

Prothrombin levels in yellow fever *

by

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Since hemorrhagic manifestations constitute one of the most constant clinical features of yellow fever, we set out to study this diathesis in an attempt to analyze the vascular and physicochemical factors that might explain its causes.

Tourniquet tests in 30 patients were negative, hence we decided no capillary fragility existed.

Contrary to some statements in the literature, we found that coagulation and bleeding times were considerably increased in some cases, while in others they fell within normal limits. Furthermore we noted at times that both were prolonged, while at other times only the coagulation time was prolonged and the bleeding time was normal.

In spite of prolonged bleeding time the platelet counts were maintained between 100,000 and 200,000 in 9 cases so studied.

Clot retraction studies provided no values showing any relevant relationships.

In 9 cases in which fibrinogen determinations were carried out we obtained no data at variance with the findings on plasma from normal control subjects.

Sedimentation rates in these same 9 cases were all within normal limits.

The determination of plasma prothrombin, however, provided very interesting results, largely accounting for the hemorrhagic diathesis in yellow fever, and proving of great prognostic value in evaluating the status of liver function.

By constructing a prothrombin curve it was possible for us to follow the evolution of the course of the disease and account for fatalities in most cases.

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The QUICK method was used for the prothrombin determinations in 86 cases of yellow fever of whom 62 recovered and 24 died. This group comprises 42 patients admitted to the hospital in 1951, 43 in 1952 and one in 1953. Of the 42 in 1951 thirteen died; of the 43 in 1952 ten died. The one in 1953 died. Of the 24 fatalities, 22 died between the 6th and 12th day of illness. One died on the 19th day and another on the 27th day. One or more prothrombin determinations were made on each of these 86 patients, with a total of 118 determinations as follows: Only one test, 60 patients; two tests, 20 patients; three tests, 6 patients.

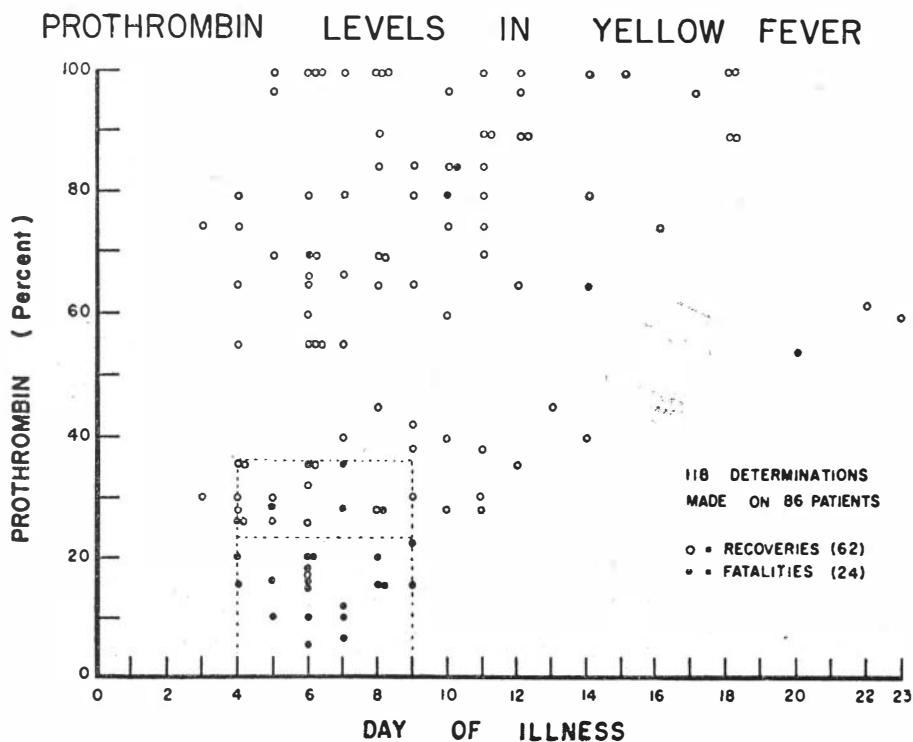
Prothrombin percentages were lower among the cases terminating fatally than among those who recovered.

The averages of the two groups were as follows:

Recoveries: In 84 determinations carried out from the 4th to the 18th day of illness the average prothrombin percentage was 66.7.

Fatalities: In 26 determinations the average was 20.25% (4 determinations made on patients who died after the 9th day of illness are not included).

On different days of illness it was noted that the prothrombin in those who recover is subject to a wide fluctuation, as shown on the chart. Determinations made in different patients from the 4th to the 8th day, for example, may range from 17% to 100%. These changes were consistent with the clinical condition of the patients on any given day of illness.



Case	PROTHROMBIN % IN THE VARIOUS DAYS OF ILLNESS																		OBSERVATIONS
	1°	2°	3°	4°	5°	6°	7°	8°	9°	10°	11°	12°	13°	14°	15°	16°	17°	18°	
7						15	10		†										decrease
12					28				22†										decrease
16				25		70				85		†							increase
75							12	15	†										small increase
80							35			80†									increase
13							40				70								
14						17						35				75			slow increase
15				35				100											rapid increase
17				25		70				97									
18				27		35				85									
20				65		100													
31											30			40					slow increase
43														100				90	slight decrease
44					25				38										
45						67				60									slight decrease
46											27				100				
52								28											100
57								70				97							
63											38		45						
69								90											slight decrease
70						32					90								
74							56												90
76									30				90						
81						56													
82											85			80					slight decrease
85			30			26		85											decrease & increase.

In those patients who underwent fatal terminations the findings fell predominantly in the region of the average for such cases. Out of 30 determinations, 25 showed, 35% or less and only 5 yielded higher values. Four of these 5 determinations were made after the 9th day of illness.

Percentages below 25 were encountered only in cases with eventual fatal terminations, with the exception of Case N^o 14 in which the typical yellow fever virus was isolated, and in which the prothrombin rose subsequently to high levels, reaching 75% on the 16th day of illness. Hence, those cases which present prothrombin levels below 25%, between the 4th and 9th day of illness, have much less chance for recovery than those with percentages above 35 during this period.

Among the determinations made between the 4th and the 9th day with percentages varying from 25-35, 13 were made in 12 cases who recovered and 6 in 6 who died.

With reference to the five determinations in the 4 cases which differ from the majority of those with fatal terminations, the clinical study was very interesting in several respects.

In a case which attained a prothrombin percentage of 80 from a prior level of only 35% (Case N^o 80), the second blood specimen was taken on the 10th day, after the patient had been under intensive treatment with Vitamin K to perform a biopsy, and it is assumed that the liver was in a stage of regeneration and capable of metabolizing Vitamin K. The cause of death was probably extra-hepatic.

Two other cases having 65% on the 14th day and 55% on the 20th day respectively, died because of the nephrotic lesions, the former with 480 mg/100 cc of blood urea, after having attained a maximum retention of 495 mg a few days before death, and the latter with 108 mg/100 cc, having already attained 138 mg/100 cc a few days before death. These two cases, however, had only single determinations.

The fourth case is that of Julio Ferreto (Case N^o 16), one of the most interesting of all, and the first in whom we observed a fatal termination in spite of rising prothrombin levels (25% on the 4th day, 70% the 6th day and 85% on the 10th day) to death on the 11th day, with a completely regenerated liver. Death was due to hemoglobinuric nephrosis.

In 5 patients who died it was possible to carry out 2 successive determinations in 4, and 3 in one. It was also possible to conduct serial determinations in 21 patients who recovered; 3 tests in 4 and 2 tests in 17. The data on these are summarized in the following chart.

N^o 16 corresponds to Julio Ferreto whose case we have already discussed. In cases 7, 12 and 75 the readings fell or exhibited only insignificant increases. In Case N^o 80 there was a definite rise, which we have already mentioned.

Among the recoveries we observed that in the majority there is a frank rise in prothrombin levels, rapid and early in some, while slow and delayed in others as the disease underwent its involution, indicative of a rapid liver regeneration

in the former group and a slower regeneration in the latter group. This hepatic regeneration permits the metabolism of Vitamin K which was given to these patients in high dosage.

In four cases there was a slight fall in the successive determinations, but, in contrast with the rises, this was always very small, never amounting to more than 10%.

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CONCLUSIONS

1. Yellow fever is accompanied by a decrease in plasma prothrombin due to liver dysfunction.
2. The degree of diminution of the prothrombin level is proportionate to the severity of the liver lesion and generally related to the clinical findings.
3. High prothrombin levels during the period of the illness are of favorable prognostic significance, whereas levels below 25% are unfavorable.

RESUMEN Y CONCLUSIONES

En vista de que las hemorragias son unas de las manifestaciones más constantes en la fiebre amarilla, se procedió a estudiar esta diátesis en un buen número de enfermos de la última epidemia que se presentó en Costa Rica.

Habiéndose descartado que las hemorragias tuvieran por causa una aumentada fragilidad capilar o trombocitopenia o fibrinopenia, se orientó la investigación hacia las determinaciones de la protrombina plasmática y estas últimas sí mostraron alteraciones importantes.

Empleando el método de Quick se realizaron determinaciones de protrombina en 86 enfermos de fiebre amarilla siendo que, de éstos, a 60 se les hizo una determinación, a 20 dos determinaciones y a 6 tres determinaciones.

Se observó que las determinaciones realizadas en individuos que sobrevivieron dan un porcentaje medio de protrombina significativamente mayor que aquellas practicadas en individuos que posteriormente murieron (66,7% en los primeros y 20,25% en los segundos).

Se hacen consideraciones con respecto al valor pronóstico de la determinación cuantitativa de la protrombina en la fiebre amarilla y se concluye que:

- 1). Debido a la lesión hepática, la fiebre amarilla determina una disminución de la protrombina plasmática.

2). La disminución más o menos acentuada está en relación directa con la gravedad de las lesiones hepáticas y en general, con la gravedad del cuadro clínico.

3). Las tasas altas de protrombina durante el período de estado son de buen pronóstico, al contrario de las tasas de menos de 25%, que son de muy mal pronóstico.

REFERENCE

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