backbone of American practice will continue to be the individual practitioner in the community and in the segment of the community where he is immediately available to the family. With regard to preventive medical service, if early diagnosis and early treatment will be stimulated by these methods we are contributing to preventive medicine.

DR. ADAMS: The discussion this morning has been limited to industrial and state plans, but there are several other types of plans which may have more universal application than any of these. First probably would come the plans organized and sponsored by physicians themselves, some of which are operating successfully throughout the country, and then other statewide medical association plans such as in the state of New Jersey. Third are the commercial insurance plans, of which there are many, one of which is operating satisfactorily in our company. Their rates are considerably higher than in our employee organizations, but they are an answer in some states where employee organizations are not permitted.

THE THERAPEUTIC EFFECT OF PARA-AMINOBENZOIC ACID IN LOUSE BORNE TYPHUS FEVER

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Many efforts have been made to find a substance of therapeutic value in typhus fever. The papers in the literature which cite the effects of various agents have been discussed in a recent editorial.[1] It is our purpose in this report to present the results of the treatment of classic epidemic louse borne typhus fever with para-aminobenzoic acid.

The possible therapeutic value of para-aminobenzoic acid was suggested by Snyder, Maier and Anderson,[2] who reported that the mortality of experimental murine typhus in white mice was reduced by the oral administration of the drug. In their experiments approximately 80 per cent of the untreated control mice died of murine typhus after intraperitoneal inoculation of infected yolk sac suspensions (Wilmington strain),[3] whereas more than four fifths of the mice which were fed on a ration containing para-aminobenzoic acid survived the same infecting dose of yolk sac. Even when the oral administration of para-aminobenzoic acid was started one or two days after the inoculation of rickettsias, there was a difference between the treated and the control groups.[4] Although large amounts of para-aminobenzoic acid were required to demonstrate this effect, the results were sufficiently encouraging to stimulate the clinical trial of the drug, which has been undertaken in the United States of America Typhus Commission ward at the Fever Hospital, Cairo, Egypt.[5] After the clinical study was in progress we received other reports which extended the observations of the effect of para-aminobenzoic acid in experimental typhus. Andrewes, King and van den Ende,[6] in testing a large number of compounds, observed a slight effect when maximal doses of para-aminobenzoic acid were given to mice infected by the intranasal route. Hamilton, Plotz and Smadel [7] noted a definite inhibitory effect of high concentrations of para-aminobenzoic acid on the growth of typhus rickettsias in the yolk sac membrane of developing chick embryos. The results of the experimental work cited are in agreement with the clinical observations which form the basis of this report.

CLINICAL STUDY OF TYPHUS FEVER IN EGYPT

Through the courtesy of the Egyptian officials, the United States of America Typhus Commission established an experimental ward in the Cairo Fever Hospital early in 1943, at the beginning of one of the most severe epidemics of typhus which Egypt has experienced. More than 2,000 cases were admitted to the Fever Hospital in May 1943 at the peak of the outbreak. Although the epidemic was less extensive in 1944, there was an excellent opportunity throughout both seasons to study the clinical aspects of the disease.

In order to provide a background for the evaluation of para-aminobenzoic acid therapy, the experience with louse borne typhus cases in 1943 and 1944 is reviewed briefly. All the cases discussed in this report were considered to be certain cases of typhus fever on the basis of clinical evidence. The diagnosis in nearly every instance was supported by definite laboratory results (rise in titer of Weil-Felix and complement fixation tests). In some cases the direct isolation of rickettsias was successful either from blood or from lice fed on the patients during the febrile period. All the strains which have been isolated from patients in the Commission ward have exhibited the characteristics of typical louse borne typhus both in 1943 [8] and in 1944.[9]

During the two seasons, 159 patients with typhus were admitted to the Commission ward. Of this number there were 44 patients who may be compared with the cases in the treated series, in that they were unvaccinated Egyptian males between the ages of 18 and 48, who entered the ward before the end of the seventh day of illness. They received no therapy other than nursing

From the United States of America Typhus Commission Unit at the Fever Hospital, Cairo, Egypt.

Lieutenant Colonel Snyder is a member of the staff of the International Health Division of the Rockefeller Foundation, on leave.

The supplies of para-aminobenzoic acid were made available by the International Health Division of the Rockefeller Foundation and Dr. Herald R. Cox (Lederle Laboratories).

The authors received generous cooperation from the officials of the Egyptian Ministry of Public Health, who facilitated the studies of the United States of America Typhus Commission in Egypt.

The director of the Cairo Fever Hospital, Dr. M. A. B. Demerdash Bey, made possible the establishment of the United States of America Typhus Commission ward and laboratory in his institution. His extensive experience with typhus, his continued interest in the work and his helpful advice and cooperation were of the greatest value.

In 1943 numerous chemical determinations for the cases in this study were performed by the 38th General Hospital laboratory staff.

In 1943 most of the serologic tests for the commission ward were performed by Col. Harry Plotz, M. C., A. U. S., and Capt. B. L. Bennett, Sn. C., A. U. S., with the technical assistance of Sergeant Guin.

Technical assistance was given by Sergeants Stephens and Dworkowitz and Corporals Stearman, Hogan, Cassell and Friedberg in the laboratory work of the commission ward.

1. Chemotherapy of Murine Typhus, editorial, J. A. M. A. **125**: 633 (July 1) 1944.

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

3. Cox, H. R.: Use of Yolk Sac of Developing Chick Embryo as Medium for Growing Rickettsiae of Rocky Mountain Spotted Fever and Typhus Groups, Pub. Health Rep. **53**: 2241-2247, 1938.

4. These experiments were performed in the Laboratories of the International Health Division of the Rockefeller Foundation, New York.

5. Bayne-Jones, Stanhope: The United States of America Typhus Commission, Army M. Bull. No. 68, pp. 4-15, July 1943.

6. Andrewes, C. H.; King, H., and van den Ende, M.: A Chemotherapeutic Agent Active Against the Rickettsiae of Typhus, British report from the National Institute for Medical Research, Hampstead, London, 1943, quoted from Hamilton, Plotz and Smadel.[7]

7. 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, report to the Director of the United States of America Typhus Commission, Dec. 16, 1943, to be published.

8. Letter of Dr. N. H. Topping to the Director of the United States of America Typhus Commission dated Nov. 6, 1943. Plotz, H.; Wertman, K., and Bennett, B. L.: The Serological Pattern in Epidemic Typhus Fever: 1. The Development of Complement Fixing Antibodies. From the Division of Virus and Rickettsial Diseases, Army Medical School, Army Medical Center, Washington, D. C., December 1943, to be published.

9. Unpublished observations of the authors.

care, fluids and appropriate measures to combat specific complications which occurred during the course of hospitalization. This group of patients is designated as the "untreated" group.

ESTIMATION OF THE SEVERITY OF ILLNESS

After discharge from the hospital each patient was classified on the basis of his clinical course. The principal factors which influenced the estimation of severity were the intensity of subjective symptoms (headache, generalized bodily aches and pains, tinnitus, deafness), the degree of prostration, the extent of central nervous system involvement (mental dulness, stupor, coma, incontinence of urine and feces, abnormal neurologic signs), the severity of cardiovascular system involvement (hypotension, tachycardia, peripheral vascular failure, myocardial damage) and finally occurrence of urinary retention, oliguria, nitrogen retention, bronchopneumonia, otitis media, parotitis, furunculosis and gangrene. With these factors in mind the following classification was made:

B. Cases with minimal symptoms and signs, yet definitely diagnosed as typhus on clinical evidence.

C. Cases of moderate severity, showing slight prostration, central nervous system involvement, cardiovascular changes or mild complications.

TABLE 1.—*Forty-Four "Untreated" Cases of Typhus Classified According to Clinical Severity* *

Number and Percentage of Cases in Each Classification				
B	C	D	E	F
1 (2%)	12 (27%)	18 (41%)	5 (11%)	8 (18%)

* Unvaccinated Egyptian males, aged 18-48 inclusive, admitted to the ward in the first week of illness. The criteria of classification are described in the text. This footnote applies also to tables 2, 3, 4 and 6.

D. Severe typhus cases with pronounced prostration, central nervous system involvement, cardiovascular changes or serious complications.

E. Cases of such severe illness that a fatal outcome was expected at some point in the clinical course.

F. Fatal cases.

SEVERITY OF "UNTREATED" TYPHUS FEVER

The classification of the 44 "untreated" cases is shown in table 1. One case was B, 12 were C, 18 were D; 5 were E and 8 were F. This distribution of severity in the 44 "untreated" cases was parallel with that encountered in the entire experience of our ward as regards unvaccinated "untreated" patients in the same, age group, irrespective of the day of illness at the time of admission to the ward. The rarity of mild cases is noteworthy.

TREATMENT WITH PARA-AMINOBENZOIC ACID

Twenty cases of typhus were treated with sufficiently large amounts of para-aminobenzoic acid to produce a measurable concentration of the substance in the blood. Before arrangements were made to determine blood levels of para-aminobenzoic acid, 3 patients were given small doses which are considered as entirely inadequate in the light of subsequent studies. Those cases are not included in this report. The treated cases are considered in three groups:

Group 1. Controlled series: 10 patients received para-aminobenzoic acid while the alternate patients were given routine ward care only.

Group 2. Consecutive series: 7 patients were treated with para-aminobenzoic acid; no alternate control cases were included.

Group 3. Miscellaneous cases: a group composed of 2 patients who had been ill with typhus longer than seven days at the time treatment was begun and 1 patient, aged 70, who received para-aminobenzoic acid in the third twenty-four hours of his illness.

Selection of Patients.—The patients selected for the controlled series and the consecutive series (groups 1 and 2) were unvaccinated males between 18 and 48 years of age, who had no obvious complicating conditions at the time of admission, whose date of onset of illness was clear and who were not later in their disease than the seventh twenty-four hours.[10]

Fifth and sixth day cases were accepted in the study group only if it was possible to make a clinical diagnosis of typhus at the time of inclusion in the series. Earlier cases were accepted without a positive clinical diagnosis at the time of admission if relatives or close personal contacts were known to have had typhus recently. Four cases were obtained from a group of family contacts who reported to the ward daily; their onset of illness actually occurred while they were under observation.

In the controlled series the decision as to which patients would receive para-aminobenzoic acid was made automatically. Alternate patients were treated in the order in which they entered the hospital. Two exceptions to this rule occurred. The series was interrupted by error when 2 patients were treated consecutively and by arbitrary decision when a man whose wife and father both died of typhus was treated with para-aminobenzoic acid although the series required a control (case 6921).

Plan of Treatment.—In all instances para-aminobenzoic acid was administered by mouth. The initial dose varied from 4 to 8 Gm. In the majority of cases the initial dose was followed by 2 Gm. every two hours unless the concentration in the blood attained excessive values. Adjustments in dosage were made in relation to fluid intake and urinary output. The fluid intake in nearly all instances was adequate to maintain the output of urine between 1,500 and 3,000 cc. in twenty-four hours.

The effort was made to keep the concentration of para-aminobenzoic acid in the blood between 10 and 20 mg. per hundred cubic centimeters. Para-aminobenzoic acid is absorbed and excreted very rapidly, so that a two hourly schedule of administration was decided on as that most likely to produce a relatively constant blood level. Determinations made at various times during treatment indicated that the two hourly schedule was effective in maintaining a satisfactory concentration of para-aminobenzoic acid throughout the period of therapy.

Para-aminobenzoic acid was continued for varying lengths of time in the first cases. Subsequently it was decided that treatment should be continued until the patient's rectal temperature was 37.5 C. (99.5 F.) or less for twenty-four hours. The average amount of

10. The study was restricted to cases in the first week of illness for two principal reasons. The response to para-aminobenzoic acid in the first few cases was not apparent for several days. There was no abrupt, dramatic change such as that produced by sulfonamide drugs in pneumococcic pneumonia, for example. It seemed unlikely that late cases could be treated with any prospect of evaluation of results unless a very much larger group of cases could be observed than the commission ward would accommodate. Furthermore, the great majority of cases in an epidemic can be diagnosed by the end of the seventh day. This time was arbitrarily chosen, therefore, as the basis of selection of cases.

para-aminobenzoic acid for each case (groups 1 and 2) was approximately 127 Gm. The patients who are the subject of discussion in this study received para-aminobenzoic acid for at least three days.

Nausea and vomiting attributable to para-aminobenzoic acid occurred in the first few cases. Thereafter, in order to lessen gastric irritation, sufficient sodium bicarbonate was given to neutralize the para-aminobenzoic acid. The acidity of the urine was determined at least once daily during para-aminobenzoic acid therapy. The amount of sodium bicarbonate was varied as required to keep the urine approximately neutral in reaction. After this plan was adopted, vomiting was encountered very infrequently.

Para-aminobenzoic acid was available in tablets of 0.5 Gm. each and in capsules of 0.3 Gm. each. Neither form was suitable for administration to typhus patients, who could not be persuaded to swallow the large number of tablets or capsules required for each dose; but they took powdered para-aminobenzoic acid readily if it was suspended in water or partially dissolved in a sufficient volume of 5 per cent sodium bicarbonate solution to render the mixture slightly alkaline. The usual amount was 2 Gm. of powdered para-aminobenzoic acid with 25 cc. of sodium bicarbonate solution. After swallowing the mixture, the patient was quickly given water to take away the slightly unpleasant taste of the drug. This method of administration was entirely satisfactory in most instances. Two patients, however, took their initial doses with difficulty, and no further attempt was made to treat them because of their uncooperative attitude. They have not been included in this report.

TABLE 2.—*Comparison of the Clinical Severity of Nine "Untreated" Control Cases and Ten Cases Treated with Para-Aminobenzoic Acid in Group 1*

	Number and Percentage of Patients in Each Classification				
	B	C	D	E	F
"Untreated" control cases.....	0	1 (11%)	3 (33%)	1 (11%)	4 (44%)
Cases treated with para-aminobenzoic acid.....	8 (80%)	1 (10%)	1 (10%)	0	0

Method of Determination of Para-Aminobenzoic Acid in the Blood.—The blood levels refer to free para-aminobenzoic acid as determined by Marshall's and Litchfield's procedure for sulfanilamide.[11] The standard solution of sulfanilamide was replaced by a standard of para-aminobenzoic acid. For some of the tests a Duboscq colorimeter was used; for the majority, however, a Coleman spectrophotometer was employed.

The Results of Treatment with Para-Aminobenzoic Acid.—In group 1, of the 10 patients who received para-aminobenzoic acid, 8 were classified as B cases, 1 was C and 1 was D. Of the 9 alternate control cases, 1 was C, 3 were D, 1 was E and 4 were F (table 2). The temperature charts of the patients in group 1 are shown in charts 1 and 2. All temperatures were taken rectally, with a single exception, patient 5768, chart 2, the values for the nineteenth day to the twenty-fourth day indicating oral temperatures. The solid line beneath the temperature curve shows the period of administration of para-aminobenzoic acid.

11. Marshall and Litchfield, quoted from technical manual Methods for Laboratory Technicians, War Department, Oct. 17, 1941, p. 134.

Group 2. The results of this consecutive series are similar to those in group 1. Of 7 cases 3 were B, 3 were C and 1 was D. Temperature curves are shown in chart 3. The temperature curve of a typical untreated case (12412) appears at the top of chart 2 for comparison with the para-aminobenzoic acid cases.

The 17 cases in groups 1 and 2 are contrasted with the 44 "untreated" cases in table 3, which shows the incidence of clinical severity in the two groups.

Group 3. Two patients in this group were treated for the purpose of extending the experience with para-aminobenzoic acid to patients admitted in the eighth and ninth day of illness. One patient, 6546, was started on para-aminobenzoic acid in his ninth day. He became progressively worse and died on the thirteenth day.

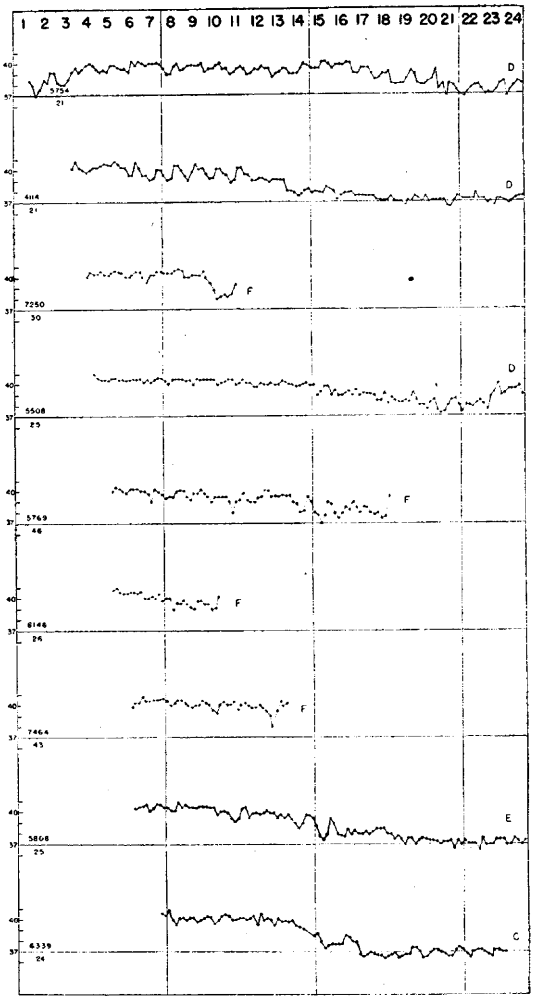

Chart 1.—Group 1 controls. Temperature charts of 9 "untreated" control typhus patients, arranged according to the day of illness at the time of admission to the hospital. The clinical classification of severity appears at the end of the fever curve. Values indicate rectal temperature in degrees centigrade. The numbers across the top of the chart refer to the day of illness. The hospital number and age of the patient appear at the beginning of each temperature curve.

Patient 7,100, admitted at the end of his eighth day of illness, was severely dehydrated. His urine contained many red cells on admission, but these disappeared in the next two days. The clinical course was complicated by a secondary rise in temperature associated with pain in the right flank, which may have been related to previous renal or ureteral disease.

Finally, patient 6,811, a man aged 70, was given para-aminobenzoic acid in the third twenty-four hours of

his illness to ascertain whether para-aminobenzoic acid would affect the outcome. The patient died on the eleventh day; aspiration of para-aminobenzoic acid and sodium bicarbonate may have contributed to the death of this patient. His case is discussed later. Temperature curves are shown in chart 4.

The pathology of the 2 fatal cases in this group will be described in a later United States of America Typhus Commission report by Lieut. Comdr. W. B. McAllister Jr. (MC), U.S.N.R.

The experience with para-aminobenzoic acid is summarized in tables 4 and 5, which show the clinical

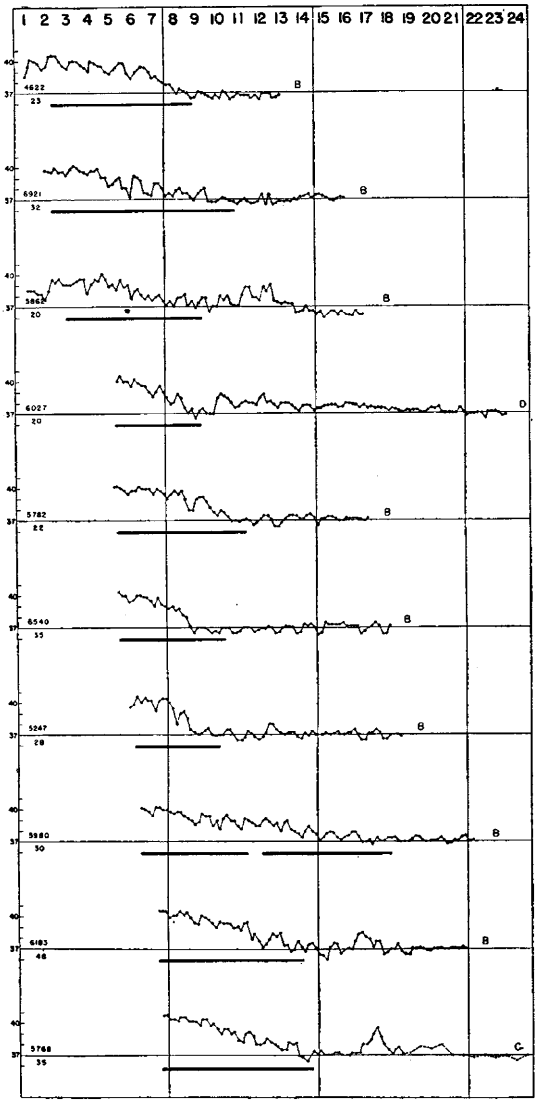

Chart 2.—Group 1 para-aminobenzoic acid cases. Temperature charts of 10 typhus patients who received para-aminobenzoic acid, arranged according to day of illness at the time para-aminobenzoic acid was started. The period of administration of para-aminobenzoic acid is indicated by the heavy line beneath the temperature curve. The clinical classification of severity appears at the end of the fever curve. Values indicate rectal temperature in degrees centigrade. The numbers across the top of the chart refer to the day of illness. The hospital number and age of the patient appear at the beginning of each temperature curve.

severity, duration of fever, total amount of para-aminobenzoic acid, complications and laboratory data.

Effect of Para-Aminobenzoic Acid on the Rash of Typhus.—Fifteen patients who received para-aminobenzoic acid had a definite rash, which was not as extensive, however, as that seen in the majority of "untreated" patients. The rash was considered to be questionable in 3 treated patients (4622, 14868 and 15080). No rash was seen at any time in 2 of the treated patients whose skins were very dark (5247 and 15000).

It was interesting to note that 2 patients who were treated in the second and third day of illness nevertheless developed a rash which was distinctive of louse borne typhus in every particular except that the lesions were relatively few in number and tended to disappear quickly.

Effect of Para-Aminobenzoic Acid on the White Blood Cells.—One patient, not tabulated in the series, developed a low white blood cell count (2,900) after twenty-four hours of treatment, and para-aminobenzoic acid therapy was discontinued. One other patient, 6540, likewise developed a low white blood cell count (2,950) but in his case the low count did not occur

TABLE 3.—*Comparison of the Clinical Severity of Forty-Four "Untreated" Cases and Seventeen Cases Treated with Para-Aminobenzoic Acid in Groups 1 and 2 Combined*

	Number and Percentage of Patients in Each Classification				
	B	C	D	E	F
44 "untreated" cases	1 (2%)	12 (27%)	18 (41%)	5 (11%)	8 (18%)
17 cases treated with para-aminobenzoic acid	11 (65%)	4 (23%)	2 (12%)	0	0

TABLE 4.—*Comparison of the Average Duration of Fever* and Clinical Severity of Forty-Four "Untreated" Cases and Seventeen Cases Treated with Para-Aminobenzoic Acid (Groups 1 and 2)*

	Average Duration of Fever, Days		
		Seventeen Cases Treated with Para-Aminobenzoic Acid	
Classification of Severity	Forty-Four "Untreated" Cases	Primary Continuous Febrile Period Only	Primary and Secondary Febrile Periods Combined
B	18	11	11
C	15	11	15.5
D	19.5	10.5	14.5
E	23.5	..	..
F	(13)	..	..
Average for all cases except F	18.5	11	12.5

* A rectal temperature above 37.5 C. (99.5 F.) is considered as evidence of fever.

until he had been afebrile for two days. Para-aminobenzoic acid had been discontinued twenty-four hours before the low value was obtained. The count fell further to 1,850 and rose thereafter to 3,500 at the time of discharge. The return of the white blood cell count toward normal values was slow in both patients, but neither one showed any other evidence of untoward drug reaction, and both had a mild, uncomplicated course. The differential count did not reveal any significant alteration in the relative percentages of polymorphonuclear leukocytes and lymphocytes. In the other para-aminobenzoic acid cases a tendency for the white blood cell count to drop to values between 5,000 and 3,500 was observed.

Effect of Para-Aminobenzoic Acid on Red Blood Cells and Hemoglobin.—No changes in red cell count or hemoglobin estimation were encountered in the para-aminobenzoic acid cases that were not consistent with typhus

Effect of Para-Aminobenzoic Acid on Kidney Function.—There was no evidence in any of the para-aminobenzoic acid cases that the drug had produced renal complications. Indeed the low incidence of nitrogen retention [12] (12 per cent) in the treated cases (groups 1 and 2) as contrasted to that in the "untreated" cases (44 per cent) suggests that para-aminobenzoic acid may prevent renal damage in typhus. This subject receives further consideration in the comment.

Secondary Rise in Temperature.—In 9 cases, after the temperature had declined either to normal or at least to a point definitely below the expected value for typhus cases, para-aminobenzoic acid was discontinued.

A secondary rise in temperature was then observed, varying from minimal brief elevations above normal to moderately high fever of several days' duration. When this phenomenon was first encountered, several explanations were considered: (*a*) that it represented a recurrence of typhus, that is to say, a release phenomenon related to the premature withdrawal of the inhibitory effect of para-aminobenzoic acid on the typhus rickettsias; (*b*) that there might be complicating infections; (*c*) that the fever was attributable to para-aminobenzoic acid alone. After careful survey of all

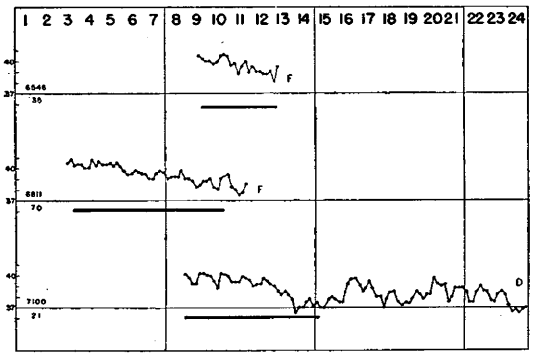

Chart 3.—Group 3 para-aminobenzoic acid cases. Temperature charts of 3 typhus patients who received para-aminobenzoic acid. Other details are explained in the description of chart 2.

the information available, it seems likely that the secondary rise was a manifestation of typhus, as postulated in *a*. Unfortunately this point was not investigated by inoculation of animals with blood taken during the secondary febrile period. One patient, 5768, had an exacerbation of chronic amebic dysentery, which offers a possible explanation of the secondary fever, although the latter did not closely coincide with the onset of diarrhea.

The high incidence of secondary febrile periods raises the question whether therapy was adequate in amount and duration. The patients who developed the secondary fever might have had such a widespread dissemination of rickettsias that they would have been D, E or F cases if untreated and might have required longer, more intensive treatment with para-aminobenzoic acid for elimination of the secondary rise in temperature.

A striking feature of the secondary febrile period was the paucity of symptoms and signs of typhus of a degree comparable to the height of the temperature. Mild headache and slight anorexia were the only constant complaints.

12. Blood nonprotein nitrogen values of 45 mg. per hundred cubic centimeters or higher are interpreted as evidence of nitrogen retention. Among the 44 "untreated" cases, blood nonprotein nitrogen determinations were made in 32 cases. Of these 14, or 44 per cent, were greater than 45 mg. per hundred cubic centimeters at some period in the course of the illness.

Importance of Early Treatment.—The best results were obtained when para-aminobenzoic acid was started on the second and third days of illness. Some effect was noted when treatment was begun as late as the seventh day. In this study the only ninth day patient who was treated, 6546, died on the thirteenth day despite large doses of para-aminobenzoic acid. It is clear that a very much more extensive experience with para-aminobenzoic acid would be required to define the limits within which beneficial results might be expected. The importance of early treatment is quite obvious, however.

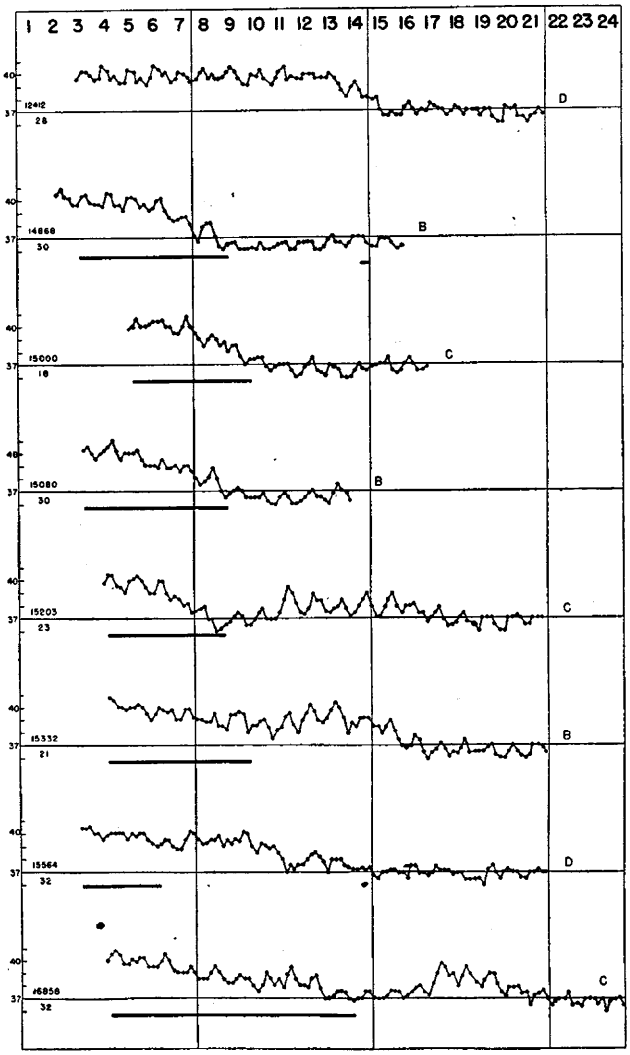

Chart 4.—Group 2 para-aminobenzoic acid cases. Temperature charts of 7 cases of typhus treated with para-aminobenzoic acid consecutively without alternate control cases. A typical fever chart of an untreated patient, 12412, appears at the top of the chart for comparison with the treated cases. Other details are explained in the description of chart 2.

Influence of Age on Results Obtained with Para-Aminobenzoic Acid.—Only 1 patient was given para-aminobenzoic acid who was outside the 18 to 48 age group. This patient was 70 years old, and treatment was started on the third day of illness. Although he received a large amount of para-aminobenzoic acid, the patient died. His case is discussed later.

Within the 18 to 48 age group, among the cases treated before the end of the seventh day of illness, the increase in age is not associated with increase in severity of illness. In the treated series the average age in the B cases is 29 years, C cases 27 years and

D cases 26 years. In the "untreated" series the average age in C and D cases is 25 years, in E cases 26 years and in F cases 33 years. Table 6 shows the relation of average age to clinical severity for both groups.

Contraindications to Para-Aminobenzoic Acid Therapy.—A white blood cell count below 3,000 has been regarded as a definite contraindication to further para-aminobenzoic acid therapy. Since there was a general tendency toward leukopenia, and since 2 patients had counts below 3,000, it is important to obtain daily white blood cell counts during the administration of para-aminobenzoic acid.

In the presence of severe dehydration and oliguria the usual plan of treatment (initial dose of 4 to 8 Gm. of para-aminobenzoic acid followed by 2 Gm. every two hours) is likely to produce excessively high blood levels. Until the output of urine has been brought at least to 1,500 cc. in twenty-four hours, the schedule of dosage should be modified according to the values obtained by frequent determinations of the blood level.

In 3 instances very high concentrations of para-aminobenzoic acid in the blood were encountered. The maximum value in the series was 49 mg. per hundred cubic centimeters. One patient became very drowsy and disoriented when his blood level was approximately 40 mg. per hundred cubic centimeters. Another patient became delirious when his blood level was 35 mg. per hundred cubic centimeters. Although these findings could be ascribed solely to typhus, nevertheless they were regarded as toxic manifestations of para-aminobenzoic acid because they promptly disappeared when the blood level fell to a low value.

If a patient is too weak or stuporous to swallow properly, the administration of para-aminobenzoic acid by mouth should not be attempted, since there is the possible danger of severe tracheitis from aspiration of the drug. One patient, 6811, aged 70, became so prostrated that he was unable to swallow rapidly. As a consequence of overzealous nursing he probably aspirated a fairly large amount of para-aminobenzoic acid and sodium bicarbonate. Oral therapy was discontinued as soon as this was discovered and penicillin was administered, but the patient died twenty-four hours later. At autopsy there was a minimal amount of pneumonitis; the principal finding was intense tracheitis and bronchitis, which was attributed largely to the aspiration of para-aminobenzoic acid and sodium bicarbonate. Although a stomach tube was not employed for the administration of para-aminobenzoic acid in the cases in this series, it is possible that the severe tracheitis of patient 6811 might have been avoided if a tube had been passed when difficulty in swallowing first developed.

TABLE 5.—*Summary of the Data from Twenty Cases Treated with Para-Aminobenzoic Acid* [1]

Case No.	Age, Years	Body Weight, Lbs.	Duration of Illness When Treatment Began, Days	Duration of Treatment, Days	Total Amount Para-Aminobenzoic Acid Given, Gm.	Duration of Continuous Fever, Days	Duration of Secondary Fever, Days	Lowest W. B. C., per Cu. Mm.	Maximum N.P.N.[3] Mg. %	Maximum Titer [2] Weil-Felix	Complement Fixation Epidemic	Complement Fixation Murine	Complications	Severity
4622	23	135	2	6½	168	8	0	7,500	30	640	1024*	16	None	B
6921	32	119	2	8½	182	9	0	5,800	31	640	512	Neg.	None	B
5862	20	132	3	6	154	12	0	4,900	24	1,280	128	..	None	B
14868	30	102	3	6	79	8	0	3,800	35	5,120	24	..	None	B
15564	32	123	3	3	62	13	0	4,700	63	640	1024*	256	Nitrogen retention;[4] ophthalmitis	D
15080	30	108	3	5½	92	8	0	4,550	..	640	....	..	None	B
15332	21	102	4	6	81	16	0	3,600	39	5,120*	1024	16	Otitis media; dental abscess	B
15203	23	114	4	4½	87	8	8	6,250	..	640	1024*	Neg.	None	C
16858	32	135	4	9½	216	13	6	3,300	36	2,560	1024*	Neg.	None	C
15000	18	100	5	4½	70	9	0	6,050	40	10,240	24	..	None	C
6027	20	123	5	4	94	8	8	5,600	29	5,120*	1024*	Neg.	Bronchopneumonia; ? transient heart failure; ? para-aminobenzoic acid intoxication	D
5782	22	125	5	6	146	10	0	5,650	32	5,120*	1024*	Neg.	None	B
6540	35	128	5	5	115	8	0	1,850	32	5,120	1024*	8	None	B
5247	28	125	6	4	100	9	1	5,100	43	2,560	1024*	256	None	B
5980	30	117	6	11	195	16	0	4,200	31	5,120*	1024*	Neg.	? Para-aminobenzoic acid intoxication	B
6183	48	125	7	6½	148	13	2	3,350	39	80	1024*	Neg.	Mild renal insufficiency	B
5768	35	110	7	7	164	13	4	3,450	46	160	1024*	256	Nitrogen retention;[4] exacerbation of chronic amebic dysentery	C
6546	35	122	9	3½	71	13	..	4,150	74	5,120*	Neg.	Neg.	Nitrogen retention [4]	F
6811	70	123	3	7	103	11	..	4,500	67	Neg.	128*	Neg.	Nitrogen retention;[4] bronchopneumonia; peripheral vascular failure; acute tracheitis	F
7100	21	91	8	6½	104	23	0	5,500	45	5,120*	1024*	Neg.	Nitrogen retention;[4] ? chronic renal or ureteral disease	D

1. Groups 1 and 2 are arranged together according to the day of disease when treatment was started. Group 3 cases appear separately at the end of the table.
2. The serologic results indicate the maximum titers obtained from a series of serum samples taken at frequent intervals throughout the period of hospitalization. However, a complete series was not available for test in cases 14868, 15000, 15080, 15203 and 15332; it is probable that somewhat higher titers would have been obtained if more samples had been tested in these cases.
3. When high blood levels of para-aminobenzoic acid were encountered, the total nonprotein value has been corrected for the nonprotein nitrogen contributed by the presence of para-aminobenzoic acid.
4. Blood nonprotein nitrogen values of 45 mg. per hundred cubic centimeters or higher are interpreted as evidence of nitrogen retention in this report.
* This symbol indicates that the end point was not reached, the value being the highest dilution tested.

TABLE 6.—*Comparison of the Average Age and Clinical Severity of Forty-Four "Untreated" Cases and Seventeen Cases Treated with Para-Aminobenzoic Acid (Groups 1 and 2)*

Classification of Severity	Average Age: 44 "Untreated" Cases	Average Age: 17 Cases Treated with Para-Aminobenzoic Acid
B	18	29
C	25	27
D	24	26
E	26	..
F	33	..

Early in the experience with para-aminobenzoic acid it was considered that the presence or the development of a bacterial infection might constitute a contraindication to para-aminobenzoic acid therapy. For example, treatment with para-aminobenzoic acid was terminated in patient 15564 when he developed suppurative ophthalmia as a complication of late stage trachoma. It is not possible, however, to conclude that bacterial infections actually constitute a contraindication to para-aminobenzoic acid on the basis of the experience gained from the observation of the 20 cases in this study. At the present time the view is held that para-aminobenzoic acid probably should be continued in cases of typhus despite the occurrence of secondary bacterial infections.

The Use of Penicillin for the Treatment of Typhus Complicated by Bacterial Infections.—If organisms susceptible to the action of penicillin are encountered in secondary bacterial infections which may complicate typhus, the use of penicillin to supplement but not to replace para-aminobenzoic acid therapy is recommended rather than sulfonamide drugs for several reasons: (*a*) Sulfonamide drugs in experimental typhus seem to have a deleterious effect;[2] (*b*) para-aminobenzoic acid inhibits the action of sulfonamide drugs on bacteria in vitro, a fact which prompts the prediction that sulfonamide drugs would be ineffective against secondary bacterial infections when administered in the presence of a high blood concentration of para-aminobenzoic acid; (*c*) penicillin has been found to exert a beneficial effect in experimental typhus by Pinkerton and his co-workers, both in mice and in the infected yolk sacs of developing chick embryos.[13] Clinical trial of penicillin primarily for the treatment of louse borne typhus in the Commission ward has been attempted in 4 cases. It is not possible to decide on the basis of such a limited experience whether penicillin, given early and in large amounts, does or does not affect the course of typhus itself. Nevertheless, by reducing or eliminating bacterial infections penicillin may offer considerable help to a seriously ill patient who would not otherwise survive the extra burden of a bacterial infection superimposed on that of typhus.

Optimum Dosage of Para-Aminobenzoic Acid.—At this time it is not possible to draw any conclusions as to the optimum dosage of para-aminobenzoic acid. It can be stated on the basis of this study that the patients who received the arbitrarily chosen dosage had relatively mild typhus. Whether the amount of para-aminobenzoic acid was excessive or minimal is not known.

COMMENT

The experience through two seasons in Egypt has clearly shown the very low incidence of mild cases of typhus in the "untreated" Egyptian patients in the 18 to 48 age group who were admitted to the Fever Hospital. Only 1 such case was encountered among 44 "untreated" patients in the Commission ward, whereas fatal cases were 18 per cent of the total. By contrast, it was very striking to find 11 mild or B cases in the same group when para-aminobenzoic acid was given before the end of the seventh day of illness among 17 patients, none of whom died. At the time the patients in group 1 were being studied, the mortality from typhus among the unvaccinated male patients aged 18 to 48 inclusive in the general wards of the Fever Hospital was 30 per cent. Furthermore, there were four deaths among 9 "untreated" cases of group 1 in the Commission ward. There can be no question that the typhus which prevailed during the period covered by this study was very severe. The high incidence of mild cases in the treated groups was therefore all the more impressive.

The length of time between the onset of illness and discharge from the hospital provides another demonstration of the difference in severity of illness between "untreated" cases and para-aminobenzoic acid cases (groups 1 and 2). For the "untreated" group the average was thirty-two days, for the para-aminobenzoic acid cases only twenty-one days. The figures do not include fatal cases.

Close daily observation of the patients convinced us, more than scrutiny of fever curves or tabulations of frequency of complications, that para-aminobenzoic acid lessened the severity of typhus. The treated patients developed few of the troublesome complications which make typhus cases so difficult for the nursing staff. The low incidence of prostration, stupor, coma, fall in blood pressure, urinary retention, oliguria, nitrogen retention and incontinence of urine and feces, which are so prominent in the untreated cases, was particularly impressive from the clinical point of view.

The drug appears to be quite safe for human administration. High blood levels (up to 49 mg. per hundred cubic centimeters) were accompanied by minimal constitutional effects. No detectable impairment of kidney function attributable to para-aminobenzoic acid was encountered in any of the cases. That typhus frequently produced severe impairment of renal function was a characteristic observation in the experience of the Commission ward. Therefore, any agent which might augment the tendency of typhus to produce oliguria and nitrogen retention is to be regarded with great suspicion. The absence of any undesirable effect of para-aminobenzoic acid on kidney function in this series is a very reassuring finding.

We wish to emphasize our conviction that a careful daily record of the fluid intake and urinary output is necessary in the care of the typhus patient. In our experience nitrogen retention, with or without oliguria, is the most serious development which may occur in typhus from the prognostic point of view. Without exception the fatal cases of typhus in which the blood chemistry was studied by the Commission, whether in the Commission ward or in the general wards of the Fever Hospital, showed a pronounced elevation of nonprotein nitrogen. Forty-four per cent of the "untreated" cases in the Commission study, despite the vigorous administration of fluids (4 to 5 liters daily), exhibited some elevation of nonprotein nitrogen in the blood. Daily examination of the urine, continuous observation of the fluid intake, the output and specific gravity of the urine, as well as determinations of the blood nonprotein nitrogen, plasma proteins, hematocrit and urea clearance, aid in the evaluation of renal insufficiency in typhus. This subject will be treated in greater detail in a later report of the United States of America Typhus Commission.

13. Greiff, D., and Pinkerton, H.: Inhibition of Growth of Typhus Rickettsiae in the Yolk Sack by Penicillin, Proc. Soc. Exper. Biol. & Med. **55**: 116-119, 1944. Moragues, V.; Pinkerton, H., and Greiff, D.: Therapeutic Effectiveness of Penicillin in Experimental Murine Typhus Infection in dba Mice, J. Exper. Med. **79**: 431-437, 1944.

Speculations on the Mode of Action of Para-Aminobenzoic Acid.—The rickettsias of typhus are known to multiply inside the endothelial cells of small blood vessels. It is in these cells that they have been demonstrated in tissues from human autopsies.[14] Multiplication of rickettsias outside living cells has not been proved. In one experiment the direct exposure of rickettsias to a concentration of 50 mg. of para-aminobenzoic acid per hundred cubic centimeters for one hour at 38 C. (100.4 F.) had no effect on their virulence for animals.[15] This suggests that para-aminobenzoic acid does not act directly on rickettsias. The clinical data are consistent with this observation. The treated cases did not show a rapid improvement following the administration of para-aminobenzoic acid. The usual finding was that the progress of the disease was arrested and that the patients did not become appreciably sicker than they were at the time treatment was instituted. In the course of four to six days the temperature fell and considerable improvement in condition was apparent, as though the natural defenses of the body had finally disposed of the rickettsias. The hypothesis which best fits this sequence of events is that para-aminobenzoic acid inhibits the multiplication of rickettsias inside the cells, thereby permitting the immunity mechanisms of the body to dispose of them, whereupon the vascular lesions begin to heal. If para-aminobenzoic acid is withdrawn before the immunity mechanisms have finally disposed of the rickettsias, these latent, previously inhibited organisms may then resume their growth and cause an increase in size of the lesions or even the formation of new lesions. The secondary febrile periods which occurred in half the para-aminobenzoic acid treated cases may be explained on the basis of this hypothesis. The usual finding, that the rash of treated cases was less extensive, likewise supports the "inhibition hypothesis." However, it should be noted that in 2 cases a definite rash appeared despite the fact that para-aminobenzoic acid was given very early in the course of the disease. This is regarded as evidence that para-aminobenzoic acid did not completely inhibit the progression of lesions which had already been established.

Para-aminobenzoic acid plays a most important role in the metabolism of many micro-organisms which ordinarily multiply outside the cells of the body. The inhibitory effect of para-aminobenzoic acid on the growth of rickettsias, which are obligate intracellular organisms, opens a wide field for speculation on the metabolism not only of rickettsias but of other intracellular micro-organisms as well. Perhaps para-aminobenzoic acid alters an intracellular enzyme system in such a way as to render the cytoplasm unsuitable for multiplication, possibly by blocking the formation of an essential metabolite which rickettsias are unable to synthesize for themselves.

It is also possible that the action of para-aminobenzoic acid is related to the mechanisms by which rickettsial toxic substances are combated. In this regard it may be pointed out that the patients who received para-aminobenzoic acid did not have the usual degree of prostration and "toxicity" which are part of the picture of typhus. Moreover, such a hypothesis may offer an explanation of the very low incidence, in the treated cases, of impairment of renal function, the importance of which is stressed elsewhere in this communication. For the purpose of our speculations we may postulate a hypothetical effect of rickettsial toxic substances on the kidney, resulting in impairment of renal function. If para-aminobenzoic acid plays a role in the detoxification mechanisms, this may explain the low incidence of nitrogen retention in the treated cases as contrasted to the high incidence in the "untreated" cases. However, there are other obvious considerations which are probably important in the development of the renal insufficiency in typhus; for example actual lesions in the kidney, severe hypotension and dehydration.

The material which is available for analysis does not permit the selection of a single hypothesis to explain our observations on the effect of para-aminobenzoic acid in typhus. Obviously a great deal of work is indicated on the problem of the mode of action of para-aminobenzoic acid.

The results of this study provide other subjects for speculation. Can compounds closely related to para-aminobenzoic acid be found which are even more effective? What is the scope of usefulness of para-aminobenzoic acid therapy in the face of an outbreak of typhus? What is the optimum dosage and plan of administration? What untoward reactions and complications may be expected? Will the course of other rickettsial diseases of man be favorably affected by para-aminobenzoic acid or closely related substances?

SUMMARY AND CONCLUSIONS

Twenty cases of louse borne typhus have been treated with para-aminobenzoic acid. Their clinical course has been compared with that of 44 "untreated" cases. The data from this study show that:

1. Large amounts of para-aminobenzoic acid were administered with ease to patients suffering from typhus.

2. There were no unfavorable effects when para-aminobenzoic acid was properly administered with the exception of a tendency to develop a low white blood cell count.

3. When treatment was started in the first week of illness, the clinical course of the patients who received para-aminobenzoic acid was much less severe than that of the "untreated" patients. The average duration of fever was considerably shorter in the treated group.

It is concluded that large doses of para-aminobenzoic acid exert a definite beneficial effect on the course of louse borne typhus if treatment is started in the first week of illness.

14. Wolbach, S. B.; Todd, J. L., and Palfrey, F. W.: The Etiology and Pathology of Typhus, Cambridge, Mass., Harvard University Press, 1922.

15. Snyder, J. C.: Unpublished observation.

Cosmic Doctrine of Aristotle.—The cosmic doctrine of Aristotle holds that the world is a living being having a soul. Since everything created is for some particular purpose, the body of man is evolved as the habitat of the soul. Matter is composed of five elements, earth, air, water, fire and ether. Every element must be looked on as living, since it is pervaded by the soul of the universe; there is an unbroken chain from the simple elements through plant and animal up to man, the different groups merging by insensible shades into one another; plants are inferior to animals inasmuch as they do not possess a single principle of life or soul but many subordinate ones, as is shown by the circumstance that when they are cut to pieces each piece is capable of independent growth or life.—Gordon, Benjamin Lee: The Romance of Medicine, Philadelphia, F. A. Davis Company, 1944.