**A Case with a Remarkable Prolongation of Blood Coagulation :—
Pseudohemophilia Hepatica (Frank). The First Case
Published under This Name in Japan, in spite of
Possibly Frequent Occurrence in the Newborn Age.**

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By

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Introduction.

A remarkable prolongation of clotting time occurs most frequently in hemophiliac blood, and it is quite fitting to take a male patient with remarkable delay of blood coagulation for hemophilia. Now, a boy was admitted into our Department in October in 1935. He had a profuse wound bleeding and was sent by a doctor to us under the possible diagnosis of hemophilia. We considered this diagnosis as correct when blood coagulation of this patient was examined, but later we found that the diagnosis was not right, and concluded that this case would in all probability be "Pseudohemophilia hepatica (Frank¹)."

This report is, we believe, very important, because to the best of our knowledge we have no report on pseudohemophilia hepatica in our country, and we wish to draw attention to this.

Case Report.

Patient: J. Shiraishi, a boy aged 36 days, native in Sendai (on Oct. 9th, 1935).

Paternal side—Grandfather had a venereal disease in his anamnesis and died from heart disease. Grandmother is well.

1) E. Frank, "Die Krankheiten des Blutes und der blutbildenden Organe" von Schittenhelm, Berlin 1925, 2, 445.

Maternal side—Grandfather and grandmother are well. An elder brother of the mother died from severe blood expectoration at the age of 19 years. The third son of an elder sister of the mother had purpura on the whole body at the age of 2 years, but later he has shown no hemorrhagic diathesis and is well, now 7 years old. We examined the clotting time, the bleeding time and the blood picture of this boy which were all normal. There is no abnormality on his body, and it is indubitable that he is not hemophilic.

Parents—Parents are well and their blood serum are negative to Wassermann's reaction. Father suffered from nephritis when 4 years old.

Mother had a miscarriage in consequence of overwork, according to her.

Patient has no brother or sister.

History: Patient was easily delivered in the maturity. His body weight at the birth was about three kilograms. He had no bleeding from the umbilical cord. He was nursed with mother's milk.

Jaundice occurred four days after the birth, which showed an exacerbation about one month later. On 8th October, a few days after the exacerbation was found by his mother, a purpura of thumb tip size on the middle of tibial edge of his right leg. The next day he vomited milk at about 7 A.M. and blood at about 9 A.M., and excreted tar like faeces soon after. He became remarkably pale and cried frequently. He was subcutaneously injected with a cardiac on the left breast by a physician, and then a bleeding from the site of the injection began and would not stop till the evening. Blood vomiting occurred again and soon the baby was admitted to our Department at about 8 P.M.. The possible diagnosis of the physician was as stated above thrombophilia. Soon after the admission, the patient vomited fresh blood once more.

Examination at the admission: The baby is in bad temper and has no appetite. The consciousness is almost lost. The face is pallid and intensely jaundiced. The pulse is somewhat weak and 120 per minute. He has a temperature of 36.7°C. The skin is pale and jaundiced, but he has no exanthema, no oedema. A purpura of thumb tip size is seen on the middle of the tibial edge of the right leg. The site of the injection below the clavicle on the left breast is still bleeding. The head has no abnormality. The bulbar conjunctiva is jaundiced and the palpebral conjunctiva is anemic. The mucous membranes of mouth and pharynx are anemic, but no bleeding spot is seen. The heart has no murmurs and lungs are normal on percussion and auscultation. The abdomen is slightly distended. The liver is enlarged, though normal in consistence and of smooth surface, and its rather sharp edge is palpable somewhere about one and half transverse fingers with below the right costal margin. The spleen is not palpable. All of the external lymphatic glands are not palpable either. The knee jerk is equal in its intensity on both sides, but slightly weak in response. No pathological reflex.

Urine: Clearly transparent, yellow. Protein (-), diazo (-), blood (-), bilirubin (-) and urobilinogen (-). In the deposit, a few epithelial cells of the bladder and a few white and red blood cells are microscopically seen.

Faeces: Tar like.

Vomited mass: Fresh blood.

Blood examination: Blood was examined four times and the results are shown in Table II. Murata's reaction of serum for syphilis is negative.

Course: Cf. Fig. and Table 1.

Fig. Course.

Discussion.

As stated above, our first probable diagnosis was, as it might seem natural, hemophilia. But the notable prolongation of coagulation very soon ceased to be pronounced and coagulation was restored to the normal. The patient had no hemorrhage in any articular cavity, which is very common in the case of hemophilia. "Hemophilia" was thus to be dropped.

Next we thought of congenital hemolytic anemia on account of the anemia and the icterus. But, then no small or spherical erythrocyte was seen, not to speak of an increase of them. Besides, the reticulo-cyte count was not large in spite of an examination at the recovering stage of anemia; and the erythrocyte resistance to hypotonic NaCl

solutions was normal. Thus, none of the trias of symptoms peculiar for the congenital hemolytic anemia asserted by Chauffard²⁾ was present, nor was an enlargement of the spleen observed, while the time of blood clotting was intensely prolonged. Congenital hemolytic anemia was thus excluded.

Purpura hemorrhagica was excluded, because of the normal blood platelet count, the normal bleeding time and the intensely delayed blood coagulation.

Henoch's purpura was excluded of course.

There was no considering of infantile scurvy; he was almost a new born and breast fed.

The hemorrhagic diathese secondary to a poisoning was very unnatural in this case. The little patient had not taken any medicine at all yet.

On the ground of the blood picture and the very favourable course of this patient, it will be easily seen that there was no special blood disease with this infant, except the secondary anemia caused by a profuse bleeding.

Now, it is a very essential question what caused the hemorrhagic diathesis accompanied by a very intensely delayed coagulation of blood with the secondary anemia as its sequela. Let us consider pseudohemophilia hepatica (Frank) in this case.

1. In this case icterus neonatorum continued for a long time and showed an exacerbation before the occurrence of hemorrhagic diathesis, so that we have a fair reason to believe that there was a disorder of the liver function.

2. By an administration of yakriton,** the detoxicating hormone of the liver, all symptoms, especially jaundice, disappeared rapidly, so we can believe that the liver function was restored more or less to the normal by the hormone and that the patient was recovered.

3. As to the non-hemophiliac disease with a hemophilia like prolongation of the coagulation time, there are two diseases to be taken into consideration. One is pseudohemophilia hepatica (Frank), and the other is fibrinopenia described at first by Rabe and Salomon³⁾ and later by Opitz and Frei⁴⁾. But fibrinopenia is perhaps out of the

2) A. Chauffard, La Sem. méd., 1909, No. 8, 95.

** Cf. A. Sato, Osaka Iji Shinsi, 1935, 6, 1.

3) F. Rabe and E. Salomon, Dtsch. Arch. f. kl. Med., 1920, 132, 240.

4) H. Opitz and M. Frei, Jahrb. f. Kinderheilk., 1921, 94, 374.

TABLE 1.

Calender day		9/X	10/X	11/X	12/X
Day* of disease		2	3	4	5
Yakriton (R.A.U.)		—	1/5	Ditto	Ditto
Oryzanin (c.c.)		—	1.0	Ditto	Ditto
Blood trans- fusion (c.c.) (into vein)		—	10.0×1 20.0×2	20.0×1	—
Vomit- ing	Blood	3	0	0	0
	Milk	0	2	1	0
Faeces		1 (tar like)	3 (soft)	3 (mucous)	3 (mucous)
Frequency of urine		4	6	5	7
A purpura on the middle part of the tibial edge of right leg		Thumb tip size, distictly purple	Ditto	Ditto	Ditto
Degree of pallidness		Very distinct	Ditto	Ditto	Ditto
Degree of jaundice		Very distinct	Ditto	Ditto	Ditto
Enlargement of the liver		About one and half transverse finger's width below the right costal arch, surface smooth	Ditto	Ditto	Ditto
Humour		Stuporous, consciousness almost lost	Ditto	Ditto	Somewhat better
Appetite		Bad	Ditto	Better at night	Somewhat better
Remarks		The bleeding from the injected part below the clavicle on the left breast stopped in a short time by the compressible appli- cation of a tampon with adrena- lin after the admission into our Department. The bleeding from the wound of the left ear lobe that was in- jured for blood taking 10.30 A.M. continued till the evening and was stopped by counterizing by lapis nitratns and repeated appli- cation of tampon with adrena- lin about 7.00 P.M.. Sometimes hyperpnoea, hic- cough and nystagmus. The large fontanelle was somewhat bulg- ing. Sometimes hyperpnoea. A clo- nic fit of the left upper extremity continued some minutes. The large fontanelle was somewhat bulging. The pupils of the eyes were of the same size and their reaction to light was prompt. There was no asymmetry of the face and no disturbance of four extremities. The tendon reflex was normal.			

* The day on which purpura was for the first time noted as the 1st day of disease.

Course.

13/X	14/X	15/X	16/X	17/X	18/X
6	7	8	9	10	11
Ditto	Ditto	Ditto	Ditto	Ditto	Ditto
Ditto	Ditto	Ditto	Ditto	—	—
—	—	—	—	—	—
0	0	0	0	0	0
0	2	0	0	0	0
2 (mucous)	5 (mucous and granular)	4 (mucous and granular)	2 (mucous and granular)	2 (mucous and granular)	—
6	10	10	13	10	—
Ditto	Thumb tip size, somewhat faded	Ditto	Ditto	Ditto	Ditto
Somewhat recovered	Ditto	Much recovered	Almost no pallidness	No pallidness	—
Somewhat faded	Ditto	Ditto	Much faded	Ditto	Almost faded
Ditto	About one trans- verse finger's width below the right costal arch, surface smooth	Ditto	Ditto	Ditto	Ditto
More or less unconscious	Somewhat better	Good	Good	Good	Good
Ditto	Ditto	Good	Good	Good	Good
Sometimes hyperpnoea. A si- milar fit occurred twice in the afternoon. The large fontanelle was somewhat bulging.	A similar fit occurred once. A large fontanell was scarcely bulging.	There was no fit. The large fontanelle was not bulging.			

TABLE 2.
Results of blood examinations.

Date	Oct. 10. (I)	Oct. 18. (II)	Oct. 23. (III)	Feb. 21. (IV)
Red cell count per cmm. (thousands)	2,030	3,530	3,800	4,750
Else	Hemoglobin Sahli's value 40	—	Reticulocytes 13%	Reticulocytes 3%
	Small or spherical erythrocytes are not seen			
Blood platelet count per cmm. (thousands)	280	--	300	850
Red cell resistance to hypotonic saline			% of saline	Hemolysis
		—	0.5 0.45 0.3 0.25	Negative Slight Distinct Intense Complete
Readings in Yoshida's micro sedi- mentator	2 mm. 5 9 14			0.5 mm. 1.0 2.5 3.5
	White cell count per cmm.	10,600	9,000	8,600
	%	Absolute count per cmm.	%	Absolute count per cmm.
Basophiles	0.5	50	0	0

Differentiation white cells	Eosinophiles	2.0	210	7.0	630	8.0	640	4	340
	Neutrophiles	54.5	5,780	29.0	3,610	37.0	2,980	31	2,670
	Monocytes	6.0	640	10.0	900	8.0	640	7	600
	Lymphocytes	46.0	4,480	54.0	4,860	47.0	3,760	58	4,990
	M	0	0	0	0	0	0	0	0
Arneeth's count of neutrophiles	J	0	0	0	0	0	0	0	0
	St	11		12		8		5	
	II	28		39		37		34	
	III	42		40		47		40	
	IV	16		8		7		19	
	V	3		1		1		2	
Bleeding time (Duke's method)		5'		—		2'		2'	
Time of coa- gulation		40'		—		5'		3'	
(Biffi-Brooks- Sato's method)		2020'		20' in test-tube		10'		5'	

question. There are only two cases[†] of fibrinopenia hitherto reported. It seems to be characteristic of the disease that blood will not coagulate. In one case of the two reported it did not coagulate as long as 4 days and in the other as long as 8 days. In our case blood coagulated in vitro in two hours and twenty minutes.

In our case, the time for blood coagulation was restored to the normal before the jaundice faded away completely, and the prolonged coagulation was probably not due to the presence of jaundice. And probably it is needless to add, from the experiments of Morawitz and Bierich⁵⁾ and Petré⁶⁾, that the delay of blood clotting observed in cases of liver diseases is not due to a hindrance of blood clotting caused by bile acids in blood.

Furthermore, the fact that the red cell sedimentation value did not run parallel to the grade of anemia in our case, led us to suppose that there might have been a want of fibrinogen in it.

Admitting that the dysfunction of liver produced experimentally in animals results in a disturbance of blood coagulation due to a disappearance of fibrinogen, Frank¹⁾ says that this fact may not be applied to the pathology of liver in human beings. And further, according to the opinions of Morawitz and Bierich⁵⁾ and of Schultz and Scheffer,⁷⁾ the want of fibrinogen is not an important cause of the prolongation of blood coagulation in a case of hepatic dysfunction.

Unfortunately we had no opportunity to perform an exhaustive examination of the mechanism of a prolonged blood coagulation in the present case.

Of course we do not claim that this case of ours is the very first case of pseudohemophilia hepatica (Frank) ever existent in Japan. Such a case with remarkable prolongation of blood coagulation due to hepatic dysfunction must, we think, be of possibly frequent occurrence among a large number of newborn patients with the diagnosis of melaena neonatorum or with a hemorrhagic diathesis. And the administration of yakriton, the liver hormon, may be a rational treatment in such a case.

† Cf. further, R. G. Macfarlane, *Lancet*, 1938, **234**, 309. (Blood did not coagulate in vitro during 3 weeks in a boy of 16 months).

5) P. Morawitz and R. Bierich, *Arch. f. Exp. Pathol. u. Pharmacol.*, 1907, **56**, 115.

6) G. Petré, *Beitr. z. klin. Chirurg.*, 1920, **120**, 501.

7) W. Schultz and W. Scheffer, *Berl. kl. Wschr.*, 1921, **58**, 789.

Conclusions.

We have had an opportunity to observe, in a case of a baby aged 36 days, a severe hemorrhagic diathesis with remarkable prolongation of blood coagulation developed after a rather long continuation and an exacerbation of icterus neonatorum, and our final diagnosis was pseudohemophilia hepatica (Frank). In this case yakriton was, we believe, a very efficacious factor for making the coagulation restore to the normal.