reports have varied from 1 to 28 per cent, but the majority ranged between 10 and 15 per cent, with an overall case fatality rate of about 5 to 7 per cent. While the average period of disability in these cases has been approximately three months, many of the patients have been unfit for duty for a much longer time. Many drugs have been tried on this disease, but until now no effective therapeutic agent has been found.

The possible value of para-aminobenzoic acid as a therapeutic agent against a rickettsial disease was first suggested by Snyder, Maier and Anderson.[1] They reported that 80 per cent of their mice inoculated with murine typhus survived when they were fed on a ration containing para-aminobenzoic acid, whereas only 20 per cent of the control mice recovered.

Hamilton, Plotz and Smadel[2] noted that large amounts of para-aminobenzoic acid inhibited the growth of epidemic and murine rickettsias in the yolk sac of developing chick embryos.

An independent discovery by Grieff, Pinkerton and Moragues[3] confirmed these results. They found that para-aminobenzoic acid inhibited the growth of murine rickettsias in both mice and eggs.

Yeomans, Snyder, Murray, Zarafonetis and Ecke[4] studied the effect of para-aminobenzoic acid in clinical louse borne typhus. They reported a series of 20 treated cases and 44 controls. The patients were given for an initial dose 4 to 8 Gm. of para-aminobenzoic acid and 2 Gm. every two hours in an effort to maintain a blood concentration of between 10 and 20 mg. per hundred cubic centimeters. These workers reported that the para-aminobenzoic acid had a good effect in decreasing both the severity of the disease and the case fatality rate.

From the United States of America Typhus Commission, War Department, Washington 25, D. C.

These studies were carried out at the 20th General Hospital and at the 94th Indian General Hospital, Ledo, Assam, India.

Sergeants Ralph Fine and Morton Hookaylo of the 20th General Hospital determined the para-aminobenzoic acid blood levels. Other assistance was rendered by nurses, corpsmen and technicians of the 20th General Hospital and the 94th Indian General Hospital.

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1. Snyder, J. C.; Maier, J., and Anderson, C. R.: Report to the Division of Medical Sciences, National Research Council, Dec. 26, 1942.

2. Hamilton, H. L.; Plotz, H., and Smadel, J. E.: Effect of p-Aminobenzoic Acid on the Growth of Typhus Rickettsiae in the Yolk Sac of the Infected Chick Embryo, Proc. Soc. Exper. Biol. & Med. **58**: 255-262, 1945.

3. Grieff, D.; Pinkerton, H., and Moragues, V.: Effect of Enzyme Inhibitors and Activators on the Multiplication of Typhus Rickettsiae, J. Exper. Med. **80**: 561-574, 1944.

4. Yeomans, A.; Snyder, J. C.; Murray, E. S.; Zarafonetis, C. J. D., and Ecke, R. S.: The Therapeutic Effect of Para-Aminobenzoic Acid in Louse Borne Typhus Fever, J. A. M. A. **126**: 349-356 (Oct. 7) 1944.

Snyder and Zarafonetis [5] and Murray, Zarafonetis and Snyder [6] reported that the oral and parenteral administration of the sodium salt of para-aminobenzoic acid to mice infected with scrub typhus definitely reduced the mortality of the experimental infection.

Through the courtesy and cooperation of Brig. Gen. I. S. Ravdin, U. S. Army, and Col. Francis C. Wood, M. C., A. U. S., of the 20th General Hospital, and Col. J. Palmer and Lieut. Col. George A. Kiloh, R. A. M. S., of the 94th Indian General Hospital, an opportunity was afforded the United States of America Typhus Commission to conduct a study of para-aminobenzoic acid on patients with tsutsugamushi disease in these institutions.

These hospitals were located at Ledo, Assam, India, which marks the beginning of the Ledo Road. This road was built through jungle territory in which tsutsugamushi infected mites abound. It was from this area of northern India and Burma that most of our tsutsugamushi admissions came.

The severity of the cases admitted to the 20th General Hospital and the 94th Indian General Hospital has varied from time to time. As a result, any study to evaluate a therapeutic agent would have been worthless unless this agent was tried in alternate cases or in a large series of consecutive cases. In view of the impossibility of the latter, it was decided to treat alternate cases. Those not receiving para-aminobenzoic acid received the best supportive treatment possible. The disease appeared somewhat less severe in the Indians than in the Americans, and consequently a separate alternate series was studied at the 94th Indian General Hospital. All the cases were alternately treated except 2. One of these was a control who turned out not to have tsutsugamushi disease. In the other instance 2 patients were treated consecutively as at that time there were so few cases being admitted that it did not seem worth while to continue the study, but subsequent results encouraged us to carry on.

METHOD OF TREATMENT

The para-aminobenzoic acid was given orally as a powder partly neutralized by a sodium bicarbonate solution, which has a tendency to lessen gastric irritation.[4] This was accomplished by mixing 10 cc. of a 5 per cent sodium bicarbonate solution with each gram of para-aminobenzoic acid powder. At first 6 Gm. of para-aminobenzoic acid was given as an initial dose, and then 2 Gm. every two hours. However, as the blood concentration of para-aminobenzoic acid was slow to rise, it was thought that valuable time was being lost by this procedure. Therefore 8 Gm. was given initially, and then 3 Gm. every two hours. On this regimen a blood concentration of 30 to 60 mg. per hundred cubic centimeters was usually reached within two days. This proved effective and was well tolerated by the patients. Since the drug is rapidly excreted in the urine, it is necessary to give it every two hours.

There is considerable variation from patient to patient in the ability to build up and maintain a satisfactory blood level of para-aminobenzoic acid. Consequently it is highly important to determine the blood concentration of para-aminobenzoic acid in each patient each day. It is only by this means that the proper amount of the drug can be administered. The drug was usually continued in each case until the temperature had been normal for one week.

General supportive treatment of the highest possible quality was given all patients. The following regimen was carried out at the 20th General Hospital: Patients were placed in an air conditioned ward and had absolute bed rest. A high protein, high caloric soft diet with supplementary vitamins and 4 Gm. of added salt was provided. If the patient was too ill to take the diet properly, Amigen [7] and glucose were given intravenously. The fluid intake was maintained at 3 to 4 liters daily and the urine output was measured. Oxygen was administered for dyspnea or cyanosis. Blood transfusions and plasma were given for impending shock. Paraldehyde was the drug of choice for extreme restlessness, and codeine for pain. Bacterial complications were treated with penicillin. Sulfonamides were considered contraindicated because of their antagonistic reaction to para-aminobenzoic acid.

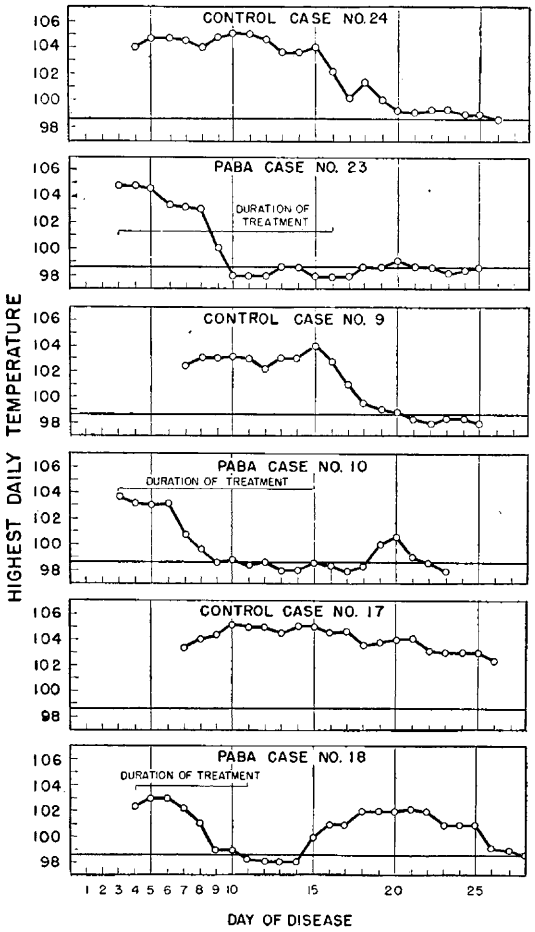

Chart 1.—Comparative Fahrenheit temperatures of 3 untreated, control cases of scrub typhus and 3 cases treated with para-aminobenzoic acid (PABA). Duration of treatment is indicated in the charts.

At the Indian General Hospital most of the preceding supportive measures were executed, with the exception of the air conditioning and the use of Amigen.

THE DETERMINATION OF PARA-AMINOBENZOIC ACID IN THE BLOOD

The method used for determining para-aminobenzoic acid in the blood was the same as that described by Marshall and Litchfield [8] for sulfanilamide with the

5. Snyder, J. C., and Zarafonetis, C. J. D.: Effects of Para-Aminobenzoic Acid in Experimental Tsutsugamushi Disease, Proc. Soc. Exper. Biol. & Med. **60**: 115-117, 1945.

6. Murray, E. S.; Zarafonetis, C. J. D., and Snyder, J. C.: Further Report on Effect of Para-Aminobenzoic Acid in Experimental Tsutsugamushi Disease, Proc. Soc. Exper. Biol. & Med. **60**: 80-84, 1945.

7. A casein hydrolysate produced by Mead Johnson & Co.

8. Marshall, E. T., and Litchfield, J. T.: The Determination of Sulfanilamide, Science **88**: 85-86, 1938.

exception that a standard solution of para-aminobenzoic acid was substituted for sulfanilamide. For the blood levels in this series, a standard solution of para-aminobenzoic acid containing 30 mg. of para-aminobenzoic acid per hundred cubic centimeters was found satisfactory. In preparing the standard, the sodium salt of para-aminobenzoic acid was used because of its solubility.

RESULTS

In this series there were 34 patients with definitely proved uncomplicated tsutsugamushi disease. Of the 34, 16 were Americans, 16 Indians and 2 Chinese. Twenty-six of them (76 per cent) had classic tsutsugamushi disease, which consisted of a typical history and physical findings, including the eschar. Five patients had neither rash nor eschar, while 3 had rashes but no eschars, but these patients had all the other signs and symptoms of this disease, including a confirmatory proteus OXK titer rise. One patient, a man aged 35, had malignant tertian malaria as well as classic tsutsugamushi disease. Treatment with quinine and atabrine was begun shortly after admission and para-

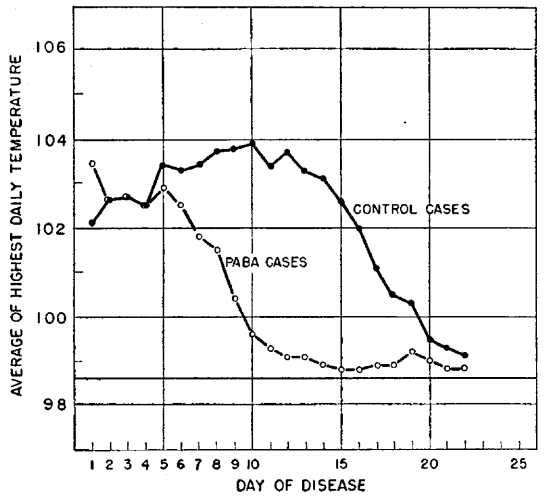

Chart 2.—Comparison of the average of the highest Fahrenheit temperature each day in 16 untreated control cases of scrub typhus and in 18 cases treated with para-aminobenzoic acid (PABA).

aminobenzoic acid was started at the end of the sixth day of the disease. There was no apparent response to therapy except for the disappearance of the malarial parasites from the peripheral blood smear after three days. In spite of para-aminobenzoic blood levels that ranged between 20 and 40 mg. per hundred cubic centimeters his condition became worse. He developed an extensive bronchopneumonia and died on the fifteenth day of the acute illness. This patient had all the clinical signs of tsutsugamushi disease, including a characteristic eschar. The proteus OXK titer rose from 1:40 to 1:640. It appeared clinically that the cause of this patient's death was tsutsugamushi disease, but the microscopic examination failed to reveal any lesions characteristic of tsutsugamushi disease. Smears of the brain and spleen were negative for malarial parasites. The pathologic diagnosis was a bacterial bronchopneumonia. Because of the complicated nature of this case, which prevented clear appraisal of the effect of treatment with para-aminobenzoic acid, the case is not included in the following statistics.

Effect of Para-Aminobenzoic Acid on Temperature.—The favorable response to para-aminobenzoic acid therapy seemed to be apparent. After approximately two days of treatment the temperature started to fall by lysis, and after five to seven days it was normal in the majority of cases. Although the change was striking in most of the individual cases, it was most impressive when one compared it to that seen in the untreated alternate controls (chart 1). The overall difference in the temperature courses is brought out by comparing the average of the highest temperature each day in all of the para-aminobenzoic acid cases to that in the controls (chart 2). There were ten more days of fever in the average of the control cases than in the average of the para-aminobenzoic acid cases.

In case 27 (table 1) the temperature was coming down until the patient developed a nonspecific diarrhea which lasted for a week, and with this there was an exacerbation of his fever. In cases 10 and 18 (fig. 1) and 29 (table 1) after the para-aminobenzoic acid was discontinued there was a secondary rise in temperature. Associated with this there was a mild recurrence of the previous symptoms, and, what was most impressive, the lymph nodes became enlarged again. Despite a thorough search for complications to account for this secondary temperature rise, none were found. The fever lasted from three to fourteen days, but the patients were not very ill and the para-aminobenzoic acid was not started again. This secondary fever had all the characteristics of typhus and it was interpreted as a mild relapse. It did not occur in the untreated cases of scrub typhus. This also was noted by Yeomans and his associates[4] in louse borne typhus treated with para-aminobenzoic acid but not in the untreated cases.

Effect of Para-Aminobenzoic Acid on the General Symptoms.—Patients with severe tsutsugamushi disease appear toxic and apathetic, and they usually complain of a very disturbing headache. The average duration of these symptoms is approximately two weeks, but in those who received para-aminobenzoic acid therapy there was an early change. After two to three days the headache was either gone or much less severe, the patient was much more alert, and in a number of cases the appetite had returned. These are observations which impressed every one who had close contact with the patients. It was quite apparent that the disease process was altered, particularly when one compared it to that in the controls.

Some of the most striking responses to therapy occurred in those patients who had a very high concentration of para-aminobenzoic acid (95 to 150 mg. per hundred cubic centimeters). In 2 of these patients the pronounced generalized lymphadenopathy disappeared within three days (cases 10 and 12, table 1). In spite of the very high drug levels, the only toxic manifestation was slight confusion. One patient (20) had two convulsions when he had a para-aminobenzoic acid blood level of 103 mg. per hundred cubic centimeters, but at that time he was acutely ill and the convulsions were probably due to the disease rather than to the drug.

Effect of Para-Aminobenzoic Acid in Decreasing the Complicating Conditions.—In the 16 control cases there was severe bronchitis in 14 and mild bronchitis in 1, while in the 18 para-aminobenzoic acid cases there was bronchitis in only 4, and this was mild and of very short duration. There was severe pneumonitis in 10 control cases but none in the para-aminobenzoic acid cases. Severe delirium occurred in 4 control cases and in 1 para-aminobenzoic acid case. Mild delirium occurred in 2 patients who had high para-aminobenzoic acid blood levels. Stupor occurred in 4 controls and

in 1 para-aminobenzoic acid case, while coma was present in only 3 controls. Convulsions were observed in only 1 case, and that was a para-aminobenzoic acid case.

Two control patients had definitely abnormal electrocardiograms, with low voltage and inverted T waves, and 1 of these patients had a gallop rhythm. One control patient developed a prothrombin level of 30 per cent of normal and had numerous subcutaneous hemorrhages. Painful, persistent peripheral neuritis occurred in only 3 control cases, and partial deafness which lasted for several weeks in 2 control cases. Bacterial complications occurred in only 2 para-aminobenzoic acid cases; 1 of these patients developed a parotitis, while the other had a recurrence of otitis media, but both of them responded to penicillin therapy. The foregoing data are presented in the general summary in table 1.

An attempt was made to classify these cases according to the degree of severity in the following manner: mild, moderate, severe, grave, fatal. The case was classified only when it was completed. Duration of fever, duration and degree of toxicity and amount of pulmonary, cerebral or cardiac involvement were some of the factors considered. If the patient's life was in jeopardy his case was called grave. That is, only those patients placed on the seriously ill list were classified as grave cases. Many of the patients classified as being mildly ill appeared very toxic and severely ill on admission, but owing to their prompt response to treatment with a short febrile course and failure to develop severe complicating conditions they were placed in this category. With this plan in mind an unprejudiced attempt was made to relate the degree of severity of the case with the treatment received.

The difference between the degree of overall severity in the patients who received para-aminobenzoic acid and those who did not was striking. The great majority of those receiving para-aminobenzoic acid had mild courses. There were no deaths, and only 1 patient became gravely ill. Of the patients who did not receive para-aminobenzoic acid 3 died and 7 were gravely ill. The classification of the whole series according to the method just described is shown in table 2.

Effect of Para-Aminobenzoic Acid in Shortening the Period Needed for Convalescence.—There was a great difference in the general condition of the patients in the para-aminobenzoic acid series and in the control series during the period of convalescence. As one would expect, it conformed to the degree of severity of the disease. The majority of the patients who received para-aminobenzoic acid required a much shorter period of convalescence than the control cases.

TABLE 1.—*Summary of Data in Thirty-Four Patients* with Tsutsugamushi Disease, Eighteen of Whom Received Para-Aminobenzoic Acid*

Case No.	Age	Day of Disease Hospitalized	Day of Disease PABA Started	Total PABA Dose, Gm.	Maximum PABA Blood Level Attained†	Days of Cont. Fever	Days of Sec. Fever	Eschar	Rash	Bronchitis	Pneumonitis	Other Complicating Conditions	Lowest White Blood Cell Count	Proteus OXK Titer Rise	Ultimate Severity of Case
1	26	2	5	254	68	9	0	0	0	0	0	0	5,200	Neg. to 1/80	Mild
2	30	5	..	0	0	24	0	0	0	++++	++++	0	2,500	Neg. to 1/160	Grave
3	22	3	3	254	52	7	0	0	++	+	0	0	4,600	1/40 to 1/640	Mild
4	21	8	..	0	0	20	0	+	0	++	0	0	6,110	Neg. to 1/320	Grave
5	24	7	7	264	43	17	0	+	++	0	0	Parotitis	3,850	Neg. to 1/320	Mild
6	22	1	..	0	0	17	0	+	0	++++	0	0	4,400	Neg. to 1/640	Severe
7	23	2	3	284	96	6	0	+	0	+	0	0	4,900	Neg. to 1/160	Mild
8	25	2	5	254	66	8	0	0	0	0	0	0	8,210	Neg. to 1/80	Mild
9	28	7	..	0	0	19	0	0	0	++++	0	0	8,300	Neg. to 1/160	Grave
10	45	3	3	246	152	8	3	+	+++	0	0	Confusion due to PABA	4,700	Neg. to 1/80	Mild
11	26	6	..	0	0	23	0	+	++++	++++	++++	0	4,800	Neg. to 1/160	Severe
12	36	6	6	291	155	11	0	+	++	+	0	Confusion due to PABA	6,900	Neg. to 1/80	Mild
13	20	5	..	0	0	20	0	0	0	++++	++++	0	6,400	Neg. to 1/320	Grave
14	40	6	6	357	55	15	0	+	++	0	0	0	3,450	1/40 to 1/640	Moderate
15	22	6	..	0	0	18	0	+	0	++++	++++	Delirium, muscle twitchings	10,000	1/80 to 1/1280	Grave
16	36	1	4	217	95	7	0	+	0	0	0	0	4,650	Neg. to 1/80	Mild
17	23	7	..	0	0	79	0	+	++	++++	++++	Stupor, azotemia, deafness, myocarditis, peripheral neuritis	5,450	Neg. to 1/160	Grave
18	26	4	4	217	28	10	14	+	++	0	0	0	3,800	Neg. to 1/1280	Mild
19	29	1	..	0	0	21	0	+	++	++++	+++	Delirium, deafness, peripheral neuritis	4,400	Neg. to 1/320	Grave
20	32	4	5	250	103	13	0	0	0	0	0	Convulsions	6,400	Neg. to 1/80	Moderate
21	32	9	..	0	0	15	0	+	++++	++++	++++	Coma	2,850	Negative	Fatal
22	23	6	6	339	60	11	0	+	++	0	0	0	4,000	1/40 to 1/40	Mild
23	22	3	3	357	56	9	0	+	0	0	0	0	3,050	Neg. to 1/320	Mild
24	37	4	..	0	0	25	0	+	0	++++	+++	Muscle twitchings	5,100	1/160 to 1/40	Grave
25	31	2	4	435	52	11	0	+	+	+	0	0	3,800	Neg. to 1/160	Mild
26	26	5	..	0	0	15	0	+	0	++	0	Stupor, muscle twitchings	4,350	1/40 to 1/40	Grave
27	24	7	7	419	52	19	0	+	++	0	0	Diarrhea, cause unknown	2,200	Neg. to 1/640	Moderate
28	37	2	..	0	0	17	0	+	++	++++	++++	Coma	5,000	1/20 to 1/2560	Fatal
29	29	2	6	513	38	14	9	+	++	0	0	Transient deafness	4,050	Neg. to 1/80	Moderate
30	22	8	..	0	0	19	0	+	++	++++	++++	Coma	10,300	Neg. to 1/2560	Fatal
31	24	4	4	466	35	11	0	+	++	0	0	0	3,600	Neg. to 1/40	Mild
32	26	3	..	0	0	10	0	0	+	0	0	0	7,300	Neg. to 1/80	Mild
33	25	4	4	273	93	14	0	0	+++	0	0	Stupor, recurrent otitis media	1,500	Neg. to 1/80	Grave
34	26	3	..	0	0	19	0	+	+	+	0	0	4,500	Neg. to 1/160	Severe

* Patients 1 to 16, Indians; 21 and 22, Chinese; 17 to 20 and 23 to 34, Americans. † Mg. per 100 Cc. PABA = para-aminobenzoic acid.

TABLE 2.—*The Ultimate Severity of the Disease With and Without Para-Aminobenzoic Acid Therapy*

	Mild	Moderate	Severe	Grave	Fatal
Para-aminobenzoic acid cases...	12	5	0	1	0
Control cases.....	1	1	4	7	3

Effect of Para-Aminobenzoic Acid on the White Blood Cell Count.—It was noted by Yeomans and his associates [4] that there was a tendency for the total white blood cell count to drop during para-aminobenzoic acid treatment, but no change was observed in the differential count. In the patients with tsutsugamushi

disease receiving para-aminobenzoic acid therapy 2 developed white blood cell counts below 3,000 per cubic millimeter. One of these patients had a count of 1,500 with 18 per cent granulocytes, the other a count of 2,200 with 8 per cent granulocytes. A third patient had a white blood cell count of 3,600 with 20 per cent granulocytes, and a fourth patient had a 4,050 white cell blood count with 20 per cent granulocytes. This leukopenia developed at the end of the course of treatment. As a result, in no case was it necessary to discontinue the drug during the acute stage of the disease, and in no case was there a relationship noted between the para-aminobenzoic acid blood level and the degree of leukopenia. In all these patients the white blood cell count started to rise within four to five days after the para-aminobenzoic acid was stopped. The regeneration in the lymphocytes preceded that in the granulocytes by three to four days. At the time of discharge the white blood cell counts were normal in all the cases. No change was noted in the red blood cell count at any time which could be attributed to para-aminobenzoic acid.

IMPORTANCE OF EARLY TREATMENT

Treatment with para-aminobenzoic acid was instituted in these cases not later than the end of the seventh day of disease. It is obvious that the earlier the treatment is begun the better, but it is not known just how late para-aminobenzoic acid may be started and still be effective. It should be worth trying even though it may be late in the case.

THE OPTIMUM AMOUNT OF PARA-AMINOBENZOIC ACID THERAPY

The high blood concentrations of para-aminobenzoic acid appeared to have a more abrupt therapeutic effect than the lower ones, but they also caused slight delirium. The patients who had para-aminobenzoic acid levels between 30 and 60 mg. per hundred cubic centimeters improved almost as quickly and had no mental reactions, so it seemed preferable to maintain the blood concentration of para-aminobenzoic acid within that range. After the patient became afebrile, the para-aminobenzoic acid concentration was frequently reduced to 10 to 20 mg. per hundred cubic centimeters without any relapse taking place.

Para-aminobenzoic acid was continued for a week after the temperature had been normal in an attempt to eliminate the secondary temperature rise. This procedure was started after the prolonged secondary fever occurred in case 18. Despite this there was a nine day secondary fever in case 29, but there was no prolonged secondary temperature rise in any of the other cases. If the drug is well tolerated by the patient, it is probably wise to continue the treatment in the manner just mentioned even though it may not be necessary.

PRECAUTIONS TO BE TAKEN DURING PARA-AMINOBENZOIC ACID THERAPY

Although no serious toxic reactions have been attributed to para-aminobenzoic acid, one cannot be careless in its use. The total white blood cell count should be determined at least every second day, and if it is below 4,000 a differential count should be done. If the percentage of granulocytes is below 30, discontinuation of the drug should be strongly considered. A total white blood cell count which has fallen below 3,000 during treatment is also a good indication for discontinuing para-aminobenzoic acid.

A complete blood count should be carried out weekly and frequent urine examinations should be made. The fluid intake and output should be followed and regulated properly and the urine kept alkaline. The para-aminobenzoic acid blood concentration should be followed closely, and if it is above 60 mg. per hundred cubic centimeters the omission of a dose and the reduction of the maintenance dose should bring about the proper correction.

COMMENT

By considering the severity of the disease in the control cases in which the case fatality rate was 19 per cent, it was apparent that, in general, we were dealing with very severe tsutsugamushi. Many of the para-aminobenzoic acid patients were very toxic toward the end of the first week of the disease when treatment was being started. If the disease ran the usual course, as was seen in the controls, one would have expected them to have become more severely ill during the second week, as the second week is usually the worst in tsutsugamushi disease. This did not happen. Instead of the disease growing worse, there was improvement. After two to three days the temperature started to fall by lysis and there was definite symptomatic improvement. In 2 patients we observed the disappearance of a pronounced lymphadenopathy after three days of para-aminobenzoic acid therapy. There were few complicating conditions in the para-aminobenzoic acid cases and many in the controls. The usual course of disease seemed to be definitely altered and made much milder by para-aminobenzoic acid.

The secondary temperature rise which occurred in 3 patients after para-aminobenzoic acid had been discontinued was associated with a recurrence of the generalized lymphadenopathy and a return of some of the original symptoms. It resembled mild tsutsugamushi disease and, since nothing else could be found to account for it, we regarded it as a mild relapse. As it occurred after the para-aminobenzoic acid had been discontinued, and after the patient had been afebrile for several days (except in case 29), it seemed to be added evidence that para-aminobenzoic acid had had a definite suppressive action on the tsutsugamushi disease. These patients probably were not able to develop sufficient immunity to the disease to prevent a relapse after para-aminobenzoic acid was discontinued.

Although the number of cases treated in this series is not large, the results indicate that para-aminobenzoic acid has been decidedly effective and should be used in all cases of tsutsugamushi disease.

Since all the rickettsial diseases conform to the same basic pattern, it is not unlikely that para-aminobenzoic acid may prove to be a general antirickettsial agent. The work of Anigstein and Bader [9] showing that para-aminobenzoic acid had a protective action on guinea pigs inoculated with spotted fever, and the report by Rose and his associates [10] on the clinical case of spotted fever treated with para-aminobenzoic acid suggest that the drug may be effective against this disease also. Thus para-aminobenzoic acid appears to be widening the field of chemotherapy by attacking a new group of diseases for which there has been no cure.

9. Anigstein, L., and Bader, M. N.: Para-Aminobenzoic Acid—Its Effectiveness in Spotted Fever in Guinea Pigs, Science **101**: 591-592, 1945.

10. Rose, H. M.; Duane, R. B., and Fischel, E. E.: The Treatment of Spotted Fever with Para-Aminobenzoic Acid, J. A. M. A. **129**: 1160-1161 (Dec. 22) 1945.

SUMMARY

1. Eighteen patients with tsutsugamushi disease were treated with large doses of para-aminobenzoic acid, and their clinical courses were compared to 16 alternate controls who received the standard treatment.

2. The difference between the course of the disease in the para-aminobenzoic acid cases and the controls was striking. The patients who were given para-aminobenzoic acid had fewer days of fever, less severe symptoms and complicating conditions, a shorter period of convalescence and a lower case fatality rate.

3. It is concluded that para-aminobenzoic acid administered in the first week of disease is an effective therapeutic agent against tsutsugamushi disease.

Clinical Notes, Suggestions and New Instruments

THE USE OF NEOSTIGMINE IN THE TREATMENT OF THE GUILLAIN-BARRÉ SYNDROME

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The Guillain-Barré syndrome has recently received increasing attention and is more frequently being differentiated as a distinct entity from similar conditions such as poliomyelitis. The use of neostigmine by Kabat and Knapp[1] in the treatment of poliomyelitis prompted the use of neostigmine in this case of the Guillain-Barré syndrome.

Neostigmine methylsulfate (1 : 2,000 solution) was given hypodermically in dosages varying from 2 to 8 cc. daily, with an average of 5 to 6 cc. being given in divided doses of 1 to 2 cc. (0.5 to 1 mg.) at two to three hour intervals. The action occurs rapidly, so that within fifteen minutes muscle spasm and incoordination are measurably reduced. The decrease in "proprioceptive reflex hyperirritability" enables a wider range of passive motion, as shown by the Kernig test, and the decrease in "skeletal muscle hypertonus" permits the patient a wider range of active motion.[1] The therapy also enables a more coordinated active movement. Atropine sulfate was given in a dosage of 1/300 to 1/150 grain (0.2 to 0.1 mg.) intermittently in the beginning of the therapy with the purpose of offsetting any possible undesirable effects of the neostigmine. No change in the efficacy of the neostigmine therapy was produced by the atropine, but no undesirable side actions were observed from the neostigmine after the atropine was discontinued. The former tends to confirm Kabat and Knapp's belief that the action of neostigmine depends on the alteration of function of synapses in the spinal cord rather than in the myoneural junction.[1]

Although Guillain felt that this disease was always benign,[2] there is ample evidence in the literature now that this is not the case. Various authors have reported mortality rates of from 8 to 30 per cent in their series, and late residual complications have been reported in as high as 31 per cent (5 cases) of a small series of 16 cases with one death in the same series of Taylor and McDonald.[3] Bradford, Bashford and Wilson[4] reported 8 deaths in 30 cases (26 per cent) and Gilpin, Moersch and Kernohan[5] recorded a 20 per cent mortality rate in their series, while Baker[6] reported a 10 per cent mortality rate (3 cases) in his series of 33 cases. These facts all tend to encourage one to use an active course of therapy rather than a course of expectant observation with only supportive therapy, and it is hoped that the present proposed neostigmine therapy will fulfil this aim.

1. Kabat, H., and Knapp, M. E.: The Use of Prostigmine in the Treatment of Poliomyelitis, J. A. M. A. **122**: 989-995 (Aug. 7) 1943.
2. Guillain, G.: Radiculoneuritis with Acellular Hyperalbuminosis of the Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **36**: 975-990 (Nov.) 1936.
3. Taylor, E. W., and McDonald, C. A.: Syndrome of Polyneuritis with Facial Diplegia, Arch. Neurol. & Psychiat. **27**: 79-112 (Jan.) 1932.
4. Bradford, J. R.; Bashford, E. S., and Wilson, J. A.: Acute Infective Polyneuritis, Quart. J. Med. **12**: 88-126, 1918-1919.
5. Gilpin, S. F.; Moersch, F. P., and Kernohan, J. W.: Polyneuritis: A Clinical and Pathological Study of a Special Group of Cases Frequently Referred to as Instances of Neuronitis, Arch. Neurol. & Psychiat. **35**: 937-963 (May) 1936.
6. Baker, A. B.: Guillain-Barré's Disease, Journal-Lancet **63**: 384-398 (Dec.) 1943.

REPORT OF CASE

History.—T. S., a white boy aged 8 years, had enjoyed good health except for chickenpox and whooping cough, which were experienced without residuals at 6 years of age. The child's parents and 2 older siblings also were healthy. The remainder of the past history was noncontributory.

Present Illness.—The child's first difficulty developed on Feb. 14, 1944, when a symmetrical paresis of the legs began. This slowly increased in severity and progressed upward during the next three days, finally involving his back and arm muscles. Concomitantly with this he had paresthesias and radicular pains in his legs. On February 18 he developed a severe headache, and the muscular involvement spread to the neck and the muscles of deglutition, causing difficulty in swallowing. The paresis progressed into a complete paralysis until on February 23 he was totally paralyzed except for the muscles of facial expression and some slight rotatory movement of the neck. In spite of the severe symptomatology there were no mental symptoms or findings suggestive of a septic process. On February 23 the patient was admitted to the Philadelphia Hospital for Contagious Diseases as a case of possible poliomyelitis.

Physical Examination.—On admission the child appeared asthenic and weighed 70 pounds (32 Kg.). His temperature was 98.6 F., the pulse rate was 80 and the respiratory rate was 18. Complete paralysis was present except as mentioned. There was a generalized depression of all reflexes. The abdominal reflexes and the knee and ankle jerks were completely absent bilaterally. Both the Kernig and Brudzinski tests were positive bilaterally. The inability to swallow or extrude saliva caused frequent accumulation of saliva in the patient's throat, which made oral suctioning necessary. Urinary and bowel incontinence were also present. The remainder of the physical examination was negative.

Laboratory Examination.—Data on admission and subsequent determinations are listed in the accompanying table.

A spinal tap revealed the acellular hyperalbuminosis or cell protein dissociation in the spinal fluid characteristic of the Guillain-Barré syndrome. The protein was elevated to 365 mg. per hundred cubic centimeters, whereas the cell count was within normal limits (3 lymphocytes per cubic millimeter). Both blood and spinal fluid cultures were sterile.

The treatment consisted in intravenous glucose feedings and supplemental doses of thiamine hydrochloride daily. The patient improved slowly, and by February 28 he was able to swallow again but continued to have pain and paresthesias of itching and tingling in his legs. On February 29 he was able to move his arms and legs a slight amount in a very slow incoordinate manner. Improvement occurred during the next three days in the control of his hands and arms, and he was able to lift his head up slightly on March 4. Severe pain in the muscles of his legs continued, and at times he cried out in pain. On March 6 he was transferred to the Philadelphia General Hospital.

On admission he was afebrile, but his pulse was 120 per minute and respirations were 22 per minute. Neurologic examination revealed that his eyes were normal aside from slight lateral nystagmus. The base of the uvula deviated slightly to the right on elevation. A slight rigidity of the neck was present. Alleviation of the paralysis was occurring with most pronounced recovery in the cephalid portion of the body, where slight movements of the hands and arms were possible, although poorly coordinated. Slight flexion and extension of the thighs were possible, but movement of the lower legs was almost imperceptible (— 3), abdominals and cremasteric reflexes were present, but knee and ankle jerks were absent. Babinski tests were normal. Deep muscle and tendon pain were increased in all extremities, but sense position was normal. The Kernig sign was positive bilaterally with a motion of