# The Prothrombin Time in Tropical Sprue[1]

## AN ANALYSIS OF THIRTY CASES

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THAT HEMORRHAGIC tendencies are quite rare in tropical sprue is evidenced by the report of Suárez.[2] Up to the present time no calculations of the prothrombin time in this condition have ever been made. Butt *et al.*[3] reported two cases of non-tropical sprue in which the prothrombin time was prolonged. There were no hemorrhagic tendencies in their cases, but they are of the opinion that fatal hemorrhagic diathesis may occur in the presence of sprue, and that the phenomenon is dependent upon a deficiency in vitamin K and a hypoprothrombinemia. Fanconi[4] has stated that in cases of coeliac disease in children there is a tendency to bleed, and this finding is explained by the abnormal or deficient absorption of fats encountered in this disease. He noticed a prothrombin deficiency as well as prolonged coagulation in his cases and suggested that this is due to a vitamin K deficiency. A few months later Engel[5] reported similar findings. Allen[6] encountered a case of non-tropical sprue that showed ecchymotic areas all over the body as well as a metrorrhagia. The prothrombin time was markedly prolonged, and with the administration of vitamin K the patient's hemorrhagic tendencies were corrected, though the response to oral and parenteral vitamin K and its substitutes was very slow, suggesting that the prothrombin deficiency was due to impairment of the hepatic elaboration of prothrombin, as well as to poor absorption of vitamin K by the intestinal mucosa.

The evidence at the present time as to the sites of absorption of vitamin K from the gastro-intestinal tract is scarce. It is known

1. Received for publication March 31, 1941.

2. R. M. Suárez, "Clinical and Hematological Review of Sprue Based on the Study of 150 Cases," *Ann.Int.Med.*, XII: 529–535. Oct., 1938.

3. H. R. Butt, A. M. Snell, and A. E. Osterberg, "Preoperative and Postoperative Administration of Vitamin K to Patients Having Jaundice," *J.A.M.A.*, CXIII, No. 5, 383–389. July, 1939.

4. G. Franconi, "Zoliakie," *Deutsche med.Wchnschr.*, LXIV:1565–1568. Oct. 28, 1938.

5. R. Engel, "Sprue und Vitamin K-Mangel," *Med.Welt*, No. 4, 120. Jan. 28, 1939.

6. J. G. Allen, "The Comparative Prothrombin Responses to Vitamin K and Several of Its Substitutes in a Case of Non-tropical Sprue," *New England J.Med.*, CCXXIV, No. 5, 195. Jan. 30, 1941.





that it is readily absorbed through the jejunum, though it is doubtful whether it passes through the gastric or colonic mucosa.

The predominance of intestinal symptoms in tropical sprue attracted the attention of early investigators to the gastro-intestinal tract. Brown[7] described sprue as being a chronic, progressive, subacute inflammation of the gastro-intestinal mucosa of a definite type, followed by degenerative and destructive changes in the affected tissues. Faber and Justi, nevertheless, contended that these changes and the destruction of the villi were to be interpreted as post mortem phenomena. Suárez' observations[8] in a case of severe sprue which was submitted to an exploratory laparotomy were: "There were variations in the caliber of the intestinal loops, as well as atrophy and dilatation of the small bowel, rendering it almost diaphanous." In his opinion, permanent gastro-intestinal damage occurs in tropical sprue, especially in older individuals, and in those cases unrelieved by liver therapy. Mackie, Miller and Rhoads[9] have described characteristic roentgenologic findings in the intestine. Rodriguez Olleros[10] and Hernández Morales[11] have found an atrophic gastritis present in the great majority of the cases of tropical sprue when examined gastroscopically, and Hernández Morales[12] has encountered atrophic rectosigmoiditis in a majority of the cases examined protoscopically.

There is no doubt that the absorptive power of the intestinal mucosa in tropical sprue is impaired. This would explain the flatness of the glucose tolerance curve when the glucose is administered *per os*. Besides, the reduction of plasma prothrombin in the few cases of non-tropical sprue that have been reported probably depends upon the impairment of absorption of vitamin K.

### MATERIALS AND METHODS

Using the bedside method of testing vitamin K deficiency devised by Smith *et al.*,[13] calculations were made in thirty cases of tropical

7. W. C. Brown (quoted), T. T. Mackie, Chapter on Sprue, *Nelson Loose Leaf Med.*, Vol. V.

8. R. M. Suárez, *loc.cit.*

9. T. T. Mackie, D. K. Miller, and C. P. Rhoads, "Sprue: Roentgenologic Changes in Small Intestine," *Am.J.Trop.Med.*, XV:495–604. 1935.

10. A. Rodríguez Olleros, "The Stomach in Tropical Sprue," *Puerto Rico J.Pub.Health & Trop.Med.*, XIII, No. 4, 503–521. June, 1938.

11. F. Hernández Morales, personal communication.

12. F. Hernández Morales, personal communication.

13. H. P. Smith, S. E. Ziffren, C. A. Owen, and G. R. Hoffman, "Clinical and Experimental Studies on Vitamin K," *J.A.M.A.* XIII, No. V, 380–383. July 29, 1939

sprue that were admitted to the University Hospital of the School of Tropical Medicine.

The thromboplastin used was freshly prepared from macerated rabbit's brain. This substance was standardized so that the prothrombin time in normal controls was around 25 seconds. The test was carried out in a normal control before calculations on the patients in question were performed. The formula used by Smith *et al.* was used for further determinations, thus:

$$\text{Clotting Activity (In percentage of normal)} = \frac{\text{Clotting time of normal control} \times 100}{\text{Clotting time of patients' blood}}$$

All patients were tested shortly after admission and before the administration of liver therapy. Only those who presented a prolonged prothrombin time were retested before discharge.

There were 24 females and 6 males in our series, the ages ranging between 15 and 55 years. All patients belonged to the white race with the exception of two, of which one was a full-blooded negro and the other a mulatto.

The duration of the disease varied between one month and seven years with an average of 1.5 years.

The outstanding symptoms were diarrhea, glossitis, and flatulence. All patients had lost weight, eight of them being in a state of cachexia. The most prominent physical findings were malnutrition, paleness, atrophic glossitis, and visible peristalsis. None of the patients was desperately ill on admission. No hemorrhagic tendencies were encountered in any of the cases.

The clinical diagnosis of sprue was confirmed by the presence of hyperchromic macrocytic anemia, a leucopenia, a flat glucose tolerance test, an atrophic gastritis, and an atrophic rectosigmoiditis, and either achlorhydria or a definite hypochlorhydria.

As complicating factors we found six (20%) of the cases with a positive Kahn reaction; twelve (40%) suffering from intestinal parasitism, of which six (20%) had hookworm ova in the stools, while four (13.3%) were suffering from intestinal schistosomiasis mansoni. One of the patients was afflicted with both hookworm and *Schistosoma mansoni* infestation.



*Tests for Hemorrhagic Diathesis:*

Clot retraction: We performed this test in eighteen (60%) of the cases. All showed normal clot retraction in four hours.

Blood calcium: All serum calcium estimations in twenty-one (70%) of the cases were within the limits of normal.

Fragility of erythrocytes: In fifteen (50%) of the cases in which this procedure was practiced, no noticeable abnormality was encountered.

Tourniquet test: Negative in all thirteen (40%) of the patients in which it was performed.

Platelet counts: Were within normal limits in all twenty (66.6%) of the cases in which the counts were made.

The prothrombin time varied from 21¼ to 48 seconds. Seventeen (56.6%) had a prothrombin time of 30 or more seconds, while in only five (16.6%) was it prolonged above 40 or more seconds.

*Clotting activity in percentage of normal:* According to Smith *et al.*, when the clotting activity is below 70 percent of normal the case is supposedly in the danger zone of hemorrhage. Nine (30%) of our cases were within the danger zone of hemorrhage. Three (10%) had a percentage clotting activity below 60 percent and in six (20%) it oscillated between 61 and 70 percent. Nineteen (63.3%) presented a percentage clotting activity below 80 percent, while in only eleven (36.7%) was it above this figure. Of the nine cases in which the prothrombin time was 40 seconds or above, and in which the percentage clotting activity was 70 or less, there were three who had a positive Kahn test and one who had hookworm disease. One of these cases had both—a positive Kahn test as well as hookworm ova in the stools.

No relation could be established between the degree of anemia, the positive serology, the intestinal parasitism, and the prothrombin time in our series.

The five cases that originally showed a prolonged prothrombin time of 40 or more seconds, with a clotting activity of 62 percent or less, were retested after having received adequate liver therapy and after the general symptoms of diarrhea, flatulence and glossitis had disappeared. The results were invariably normal.

SUMMARY

1. We have studied the prothrombin time in 30 typical acute sprue cases.

2. All patients were suffering from diarrhea, glossitis, flatulence and loss of weight; eight of them were in a cachetic state.

3. The most prominent physical findings were malnutrition, paleness, atrophic glossitis, and visible peristalsis.

4. None of the patients showed hemorrhagic tendencies.

5. As complicating factors, we found that six (20%) had a positive Kahn test and twelve (40%) had intestinal parasitism.

6. All other tests for hemorrhagic diasthesis were essentially negative.

7. The prothrombin time varied from 21¼ to 48 seconds. Seventeen (56.6%) of the cases had a prothrombin time of 30 seconds or more. In nine (30%) the prothrombin time was prolonged above 36 seconds, but in only five (16.6%) was it 40 or more seconds.

8. In only nine (30%) of the cases was the percentage clotting activity within the danger zone of hemorrhage. Three of these (10%) had a clotting activity of below 60 percent and in six (20%) it was between 61 to 70 percent. Nineteen (63.3%) presented a percentage clotting activity of less than 80, while in the remaining cases it was above this figure.

9. In spite of the fact that nine of our patients had a markedly prolonged prothrombin time and a reduced clotting activity, no hemorrhagic tendencies were present in any of them.

10. Although all patients had severe diarrhea, only 30 percent showed an increased prothrombin time—that is, none above 40 seconds.

11. It seems that the prothrombin time, when prolonged initially, is shortened by adequate liver therapy in cases of tropical sprue.

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