It may be noted in this connection that Hertz, Allen, Tullner and Westfall(22) have recently remarked upon the association of anesthetic and endocrine properties in the non-steroid compound Amphenone "B".

Summary. Ovulatory reactions of the first follicle of the hen's ovulation sequence to barbiturates, and to barbiturates with progesterone, are described. Ovulation was found to occur prematurely in a significant proportion of hens following the administration of some barbiturates (Dial, Ipral and Nembutal), rarely with barbital, and not at all with phenobarbital. Near subovulatory dosages of progesterone acted synergistically with two of the barbiturates (Dial and Nembutal) which themselves effect ovulation prematurely, an effect which was not found when progesterone was similarly administered with phenobarbital (preliminary observations). These several observations are consonant with the supposition that prematurity of ovulation following the administration of effective barbiturates results from neural excitation secondary to depression, excitation effecting over a humoral pathway the release of ovulation-inducing gonadotrophin from the anterior pituitary body.

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New Hemophilia-like Disease Caused by Deficiency of a Third Plasma Thromboplastin Factor.* (20057)

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(Introduced by W. Antopol.)

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Hemophilia has been generally recognized as a hereditary disease characterized by the deficiency of a plasma factor which reacts with platelets to form thromboplastin(1-3). This factor, designated as anti-hemophilic globulin (AHG), is essential for the normal conversion of prothrombin to thrombin(4,5). Recently, evidence for a second plasma thromboplastin factor has been presented on the basis of 2 reports of male patients with hemorrhagic disease and coagulation findings similar to hemophilia except that the blood of these

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TABLE I. Matching Experiments Performed on Mixtures of Whole Blood of Patients with Anti-Hemophilic Globulin (AHG), Plasma Thromboplastin Component (PTC) and Plasma Thromboplastin Antecedent (PTA) Deficiencies.

Exp. 1	B.Y. (Family A, PTA deficiency)	cc	2	1	0
	P.B. (AHG deficiency)	"	0	1	2
	Clotting time	min.*	24	5	62
	Serum prothrombin time	sec.†	15	24	12
Exp. 2	D.R. (PTC deficiency)	cc	2	1	0
	P.B. (AHG deficiency)	"	0	1	2
	Clotting time	min.	47	5	85
	Serum prothrombin time	sec.	8	35	10
Exp. 3	D.R. (PTC deficiency)	cc	2	1	0
	B.Y. (PTA deficiency)	"	0	1	2
	Clotting time	min.	35	9	25
	Serum prothrombin time	sec.	12	37	12

* Measured in glass tubes 13 × 100 mm at 37°C.
† Determined by the one-stage method of Dreskin(8).

patients mutually corrected the clotting defect in "true" hemophilia(6,7). For the past 3 years, we have been following 3 patients in one family, who have also had a hemophilia-like disease which was mutually corrected by hemophilic blood. Matching experiments were performed upon these patients (Family A), an unclassified hemophiliac (D.R.), true hemophiliacs and the patient reported by Aggeler, White *et al.*(6). The results provided conclusive evidence that there are 3 different plasma thromboplastin factors or precursors which can account for at least 3 types of hemorrhagic disease resembling hemophilia. The factors are AHG, plasma thromboplastin component (PTC) described by Aggeler(6) and the factor described in this paper and tentatively designated as *plasma thromboplastin antecedent* (PTA).

The patients in Family A, a 50-year-old maternal uncle (A.A.) and 2 nieces (B.Y. and M.W.), aged 29 and 25 years, have shown since childhood only slight to moderate evidences of hemorrhage, marked chiefly by bleeding after tooth extractions. Their clotting times have ranged from 15 to 29 minutes (normally 5 to 11 min.) and the serum prothrombin times have been between 12 to 17 sec.(8). Clotting results were the same for the uncle and both female members of the family. Other studies including platelet count, clot retraction, prothrombin time, tourniquet test and bleeding time have been normal. No anticoagulant was present. Matching experiments revealed that the 3 members of the family did not correct each other and, hence, had a similar clotting defect. Further experiments revealed that these patients' bloods mutually corrected bloods from patients presumed to be true hemophiliacs as evidenced both by the clotting time and serum prothrombin time (Table I, mixture of bloods from B.Y. and P.B., a "true" hemophiliac).

Patient D.R., a 4-year-old male, has had intermittent episodes of severe bleeding and subcutaneous hematomas dating from circumcision in the first week of life. There is no family history of bleeding. His clotting time has ranged from 35 to 47 minutes and serum prothrombin time from 9 to 13 sec. Other routine clotting tests have been normal. An anticoagulant was not present, and the patient's blood mutually corrected blood obtained from hemophilic patient P.B. (Table I). Additional experiments then revealed that patients D.R. and B.Y. (Family A) corrected each other (Table I). A number of experiments using other hemophiliacs and employing both blood and plasma mixtures have consistently yielded the same results. Experiments performed with plasma‡ of the patient reported by Aggeler, White *et al.*(6) revealed that Aggeler's case was identical with our patient D.R. (Table II). Thus, Family A represents the third type of deficiency which has been designated as plasma thromboplastin antecedent (PTA) deficiency.

In addition to matching experiments, it appears that the 3 types of hemophilia-like disease or plasma thromboplastin factor de-

‡ We wish to thank Drs. Sidney White and Paul Aggeler for providing the plasma from their patient.

TABLE II. Mixture Experiments Using the Recalcified Plasma Clotting Time Performed on Aggeler's Case of PTC Deficiency, Patient D.R. and Patient P.B., a True Hemophiliac.

P.B.	cc	.2	.15	.1	.05	0
Aggeler's case	"	0	.05	.1	.15	.2
$CaCl_2$ .025 M	"	.2	.2	.2	.2	.2
Plasma clotting time	min.	18	5	6	5	22
Serum prothrombin time	sec.	8	35	25	20	11
D.R.	cc	.2	.15	.1	.05	0
Aggeler's case	"	0	.05	.1	.15	.2
$CaCl_2$ .025 M	"	.2	.2	.2	.2	.2
Plasma clotting time	min.	23	20	17	15	17
Serum prothrombin time	sec.	7	13	15	15	11

TABLE III. Effect of Normal Serum, $BaSO_4$-Treated Normal Plasma and PTC Fraction on Plasma from Patients with AHG, PTC and PTA Deficiencies. Results represent recalcified plasma clotting times in min.

	cc	AHG def., .1 cc plasma	PTC def., .1 cc plasma	PTA def., .1 cc plasma
Normal serum	.1	10.5	3	4.5
$BaSO_4$-treated plasma	.1	4	15	5.5
PTC fraction	.05	10	3	3.5

ficiencies can be readily distinguished as follows: AHG deficiency (true hemophilia) is corrected by $BaSO_4$-treated normal plasma but is not corrected by normal serum(9); PTC deficiency is not corrected by $BaSO_4$-treated plasma but is corrected by normal serum(6); PTA deficiency is corrected by both $BaSO_4$-treated plasma and by normal serum. PTA deficiency was also corrected by the lyophilized PTC fraction obtained from Drs. Aggeler and White(6). (Table III).

Clinically, certain distinctions can tentatively be made among the 3 types of deficiencies. PTA deficiency can occur in both sexes and is inherited. The hemorrhagic manifestations appear to be relatively mild and the clotting times are not very prolonged, ranging from 15 to 29 min. PTC deficiency, as exemplified by 2 proven cases, occurs in males without a family history of bleeding. The hemorrhagic manifestations are more severe and the clotting times longer than in PTA deficiency. Cases previously designated as hemophilia have shown a wide range in degree of hemorrhage and prolongation of clotting time(10,11). It is possible that some of these differences can be attributed to the type of clotting defect as contrasted with explanations based upon differences in degree of a single clotting defect. Various combinations of AHG, PTC or PTA deficiencies in a single patient or the occurrence of specific anticoagulants could account for different degrees of the hemorrhagic syndromes now classified under hemophilia.

Summary. 1. A third type of hemophilia characterized by a deficiency in a plasma thromboplastin factor other than anti-hemophilic globulin and plasma thromboplastin component (PTC) has been identified in 3 patients in one family, a maternal uncle and 2 nieces. 2. These patients reveal a mild hemorrhagic disease, and their clotting times are only moderately prolonged. 3. This newly described clotting factor, designated as *plasma thromboplastin antecedent* (PTA) is present in $BaSO_4$-treated normal plasma and normal serum.

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