of sets of litter mates taken from the assay procedures.

Conclusion. On the basis of these experiments carried out with rats, it is our conclusion, in agreement with other observers, that for animals of both sexes the female sex hormone (a) stunts the growth of young animals, (b) increases the density of the bone-shaft, (c) accelerates epiphyseal closure, (d) increases the percentage of bone-ash.

These postulates confirm the depressing effect of this hormone on the parathyroid glands; further confirmed by the greater response in this effect when female animals were used (Experiment I).

The male hormone, on the other hand, in both sexes (a) stunts the growth of the animal, (b) diminishes the density of the bone-shaft, (c) diminishes the percentage of bone-ash, (d) delays epiphyseal closure, (e) depresses slightly the blood calcium, but does not increase the serum inorganic phosphorus.

To summarize: The male sex hormone is rachitogenic; the female sex hormone is antirachitic. The use of the female hormone is suggested either alone or in conjunction with vitamin D in the treatment of either sex where there is overaction of the parathyroids.

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16219 P

Activation of Plasma Thromboplastinogen and Evidence of an Inhibitor.*

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Evidence has been presented earlier indicating that the first reaction in the coagulation of the blood is the conversion of the precursor of thromboplastin, thromboplastinogen, to the active form.[1] This is brought about by a factor in the platelets. Hemophilic platelets appear equally as active as those of normal blood. The reaction can readily be studied by the prothrombin consumption test, which consists in determining the prothrombin before and after coagulation. Typical results are presented in Table I.

Recently Milstone[2] has also obtained data showing that the thromboplastin in plasma occurs in an inactive form which he names prothrombokinase. He observed that it is activated in the presence of calcium, but he does not mention or apparently consider the platelets as a possible activation factor. From recent studies[1] it appears more likely that thromboplastin is not an enzyme but that its activation is enzymatic.

Recently it was found that the blood of a patient who developed a hemophilia-like disease (presumably as a sequela to pemphigus) contains an agent which inhibits the activation of thromboplastinogen. Significant results obtained in the study of the patient's blood are given in Table II. In addition it was found that the prothrombin time response of the patient's plasma to serial dilutions of thromboplastin is identical with that of normal plasma.

It seems clear that the impaired coagulation is not due to an anti-thromboplastin. The cause must be due either to a lack of thromboplastinogen or to failure of the latter

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1 Quick, A. J., *Am. J. Med. Sci.*, 1947, **214**, 272.

2 Milstone, J. H., *Science*, 1947, **106**, 546.

TABLE I.
Prothrombin Consumption in the Coagulation of Normal Blood, of Normal Deplateletized Plasma and of Normal Deplateletized Plasma Mixed with Hemophilic Platelets.

	One hour after coagulation	
	Prothrombin time of serum‡ sec	Prothrombin activity remaining %
Normal blood	37	10
Deplateletized* normal plasma	10½	100
Deplateletized normal plasma mixed with hemophilic platelets†	37	10

* The needle and syringe used for collecting the blood were coated with methyl-chloro silane (Dri-Film). The blood was transferred to a tube similarly coated and centrifuged at 6000 rpm in an angle centrifuge for 10 minutes.

† Washed platelets obtained from 3 cc of hemophilic plasma by means of differential centrifugation were mixed with 1 cc of deplateletized plasma.

‡ To a mixture of 0.1 cc of 0.02 M $CaCl_2$, 0.1 cc thromboplastin and 0.1 cc fresh oxalated plasma treated with $Ca_3(PO_4)_2$, 0.1 cc of serum was added.

TABLE II.
Evidence of a Substance (in the Blood of a Patient with a Hemophilia-like Condition) Which Inhibits the Activation of Thromboplastinogen.

	Coagulation time (Lee-White) min	Prothrombin activity remaining in serum 1½ hr after coagulation %
Normal blood	6	15 (32 sec)
Hemophilia-like blood	35	80+ (12 '')
Hemophilia-like blood, 1 vol., normal blood, 1 vol.	30	80+ (12 '')

to be activated. If it be a simple lack of thromboplastinogen, the addition of normal blood should restore the coagulation time approximately to normal and significantly increase the prothrombin consumption as is observed with hemophilic blood. This does not occur. In fact when one volume of the patient's blood is mixed with one volume of normal blood, the mixture has nearly as long a coagulation time as that of the patient's blood. The most obvious explanation is that this hemophilia-like blood contains an excess of a substance which inhibits the conversion of thromboplastinogen to active thromboplastin. This also explains why patients of this type are refractory to transfusions and to anti-hemophilic globulin. In uncomplicated hemophilia, the defect appears to be essentially a deficiency of thromboplastinogen, but the reports of Munro and Munro[3] and of Lawrence and Craddock[4] suggest that the disease can be complicated by the appearance in the blood of an inhibitor. It is likely that the agent is the same as the one occurring in the patient of this report.

From these results it can be concluded that a thromboplastin deficiency may arise either from a lack of thromboplastinogen in the plasma or from an agent which inhibits the platelet factor. A third possible cause may be postulated, namely, a lack of the platelet factor. All three conditions are characterized by a markedly incomplete conversion of prothrombin.

Summary. The first step in coagulation is the conversion of thromboplastinogen to active thromplastin by a platelet factor. The platelets from hemophilic blood react equally as well as those of normal blood. Evidence of a factor which inhibits the activation of thromboplastinogen has been found in the blood of a patient who has an acquired hemophilia-like condition.

[3] Munro, F. L., and Munro, M. P., *J. Clin. Invest.*, 1946, **25**, 814.

[4] Lawrence, J. S., and Craddock, C. G., *Science*, 1947, **106**, 473.