Afibrinogenemia and Thrombocytopenia in Guinea Pigs Following Injection of Echis Colorata Venom

By Jadwiga Rechnic, Pola Trachtenberg, Julian Casper, Chaja Moroz and André de Vries

HEMORRHAGE is the outstanding phenomenon observed following the bite by snakes of the Viperidae and Crotalidae families. Subjects bitten by these snakes show local hemorrhage near the site of the bite, slowly extending proximally, and, after death, widespread hemorrhage in many internal organs. In the explanation of the hemorrhage, two mechanisms have been invoked; damage to the vessel wall caused by venom hemorrhagins,\(^1\)\(^3\) and blood coagulation disturbances due to the action of venom agents on plasmatic coagulation factors\(^4\)\(^6\) and on blood platelets.\(^7\)\(^8\) Both intravascular clotting and incoagulability of the blood have been described following the inoculation of snake venoms such as of the Bothrops jararaca,\(^9\) Echis carinata,\(^10\) Vipera russelli\(^11\)\(^-\)^\(^12\) and Crotalus adamanteus,\(^13\) possessing various coagulation-promoting, coagulation-inhibiting and fibrinolytic activities.\(^5\)

In a study reported from this laboratory on the venom of Echis colorata, a snake prevalent in the Middle East,\(^3\) evidence has been obtained that the hemorrhages induced by this venom are primarily due to the action of its hemorrhagins on the vessel wall. Injection into mice of Echis colorata venom caused widespread hemorrhage, afibrinogenemia and severe thrombocytopenia. When, however, the venom was treated with specific antivenin, the mice were protected from hemorrhage and death, while afibrinogenemia and thrombocytopenia did occur.

In the present communication we report observations on the afibrinogenemia and thrombocytopenia induced by Echis colorata venom in the guinea pig. Also in this animal it was possible to separate the hemorrhagic from the coagulation-disturbing action of the venom. Evidence was obtained that this venom contains agents able to produce afibrinogenemia by two different mechanisms: fibrinogenolysis and intravascular clotting followed by fibrinolysis.

MATERIALS AND METHODS

The experiments were carried out on healthy guinea pigs weighing 250–300 Gm. Echis colorata venom, obtained by milking an adult specimen kept in the serpentarium of the Department of Zoology of the Tel Aviv University, was dried from the frozen state and stored at \(-20\) C. The dried material constituted about 20 per cent (w/w) of the fresh venom. Chromatographic fractionation of the venom on a diethylaminoethyl (DEAE) cel-
lulose column and the methods for determination of toxicity, protein content and gelatinase
activity of the venom and venom fractions were as described previously.\(^3,15\) One \(\text{LD}_{50}\)
of whole venom determined by the method of Reed and Munch\(^6\) in 18–20 Gm. white
mice by the intraperitoneal route corresponded to 35 \(\mu\text{g.}\) of the dried material. The mini-
imum lethal dose of whole venom, for guinea pigs weighing 250–300 Gm., by the intrave-
rous route was 400 \(\mu\text{g.}\).

Antivenin against whole \textit{Echis colorata} venom was prepared in rabbits.\(^3\) One ml. of the
antiserum was able to neutralize 1.25 mg. of dried venom, corresponding to 35 \(\text{LD}_{50}\) of
whole venom, by the intraperitoneal route in white mice weighing 18–20 Gm.

The venom and venom fractions were administered to the guinea pigs by injection into
a leg vein. In neutralization experiments venom or venom fractions were preincubated with
the antivenin at 37 C. for one hour. The precipitate was discarded by centrifugation at
3000 rpm for 20 minutes, and the supernatant injected intravenously. Blood samples were
obtained by cardiac puncture and partly collected over one-ninth volume of 0.1 M potas-
sium oxalate.

Whole blood clotting time was determined according to the procedure of Lee and
White\(^17\) and the time at which clot retraction at 37 C. was complete, was registered. Re-
calcification time was determined by the method of Quick,\(^18\) fibrinogen according to Rat-
noff and Menzie,\(^19\) factor V by the method of Stefanini,\(^20\) for the latter using a human
plasma standard curve but taking normal guinea pig plasma factor V activity as 100 per
cent. Fibrinolysis was observed at clots from whole blood,\(^21\) from recalcificated plasma,
and by the serum euglobulin lysis test according to Latallo et al.\(^22\) For demonstration of
direct fibrinolytic activity as distinct from plasminogen activation, heated plasminogen-
deficient human fibrin clots, prepared according to Alkjaersig et al.\(^23\) were added to the
serum euglobulin.

Platelet counts were carried out by phase microscopy according to Brecher and Cronkite\(^24\)
on blood obtained by puncture of a leg vein.

For pathologic examination, the animals were sacrificed by cutting the throat with a
scissor. Tissues were fixed in formalin and Zenker’s solution. The sections were stained
with hematoxylin-eosin, Weigert’s fibrin stain, phosphotungstic acid hematoxylin (PTAH)
and Sudan III.\(^25\)

**Results**

\textbf{The Effect of Intravenously Administered \textit{Echis Colorata} Venom}

\textit{Lethal doses of whole venom}: Intravenous injection of 400 \(\mu\text{g.}\) or more of
\textit{Echis colorata} venom into guinea pigs (in a total of six animals) caused death
with widespread hemorrhages in all internal organs. The time interval after
which death occurred depended on the dose administered, the animals dying
90–120 minutes after having received 5 mg. of venom (about 12 minimum
lethal doses) and about 6 hours after 400–800 \(\mu\text{g.}\) (1–2 minimum lethal doses).
At autopsy the blood was found incoagulable and severely thrombocytopenic
with platelet counts of 10,000–20,000 per cu.mm. (normal values 300,000–
600,000 per cu.mm.). The blood did not clot on addition of thrombin.

When animals receiving 5 mg. of venom were sacrificed 5 minutes after
injection, no hemorrhages were found, but there was widespread intravascular
clotting. The blood in the inferior caval vein was clotted (fig. 1b) and the
blood which entered the abdominal cavity on performing the autopsy clotted
immediately. These blood clots rapidly lysed \textit{in situ} and, about 10 minutes
after the animals had been sacrificed, the content of the inferior caval vein
(fig. 1c) and the clots in the abdominal cavity had become fluid. The organs,
removed for examination after a further 5 minutes, did not show hemorrhages
EFFECTS OF ECHIS COLORATA VENOM IN GUINEA PIGS

737

Fig. 1.—Intravascular clotting followed by lysis in situ. a) Inferior caval vein (arrow) in control animal. b) Clotted blood in inferior caval vein (arrow) of guinea pig sacrificed 5 minutes after intravenous administration of 5 mg. of whole *Echis colorata* venom. Pressure of pincet does not empty the vein. c) Fluid content of inferior caval vein after 5 additional minutes. Pressure of pincet empties the vein partly.

macroscopically. Histologic examination (in two animals) revealed the presence of fibrin in the blood vessels of various organs, in the form of fibers with a net-like or parallel arrangement or as small granules. In the kidney there were fibrin thrombi in the glomerular loops (fig. 2). Some blood vessels of the spleen contained thrombi in which fibrin fibers could be distinguished. Also, in the larger lung veins fibrin was found. Hemorrhages were not seen microscopically.

When animals receiving this large dose of 5 mg. venom were sacrificed 60–90 minutes after injection, i.e., close to dying, there were many hemorrhages and the blood was incoagulable but no intra- or extravascular clots were found macroscopically. Histologic examination in two of such animals revealed damage to the vascular endothelium, conspicuous in the sinuses of the spleen and in the endocardium of the left ventricle. Endothelial cells were seen detached from the vessel wall and found sometimes in clumps within the sinuses of the spleen, or adherent to the endocardium. In one of these animals small amounts of fibrin were demonstrated within the clumps between the detached endothelial cells. No fibrin was seen within the blood vessels of other organs, such as the kidney, the lungs and the liver.

After administration of smaller lethal doses of venom—400 μg.—no intra- or extravascular clots were found, and no intravascular fibrin was demonstrated, microscopically, when the animals were sacrificed early after injection. Neither was intravascular fibrin found when such animals were sacrificed near to death, i.e., 4–6 hours after injection. At this time many hemorrhages were found and the blood was incoagulable.

Sublethal doses of whole venom: When administering sublethal doses it became possible to separate the occurrence of hemorrhage from the coagula-
738

Fig. 2.—Thrombi in glomerular loops of kidney of guinea pig sacrificed 5 minutes after intravenous injection of 5 mg. of whole *Echis colorata* venom. Zenker fixation, PTAH stain, x 400.

Disturbance of platelet function after receiving sublethal doses of venom was indicated by marked decrease in the platelet count, plasma fibrinogen level, and plasma factor V concentration. In animals, sacrificed a few hours after having received 200 μg. of venom, hemorrhages were found in the lungs, spleen, kidneys and diaphragm. Following injection of 100 μg. of venom (into six animals), however, no hemorrhages were observed macroscopically, although the blood of these animals was severely thrombocytopenic and did not clot even after addition of thrombin. Histologic examination of two of these animals did not reveal fibrin in the blood vessels of the various organs examined, except for minute amounts of granular-fibrous fibrin material in the trabecular vessels of the spleen. There were some intraalveolar hemorrhages in the lungs, but not in the other internal organs. Marked congestion in the kidneys was noted.

The decrease in platelet count and in plasma fibrinogen level following sublethal venom doses of 100 and 50 μg. is illustrated in a representative experiment in figure 3. It will be seen that parallel with these changes there was a marked drop in plasma factor V concentration. About 30 hours following the injection of 100 μg. of venom, the plasma fibrinogen and factor V levels, as well as the platelet count, had returned to about the preinjection level. The smaller dose of 50 μg. produced a lesser drop in the two coagulation factors and the platelet count, all three regaining normal values within 6–12 hours after injection. The blood of guinea pigs injected with sublethal doses of whole venom showed fibrinolytic activity at the time when the plasma fibrinogen level was decreased (fig. 3, FI), as demonstrated, at the stage of hypofibrinogenemia, by rapid lysis of whole blood clots and of recalcified plasma clots, or, at the stage of total afibrinogenemia, by the euglobulin lysis test.
The Effect of Intravenously Administered Chromatographic Venom Fractions

Two fractions, I and II, consisting each of pools of eluate from consecutive test tubes corresponding to the protein peaks shown in figure 4, were used. Both fractions had gelatinase activity. Fraction I, first eluted from the column, had low toxicity and strong fibrinogenolytic-fibrinolytic activity. Fraction II was highly toxic and contained strong procoagulant activity, but its fibrinogenolytic activity was much weaker than that of fraction I (the fibrinogenolytic activity of fraction II was tested on purified bovine fibrinogen in order to avoid clotting by the prothrombin-converting procoagulant*). Both fractions were shown, by using heated clots, to lyse fibrin directly, but additional plasminogen activation was not excluded.

Lethal doses of venom fractions: Injection of 0.5 ml. of each of the undiluted fractions, separately (each fraction 3 animals), caused death with widespread internal hemorrhages, incoagulability of the blood and severe thrombocytopenia, the animals dying within 20 minutes after injection of fraction II and about 90 minutes after injection of fraction I. No intravascular clots were found in these animals.
In two animals sacrificed 5 minutes following administration of undiluted fraction II, the blood was found to be coagulated in the inferior caval vein, the left ventricle of the heart and the left bronchial artery. In addition, the blood which entered the abdominal cavity on performing the autopsy clotted rapidly. Both the intravascular and the free extravascular clots lysed in situ within 5 to 10 minutes. Histologic examination of the organs, removed after a further 5 minutes, revealed fibrin in the larger blood vessels and in the glomerular loops of the kidney. There were fibrin thrombi in the larger blood vessels of the lungs (fig. 5); also, the lung venules contained fibrin (fig. 6). Net-like fibrin fibers were found in the blood vessels of the liver. Hemorrhages were not seen, macroscopically or microscopically, except occasionally in the lungs. Two animals, sacrificed 5 minutes following injection of undiluted fraction I, did not show hemorrhages. The autopsy finding, however, differed from that in the animals which had received fraction II in that no clots and, microscopically, no intravascular fibrin were found.

Sublethal doses of venom fractions: Similar to the observations with whole venom, sublethal doses of each of the fractions I and II separately (three and
three animals, respectively), produced incoagulability of the blood and marked thrombocytopenia without hemorrhages.

Two animals, sacrificed 5 minutes after injection of a sublethal dose of 0.5 ml. of fraction II, diluted 1:125, did not show hemorrhages, macroscopically or microscopically. In none of the organs could intravascular clots or fibrin be demonstrated, except in the liver, where in the small radicles of the portal vein, minute amounts of granular fibrin material were found. Such minute quantities of fibrin, however, could be found also in control animals, not injected with the venom.

Figure 7 illustrates the findings in the blood in representative experiments on guinea pigs injected with sublethal non-hemorrhagic doses of the separate venom fractions. The amounts used, 0.5 ml. of fraction I diluted 1:8, or fraction II diluted 1:125, were determined by preliminary in vivo titration of their hemorrhagic and coagulation activities. It will be seen that each fraction, separately, was capable of producing total afibrinogenemia, marked
thrombocytopenia and decrease in factor V concentration within 1½–2 hours following injection. The values returned to normal after about 24 hours, similar to what was observed after administration of 100 µg. of whole venom.

The blood of these injected animals was found to have fibrinolytic activity at the time when plasma fibrinogen level was low, and disappearing with rising fibrinogen concentration. A difference was observed in the thrombocytopenia-producing activity of the two fractions, that of fraction II being weaker than that of fraction I when related to their fibrinogenopenic potency. As shown in figure 7, fraction II in a maximal dilution (1:125), still producing total afibrinogenemia, decreased the platelet count to about one-half the initial level. On the other hand, following injection of fraction I the afibrinogenemia was associated with a drop in the platelet count to about one-twentieth of the initial value.

Another difference in the action of the two fractions was the finding of procoagulant activity (fig. 7, PC) in the plasma of animals injected with fraction II, but not in those which received fraction I. The oxalated plasma obtained 12 hours following injection of fraction II (dilution 1:125) was found to clot without the addition of calcium ions after 15 minutes standing at room temperature, and the recalcification time determined in the plasma immediately after centrifugation of the blood was shortened to 14 seconds from a preinjection normal of 30 seconds, this although the fibrinogen level of the plasma was still only 20 mg. per cent. Addition of such plasma to oxalated plasma obtained from a control guinea pig (1:1) shortened the recalcification time from 35 to 16 seconds. This difference in the two fractions

Fig. 6.—Fibrin (arrow) in lung venule of guinea pig sacrificed 10 minutes after intravenous injection of 0.5 ml. fraction II. Zenker fixation, PTAH stain, x 190.
corresponds to the finding of intravascular clotting only in those animals injected with undiluted fraction II.

The question arose whether the hypofibrinogenemec activity of fraction II was mainly due to its fibrinogenolytic action or to its procoagulant causing intravascular defibrination. Fraction I, the in vitro fibrinolysin titer of which was 10 times stronger than that of fraction II, was injected in a dilution (1:1250) having fibrinolytic activity equal to that of fraction II diluted 1:125. It was found that fraction I, which is devoid of procoagulant, in this dilution did not cause a drop in plasma fibrinogen and even at a dilution of 1:125 with a fibrinolysin titer 10 times higher than that of 1:125 diluted fraction II, no drop in plasma fibrinogen occurred. Apparently, therefore, fraction II caused afibrinogenemia mainly by virtue of its procoagulant, the action of which was followed by intravascular fibrinolysis. It is noteworthy that high dilutions of fraction I (1:125), which did not cause a significant drop in fibrinogen nor in factor V, did produce thrombocytopenia (drop from 310,000 to 100,000 platelets per cu.mm.) Even at a dilution of 1:1250, fraction I caused a drop in platelet count from 320,000 to 210,000 per cu.mm.
Fig. 8.— Effect of antivenin on the action of lethal and sublethal doses of *Echis colorata* venom. 0.5 ml. of venom preincubated with 0.6 ml. antivenin for 1 hour at 37 C. Graphs for a specific dose relate to one guinea pig. Both animals survived.

**Effect of Antivenin**

Antivenin was able to neutralize the lethal, the hemorrhagic, the hypofibrinogenemic, hypoaccelerinemic and thrombocytopenic activities of the venom (fig. 8, cf. fig. 3) and of the separate venom fractions. At large doses of whole venom the antiserum was able to neutralize its lethal and hemorrhagic activities, but afibrinogenemia, thrombocytopenia and factor V deficiency did occur. The animals injected with venom-antivenin mixture showed behavior similar to those injected with smaller sublethal doses of whole venom (100 μg.) or venom fractions (I diluted 1:8, II diluted 1:125).

**Discussion**

The present observations show that the venom of *Echis colorata*, in sublethal doses, may produce in vivo severe coagulation disturbances—afibrinogenemia, factor V deficiency and thrombocytopenia—without hemorrhage. The production of this non-hemorrhagic coagulation defect in different ani-
EFFECTS OF ECHIS COLORATA VENOM IN GUINEA PIGS

mals, the mouse and the guinea pig, establishes firmly the primary importance of vessel-wall damaging agents in the causation of snake bite hemorrhage. The coagulation disturbance produced by hemorrhagic snake venoms probably aggravates the bleeding.

This phenomenon is a further instance of conditions in which afibrinogenemia may exist without necessarily leading to hemorrhage, such as congenital afibrinogenemia and experimental afibrinogenemia induced by slow intravenous thromboplastin, thrombin or trypsin injection. Similarly, marked thrombocytopenia may be present in the human for prolonged periods of time without spontaneous bleeding taking place.

As the rapidity of the appearance of afibrinogenemia following the venom injection excludes the impairment of fibrinogen production from being its sole cause, two main mechanisms may be considered: intravascular fibrinolysis, and intravascular clotting followed by fibrinolysis.

The results obtained with the separated chromatographic fraction I show conclusively that one mechanism by which Echis colorata venom can produce afibrinogenemia in vivo is fibrinogenolysis. The afibrinogenemia produced by this fraction, which possesses a strong fibrinogenolysin, cannot be due, either wholly or in part, to intravascular clotting since it is devoid of procoagulant.

On the other hand, there is evidence that the venom of Echis colorata and other snakes can produce afibrinogenemia by a second mechanism—intravascular clotting followed by fibrinolysis. Taylor et al., Lamb and Hanna, Houssay and Sordelli and Klobusitzky and König observed early intravascular clotting following the injection of large amounts of various snake venoms known to produce afibrinogenemia. Similarly, both whole Echis colorata venom and its procoagulant, containing chromatographic fraction II in high doses, produced early intravascular clotting in the guinea pig. Indeed, after the injection of Echis colorata venom or fraction II, procoagulant activity could be demonstrated in the blood of the animals. The rapidly occurring lysis of the intravascular and extravascular clots observed in these animals makes it understandable why the in vivo clots could be found only when the animals were sacrificed early after the injection of the venom. Such observations should make one cautious in ascribing afibrinogenemia to fibrinogenolysis exclusively, in pathologic conditions such as snake bite and obstetric shock, where both clot-promoting factors and fibrinogenolysin-fibrinolysin may be involved.

It is possible that the afibrinogenemia caused by the injection of whole venom is due to the action of both the procoagulant and the fibrinogenolysin. A similar situation may exist in afibrinogenemia associated with abruptio placentae, where both intravascular clotting and fibrinogenolysis may be involved.

The present experimental results do not allow the evaluation of the relative importance of the role of each of these two factors in the causation of afibrinogenemia following the administration of Echis colorata venom in the whole range of doses applied in this study. Whereas at high doses of the venom, early intravascular clotting was observed, no intravascular fibrin or practically
none could be demonstrated following the administration of lower sublethal afibrinogenemia-producing amounts. There is indirect evidence, however, that the afibrinogenemia produced by the smaller sublethal doses of whole venom and of fraction II, which possesses both fibrinogenolysin and procoagulant, is mainly due to the latter. Fraction I diluted so as to provide an in vitro fibrinolytic titer equal to that of a 1:125 dilution of fraction II did not result in any decrease of fibrinogen in vivo, whereas the procoagulant containing fraction II at this titer rapidly produced complete afibrinogenemia. Furthermore, previously reported findings on the effect of *Echis colorata* venom on blood in vitro³⁶ make it probable that the chief factor, responsible for the in vivo afibrinogenemia produced by the whole venom, is the procoagulant, since very high concentrations of whole venom (2.5 mg. per ml.) were required to obtain incoagulable blood without preceding coagulation. The failure to demonstrate intravascular clotting following sublethal afibrinogenemia-producing doses of whole venom or of fraction II apparently is due to rapid fibrinolysis of small fibrin clots.

Since the plasma fibrinogen level is determined not only by its rate of disappearance from the circulation but also by its rate of inflow, it is unfortunate that no information has been obtained on a possible effect of snake venom intoxication on the latter. The observation that the fibrinolytic and procoagulant activities demonstrable in the blood during the hypo fibrinogenemia had disappeared from the blood at the time when the fibrinogen concentration had returned to about normal suggests that fibrinogen inflow into the blood stream is continuing during the venom intoxication. Apparently the continuing inflow of fibrinogen leads to normalization of the plasma fibrinogen only when it is not being attacked any more by the circulating procoagulant and fibrinogenolysin. A similar explanation has been given by Rosenfeld et al.34 concerning the afibrinogenemia in dogs injected with *Bothrops jararaca* venom.

Whether the decrease in factor V occurring coincident with the afibrinogenemia is due to consumption in the clotting process or to a possible destruction by the fibrinolysin⁵⁵ is not known.

The thrombocytopenia in clinical and experimental snake venom intoxication has not been satisfactorily explained. No doubt the thrombocytopenia is not solely a sequel of the hemorrhage, since in the present experiments severe thrombocytopenia has been produced by sublethal venom doses or, as reported previously,³ by large amounts of venom pretreated with antivenin without any bleeding occurring. A direct lytic action of snake venom on the platelets has been claimed for the *Bothrops*,³⁶ and Russell viper venoms.⁵⁷ *Echis colorata* has been shown to inhibit the clot-retracting activity of human blood platelets and, at high concentrations, to lyse them.⁸ Whether the thrombocytopenia occurring following the injection of *Echis colorata* venom is a consequence of intravascular clot formation or of a direct lytic action of the venom, or both, is not known. A direct action of the venom on the circulating platelets is consistent with the occurrence of thrombocytopenia without any decrease of plasma fibrinogen observed after injection of diluted fraction I. Until now, however, we have not been able by chromatographic fractionation to separate between platelet damaging factor and fibrinolysin. It is noteworthy that the
EFFECTS OF ECHIS COLORATA VENOM IN GUINEA PIGS

hypofibrinogenemia, developing in the human consequent to intravenous streptokinase administration, is not accompanied by a fall in the platelet count, indicating that fibrinolysis per se is not conducive to thrombocytopenia.

A possible role of fibrinogen and fibrin split products in the pathogenesis of the coagulation disturbance due to Echis colorata venom injection has not been studied. Fletcher and co-workers have pointed out that such split products, appearing in the circulation following streptokinase infusion, may render fibrin polymerization defective. It is improbable, however, that in Echis colorata venom intoxication, the fibrinogen or fibrin split products are responsible for the hemorrhage, as hemorrhage may be absent even at total afibrinogenemia.

SUMMARY

Intravenous injection into the guinea pig of lethal doses of Echis colorata venom or of each of its two chromatographic fractions, separately, caused hemorrhage, afibrinogenemia, factor V deficiency and thrombocytopenia. Sublethal venom doses caused afibrinogenemia, factor V deficiency and thrombocytopenia in the absence of hemorrhage.

Early intravascular clotting was observed following injection of high lethal doses of both whole venom and of procoagulant-containing fraction II, but not of fraction I which was devoid of procoagulant activity.

The afibrinogenemia produced by fraction I was due to its fibrinogenolytic activity, whereas the afibrinogenemia produced by fraction II, which also had fibrinogenolytic activity, was due chiefly to its procoagulant.

Anti-Echis colorata venom rabbit serum inhibited the fibrinogenolytic, the procoagulant and the thrombocytopenic activities of the venom.

SUMMARIO IN INTERLINGUA

Le injection intravenose, in porcos de India, de doses letal de veneno de Echis colorata (o—separatamentemente—del un o del altere de su duo fractiones chromatographic) causava hemorrhagia, afibrinogenemia, carentia de factor V, e thrombocytopenia. Doses subletal del veneno causava afibrinogenemia, carentia de factor V, e thrombocytopenia in le absentia de hemorrhagia.

Un precoce coagulation intravascular esseva observate post le injection de alte doses letal tanto de veneno total e del fraction II, le qual contine un agente procoagulatori, sed non del fraction I, le qual se monstrava disproviste de activitate procoagulatori.

Le afibrinogenemia producite per fraction I esseva causate per su fibrinogenolysina, durante que le afibrinogenemia producite per fraction II (que etiam possede activitate fibrinogenolytic) resultava primarimente de su component procoagulatori.

Sero de conilio anti veneno de Echis colorata inhibiva le activitates fibrinogenolytic, procoagulatori, e thrombocytopenic del veneno.

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EFFECTS OF ECHIS COLORATA VENOM IN GUINEA PIGS


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