

## **THROMBOEMBOLIC DISEASE COMPLICATING PREGNANCY AND THE PUERPERIUM\***

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THE occurrence and serious results of thromboembolic disease in obstetric patients constitute some of our most challenging problems. Throughout the history of childbirth physicians have been acutely aware of the tendencies toward hemorrhage and thrombosis during pregnancy or after delivery.

Until recently little could be done for thrombosis except to observe with respect and humility the devastating effects of this disease in the living patient or at the autopsy table. In the past few years the development of new laboratory methods, the discovery of anticoagulant drugs, and improved surgical techniques have provided us with the tools to investigate in greater detail the mechanism of thromboembolic disease in pregnancy, and to prevent and treat it with greater success than was formerly believed possible.

The purpose of this presentation is to review the mechanism of thromboembolic disease in pregnancy and the puerperium and to analyze the cases treated at the Philadelphia Lying-In Division of the Pennsylvania Hospital, Philadelphia, Pennsylvania, for a twenty-year period, 1933-1953. The study is divided into three parts:

### **THROMBOEMBOLIC DISEASE IN PREGNANCY AND THE PUERPERIUM:**

#### **I. Thrombus Formation in Relation to Pregnancy.**

1. Mechanism.
2. Etiology.
3. Classification.

#### **II. Antepartum Thromboembolic Disease.**

1. An analysis of the literature and cases treated at the Pennsylvania Hospital, 1933-1953.

#### **III. Postpartum Thromboembolic Disease.**

1. Analysis of 172 cases treated at the Pennsylvania Hospital, 1933-1953.
2. Methods of treatment.
  - a. Prophylactic.
  - b. Active.

#### **I. Thrombus Formation in Relation to Pregnancy**

##### **1. Mechanism.—**

An understanding of the basic concepts of the mechanism of intra-vascular clotting, together with the recognition of certain predisposing fac-

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tors, is indispensable to the clinician if he is to be aware of and treat the processes occurring in his patient with this disease.

The control of thromboembolism is based upon an understanding of the physiology and pathology that lead to the formation and propagation of a thrombus or clot in the vein.

The exact mechanism of intravascular clotting and venous thrombosis is unknown. Many theories have been advanced, but none has been completely acceptable in answering all the problems of coagulation in the human body. Extensive research has shown the clinical and physical properties of in vitro clotting to be well understood, but in vivo intravascular clotting still remains an enigma.

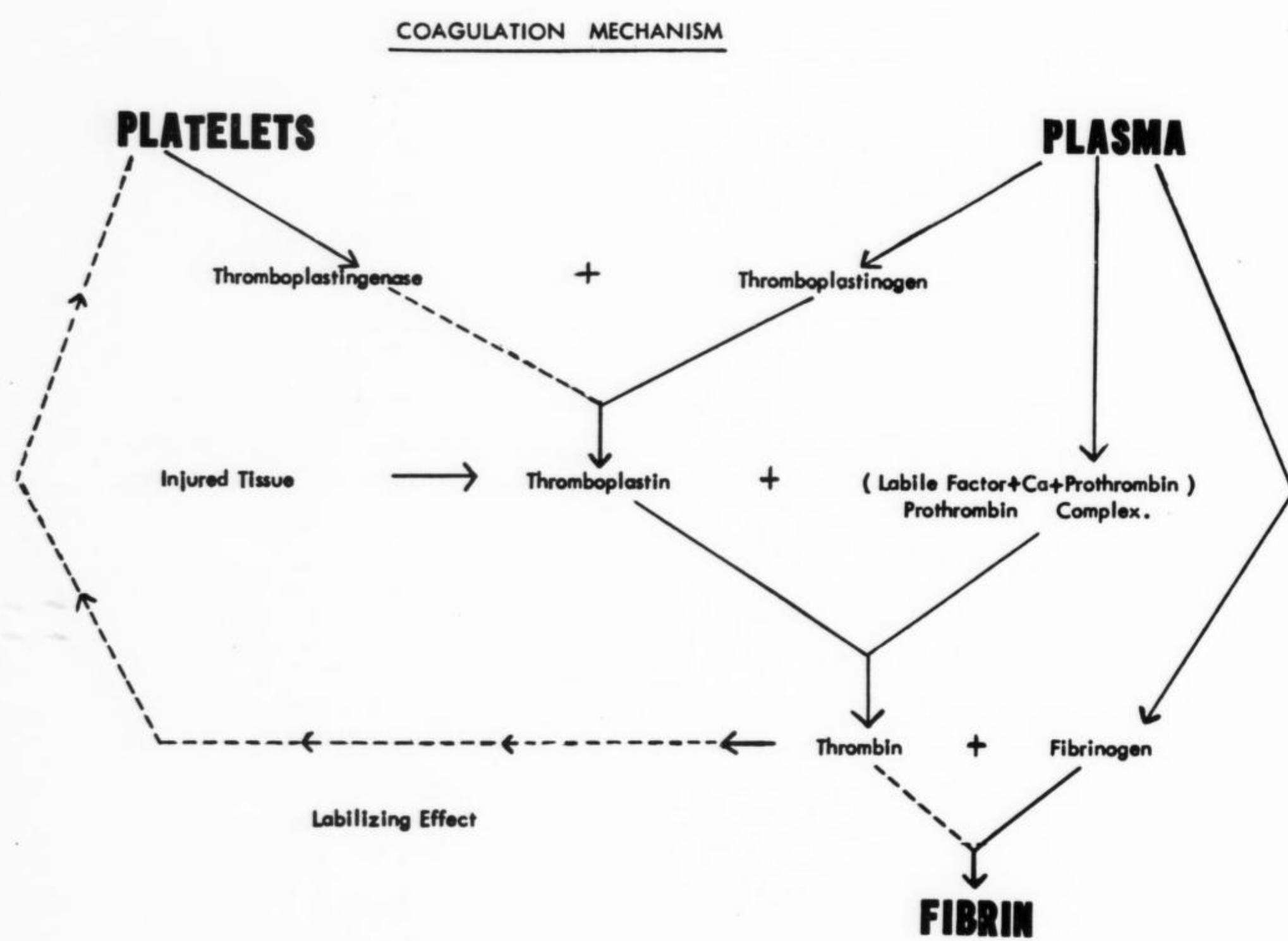


Fig. 1.—The coagulation mechanism. (Modified from Quick, A. J.: Surg., Gynec. & Obst. 91: 296, 1950.)  
Figs. 1-3 by permission of *Surgery, Gynecology and Obstetrics*.

Stefanini in 1953 showed that most investigators are in accord on certain basic principles of the coagulation mechanism. These are shown in Fig. 1. Although not complete, the diagram modified from Quick's presentation explains these principles and aids in an understanding of the process of venous thrombosis; it also formulates a rational basis for therapy in thromboembolic disease. It may be seen that the platelets and plasma are the two main constituents of the blood that produce fibrin or coagulation in the presence of disease, injury, or abnormality of the vascular endothelium. The vital step

in the mechanism is the production of thrombin. When platelets adhere to the surface of the abnormal endothelium, they rupture or disintegrate and liberate thromboplastinogenase which activates the thromboplastinogen of the plasma to form thromboplastin. The action of thromboplastin on the pro-thrombin complex of the plasma forms thrombin. As the thrombin combines with fibrinogen to form fibrin or the end product of coagulation, a chain reaction occurs from the labilizing effect of thrombin on the platelets. The absorption of thrombin to fibrin is the primary factor in the control of the chain reaction. Thrombin, because of its action on platelets, has the power to set off a chain reaction that potentially could coagulate all the fibrinogen and convert all the circulating blood into a solid clot. Because of the

SEQUENCE IN THE FORMATION OF A THROMBUS

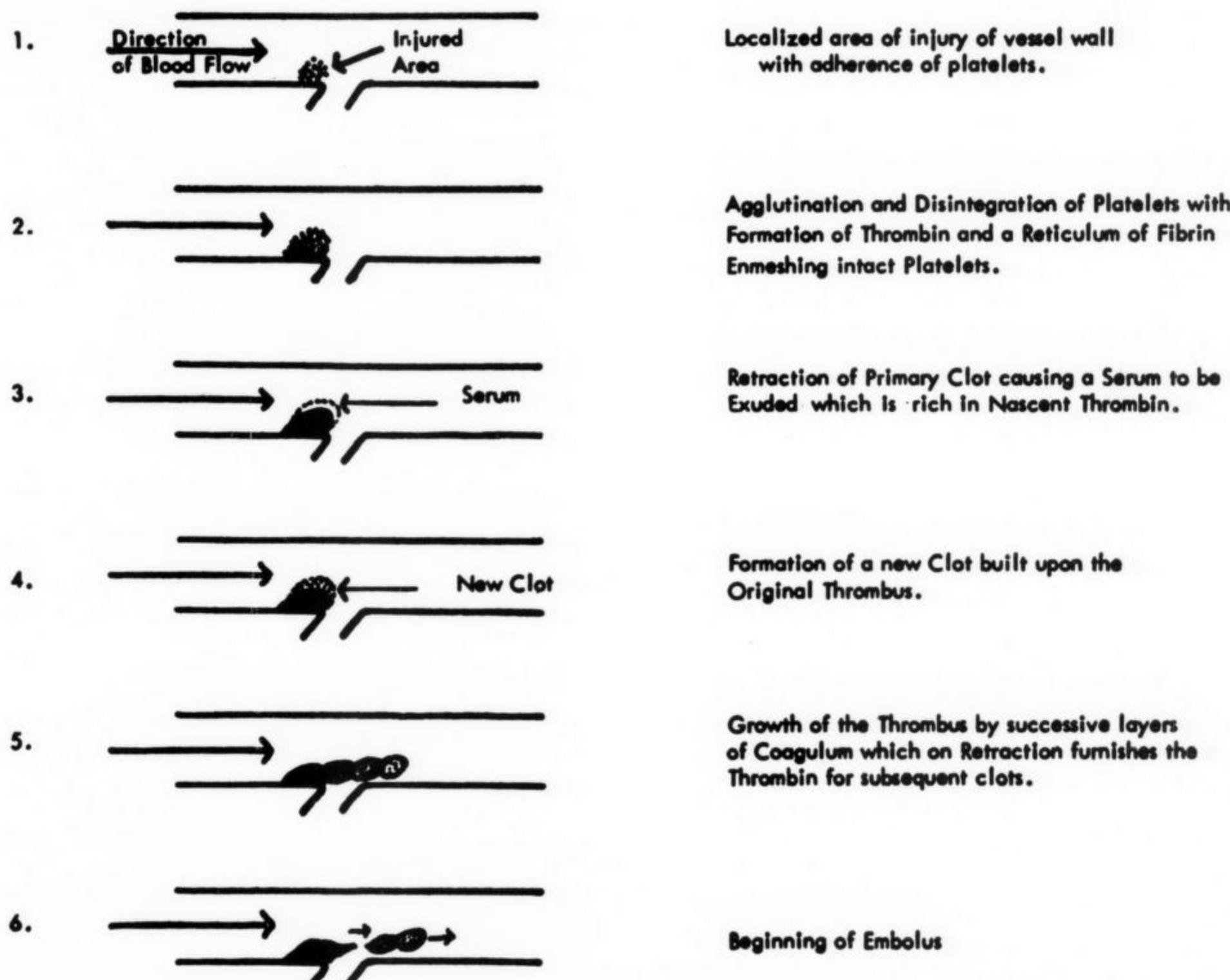


Fig. 2.—Sequence in the formation of a thrombus. (Modified from Quick, A. J.: Surg., Gynec. & Obst. 91: 296, 1950.)

enormous surface of the fibrin reticulum in the clot, however, the thrombin is promptly removed by absorption, and because of this mechanism together with antithrombin, the chain reaction cannot be initiated.

With this theory of hemostasis, or the coagulation mechanism, the problem of thromboembolic disease can be analyzed. Since coagulation necessitates disintegrating platelets as the initial cause, the following sequence occurs in the formation of a thrombus (Fig. 2 modified from Quick): (1) a localized

area of injury of a vessel wall with adherence of platelets, (2) agglutination and disintegration of platelets with formation of thrombin and a reticulum of fibrin enmeshing intact platelets, (3) retraction of the primary clot, causing a serum to be exuded which is rich in nascent thrombin, (4) formation of a new clot built upon the original thrombus, (5) growth of the thrombus by successive layers of coagulum which, on retraction, furnishes the thrombin for subsequent clots, (6) beginning of embolus.

Thus it can be seen that, if the circulation is rapid, the serum is promptly washed away and the thrombus fails to propagate. When the circulation is sluggish, the exuded serum causes the clotting of blood about the thrombus, and a new clot is built on the old thrombus. It in turn retracts, and fresh serum brings an additional extension of the thrombus.

Because of the flow of blood, the growth of the clot is principally at the tip and in the direction of the blood stream. Thus the retraction of the clot explains why the thrombus propagates itself and accounts for the observation that the clot may be entirely unattached to the walls of the vessel except at the point of origin. Such a clot is called the phlebothrombotic type.

Of greatest significance in the treatment of thrombophlebitis and phlebothrombosis is the clot retraction that occurs in the thrombus. On it depends first, the growth of the thrombus, and, second, the shrinking of the propagating mass which prevents it from staying in contact with the vessel wall. It is influenced by (1) the number of circulating platelets, (2) the speed and quantity of thrombin production, and (3) the cell volume of the blood.

Thus the logical approach to the prevention or treatment of venous thrombosis is either to reduce the clot retraction in the blood, by lowering the number of circulating platelets, or to regulate the production of thrombin. The former cannot be accomplished as yet, for too little is known about influencing the number of platelets. For the second approach we have several therapeutic agents which regulate the production of thrombin: heparin, Dicumarol, Tromexan, and Danilone (Fig. 3).

Heparin acts as an antiprothrombin as well as an antithrombin. Dicumarol, Tromexan, and Danilone reduce the production of thrombin by lowering the prothrombin level of the blood. Any reduction of thrombin formation lowers the clot retraction, and therefore the thrombotic tendency.

The third factor which influences clot retraction, the cell volume of the blood, is mechanical. The greater the number of cells the larger the bulk of the nonretractile part of the clot. Thus it can be seen that clot retraction is accelerated and more pronounced in anemic than in normal blood.

The whole process of intravascular clotting and thrombus formation is enormously complex and many changes (chemical, physical, physiological, and pathological) are taking place at the same time. If these previously mentioned basic concepts are known to the clinician, progress in therapy can more logically be made.

## 2. Etiology.—

In addition to this mechanism of thrombus formation, certain predisposing factors are known. For instance, anesthesia, infection, and nutritional de-

ficiencies cause increased blood platelet agglutination. Bacterial toxins and histamine production not only cause platelet agglutination but, in addition, stimulate thrombopoiesis and thus increase coagulative tendencies by increasing fibrinogen, prothrombin, and platelets.

Also included as etiological agents are trauma to blood vessels, stasis, increased viscosity due to dehydration, and absorption of large amounts of substances from damaged tissues. Thus it is not surprising to find that thromboembolic disease is encountered in obstetric patients, as they frequently meet these predisposing requirements. In the puerperium immobility of the lower extremities, the wearing of tight abdominal binders, pressure on the popliteal spaces from improperly designed leg holders, all increase the possibility of intravascular clotting. Obesity, anemia, hemorrhage, dehydration, and the presence of infection also may contribute to the danger of thrombosis.

THE ACTION OF HEPARIN AND DICUMAROL

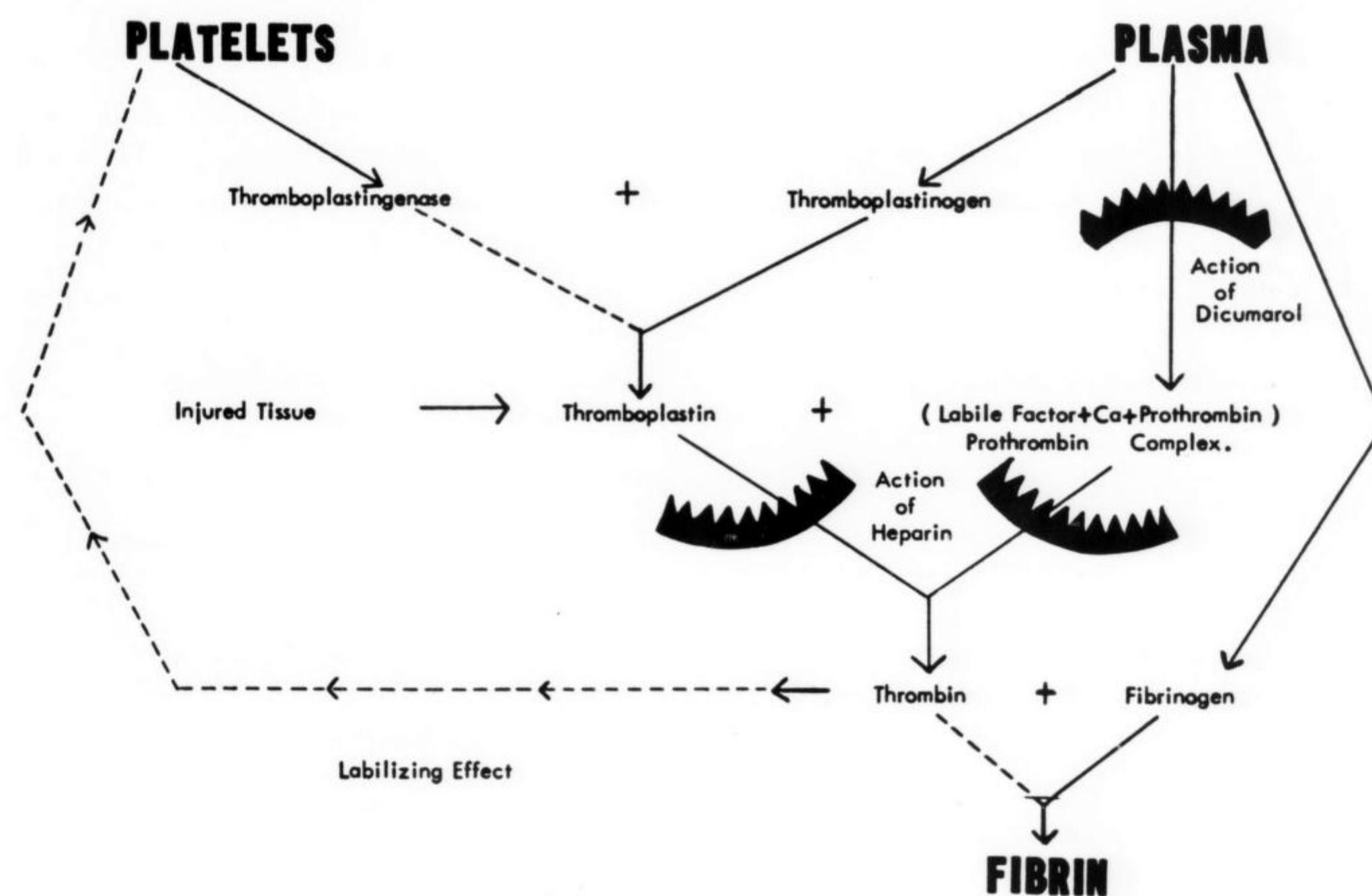


Fig. 3.—The action of heparin and Dicumarol upon the coagulation mechanism. (Modified from Quick, A. J.: Surg., Gynec. & Obst. 91: 296, 1950.)

3. Classification.—

We have classified our cases of antepartum and postpartum thrombosis in the twenty-year period of 1933-1953 as follows:

I. Adherent or obstructing thrombophlebitis.

II. Silent or nonobstructing thrombophlebitis (phlebothrombosis).

III. Septic thrombophlebitis.

Associated with pelvic sepsis in septic abortion or puerperal sepsis.  
Not included in our series except if complicating puerperal sepsis.

**IV. Superficial thrombophlebitis.**

Occurs in varicose veins of leg or vulva. Not included in our series.

**II. Antepartum Thromboembolic Disease****1. Analysis of the Literature and Cases Treated at the Pennsylvania Hospital, 1933-1953.—**

The occurrence of obstructive thrombophlebitis or phlebothrombosis as a complication of the antepartum period is apparently rare. Available figures vary from 0.037 per cent to 0.1 per cent. The frequency is difficult to ascertain, as most of the records do not mention the number of antepartum patients involved. A review of the literature to date reveals 126 cases of antepartum thrombosis. Probably more cases do occur but are not reported. If all pregnancies with this complication were reported, better assessment of therapy could be made for differences of opinion as to the conservative, surgical, or anticoagulant treatment affect the prognosis in such cases.

In addition to these 126 collected cases of antepartum thrombosis, a study of our records from 1933 to 1953 revealed 9 patients with this disease. These nine instances occurred in 50,332 patients seen during pregnancy and delivered in the hospital, an incidence of 0.018 per cent. Seven were not treated with anticoagulants and, of these, 2 developed pulmonary embolism and died. Two patients were treated with anticoagulants successfully, one in the third month of pregnancy and the other in the eighth month. Both were delivered at term without further complications, and their babies were living and well with no evidence of hemorrhage.

TABLE I. ANTEPARTUM THROMBOEMBOLIC DISEASE, PENNSYLVANIA HOSPITAL, 1933-1953

PATIENT	YEAR	DURATION OF PREGNANCY AT ONSET OF THROMBOSIS	LOCATION OF THROMBOSIS	PULMONARY EMBOLUS	THERAPY	CONDITION OF BABY AFTER DELIVERY
K. B.	1937	32 weeks	Left femoral-iliac veins	0	Heat, elevation	Living
E. B.	1938	32 weeks	Right femoral veins	0	Heat, elevation	Living
R. K.	1939	39 weeks	Left popliteal veins	0	Heat, elevation	Living
D. G.	1942	36 weeks	Right femoral veins	1 after delivery	Heat, elevation	Living
M. B.	1943	24 weeks	Left femoral veins	0	Heat, elevation	Living
M. F.	1946	16 weeks	Left saphe-nous	1 (fatal) after term delivery	Ligation at sixteenth week	Living
H. I.	1949	36 weeks	Left femoral and popliteal	0	Heparin 210 mg.; penicillin 12,500 units	Living
M. C.	1949	11 weeks	Left femoral and iliac	0	Heparin 550 mg.; Dicumarol 2,150 mg.	Living
R. M. (unreg.)	1951	38 weeks	Bilateral femoral and iliac	1 (fatal) $\frac{1}{2}$ hour after admission	None	Dead

Of the 135 cases of antepartum thrombosis reviewed in the literature (including 9 of our own) 97 were not treated with anticoagulants. Among the 97 patients not treated with anticoagulants there occurred 18 cases of pulmonary embolus with 15 fatalities, a maternal mortality of 15 per cent.

TABLE II. ANTEPARTUM THROMBOEMBOLIC DISEASE NOT TREATED WITH ANTICOAGULANTS

AUTHORS	YEAR	NO. OF CASES RECORDED	CASES WITH PULMONARY INFARCTS	FATAL EMBOLI
Remy	1922	3	3	3
Holzmann	1924	10	1	1
Knauer	1927	4	4	4
Bansillon and Pigeaud	1931	1	0	0
Laffont and Schebat	1932	1	1	1
Friedlander	1936	1	0	0
Rochat	1939	2	1	1
Faureau	1939	1	0	0
Simard	1939	6	0	0
Maxwell	1939	1	0	0
Walsh and Barone	1947	3	1	1
Nyklicek	1948	1	1	0
Donaldson	1950	48	3	2
Davis	1951	2	0	0
Hallum and Newham	1951	5	1	0
Thornton	1951	1	0	0
Ullery	1954	7	2	2
Total		97	18	15 (15%)

Thirty-eight cases were found in the literature in which anticoagulants were used. Although 7 of these 38 treated patients had pulmonary embolism prior to anticoagulant therapy, there were no fatalities.

TABLE III. ANTEPARTUM THROMBOEMBOLIC DISEASE TREATED WITH ANTICOAGULANTS

AUTHORS	YEAR	NO. OF CASES RECORDED	CASES WITH PULMONARY INFARCTS	FATAL EMBOLI
Yahr, Reich, and Egger	1945	2	0	0
Green and Loewe	1947	1	0	0
von Syndow	1947	1	0	0
Felder	1949	2	0	0
Sachs and Labate	1949	1	1	0
Weiss and Turner	1949	1	0	0
Adamson, Weaver, and Jaimet	1950	5	1	0
Davis	1951	1	0	0
Thornton	1951	2	0	0
Ware	1951	3	0	0
Wright, H. P.	1951	10	2	0
Mansell	1952	5	1	0
Flood	1953	2	2	0
Ullery	1954	2	0	0
Total		38	7	0

The data on the treatment of antenatal thrombosis obtained from the literature and from our experience with 9 cases are too few to draw absolute conclusions on any given method of therapy. The fact, however, that among 97 cases of antepartum thrombosis not treated with anticoagulants there were 15 fatal emboli (15 per cent) indicates the serious consequences that may occur. In the 38 patients in the literature with antenatal thrombosis who had

anticoagulant therapy no fatal embolism occurred. These figures, though small, are statistically significant, indicating that this method of treatment is of benefit in reducing fatalities. It seems most logical to provide the antepartum patient with the benefits of anticoagulant treatment provided the risk of hemorrhage to mother and child is not too great.

We believe the effects of anticoagulants on the mother and child are minimal and safe if the prothrombin time of the patient is maintained within safe limits of 18 to 23 seconds (20 to 30 per cent of normal) regardless of the stage of pregnancy at which the drug is used. In Case 8 (M. C.) of our group, heparin and Dicumarol were given at 11 weeks of pregnancy and within a few days after vaginal bleeding due to threatened abortion. Although the drugs were used in the most critical stage of the life of the fetus, no deformities or hemorrhagic tendencies occurred, either in the remaining portion of the antenatal period, at term, or after delivery.

In Case 7 (H. I.) the patient was on controlled heparin therapy for thrombosis at the time of the onset of labor. There were no untoward effects on the mother or baby during delivery or in the puerperium.

It should be emphasized that vigilance must be unending, with careful regulation of prothrombin times and constant supervision and observation. In this capacity, the cardiologist-internist and the vascular surgeon of the hospital see all such patients in consultation with the obstetrician, to determine the treatment which seems most suited to the individual patient. This teamwork has been of inestimable value.

### III. Postpartum Thromboembolic Disease

Obstructing thrombophlebitis and nonobstructing venous thrombosis (phlebothrombosis), although rare during pregnancy, are more frequent after delivery. They may be the cause of severe and prolonged disability or a precursor of pulmonary embolism. These thromboembolic diseases may be precipitated in the puerperium as follows: (1) spontaneously with no known cause; (2) following febrile disease or infections; (3) following operative obstetrical procedures; (4) following trauma.

In the silent or nonobstructing thrombophlebitis (phlebothrombosis) relatively few clinical manifestations may occur. This is more dangerous than obstructive thrombophlebitis because embolic phenomena occur more readily. Indeed, it may not be recognized until pulmonary embolism has occurred. The most important symptoms and signs to diagnose its presence are a positive Homans' sign, pulse rate increased out of proportion to the body temperature, an increase occasionally in circumference of the involved limb, and regional pain or tenderness.

#### *1. Analysis of 172 Cases Treated at the Pennsylvania Hospital, 1933-1953.—*

In the twenty-year period of 1933-1953 there were 172 patients in whom the diagnosis of venous thrombosis of the lower extremities was made during the postpartum period at the Pennsylvania Hospital. There were 50,332 deliveries in this twenty-year period, an over-all incidence of 0.34 per cent (Fig.

4). Twelve patients gave a history of venous thrombosis in prior pregnancies. Pulmonary embolism was recognized 29 times and was the primary cause of death in 7 patients. The incidence of known pulmonary embolism thus was 16.9 per cent in the 172 patients and the death rate was 4 per cent. Of the 29 patients with known pulmonary emboli, 24 per cent died. It is only within the past several years, however, that we have become more aware of the varied manifestations of less serious pulmonary emboli, with or without infarction. Unquestionably, numerous patients had pulmonary emboli in the puerperium which were diagnosed as pneumonia, atelectasis, pleuritis, or possibly acute cardiac failure.

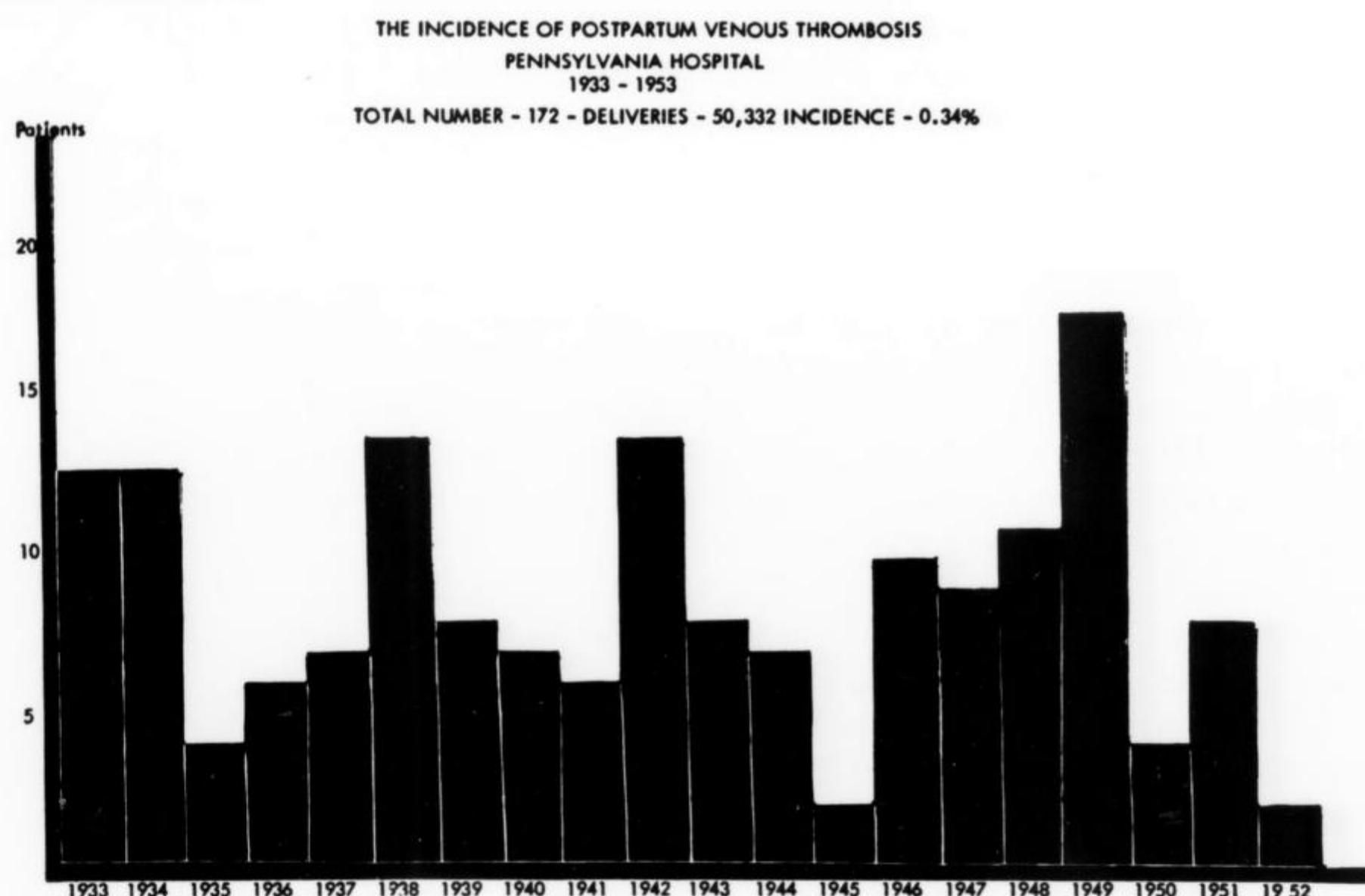


Fig. 4.—The incidence of postpartum venous thrombosis, Pennsylvania Hospital, 1933-1953.

A study of the complications or added operative interventions following delivery of 170 patients who developed venous thrombosis revealed 43 cases, or 25 per cent, with some added factor of trauma, infection, or disease which could have been contributory.

TABLE IV. THE INCIDENCE OF POSTPARTUM COMPLICATIONS DUE TO VENOUS THROMBOSIS

COMPLICATIONS	NUMBER OF CASES
Pyelitis	10
Endometritis	7
Sterilization	5
Toxemia	3
Sulcus laceration	3
Hemorrhage	3
Appendectomy	1
Psychosis	2
Wound infection	2
Pneumonia	2
Syphilis	1
Peritonitis	1
Tonsillitis	1
Rheumatic heart disease	1
Septicemia	1
Total	43

*Types of Delivery Employed:* The various methods used for the termination of pregnancy and delivery of the fetus in the 172 patients who developed postpartum venous thrombosis are given in Table V in order of their frequency.

TABLE V. METHODS UTILIZED FOR DELIVERY OR TERMINATION OF PREGNANCY IN 172 PATIENTS WHO DEVELOPED POSTPARTUM VENOUS THROMBOSIS

METHOD	NUMBER OF CASES
Low forceps	68
Cesarean section	51
Spontaneous	35
Breech extraction	6
Version	5
Midforceps	4
Spontaneous breech	3
Total	172

Table V shows that 51 (or 30 per cent) of our 172 patients with postpartum venous thrombosis were delivered by cesarean section. This figure leaves little doubt as to the increased hazard of venous thrombosis following abdominal delivery. Difficult operative procedures as breech extraction, version, and midforceps delivery also increase the factor of trauma and the predisposing cause of venous thrombosis.

*Anesthesia:* The types and frequency of anesthesia used in this series are listed in Table VI. Ether, or nitrous oxide and ether, were most often used in patients admitted to the hospital before 1940. More recently, spinal, continuous caudal, and nitrous oxide have been in general use. As the employment of these methods was not strictly controlled, no conclusions can be drawn regarding the superiority of any one of these methods in preventing venous thrombosis of the lower extremities. It is our impression, however, that regional or local analgesia may aid in lowering the incidence of thrombosis by their action of peripheral dilation of the circulatory system of the legs and thus decreasing the spasticity of the vessels.

Table VI reveals that 50 patients (or 30 per cent) had regional analgesia for delivery, and 122 patients (or 70 per cent) received general anesthetics. Since approximately 80 per cent of our patients delivered in the hospital have regional analgesia, it is seen that the relative incidence of venous thrombosis is lower in this group.

TABLE VI. TYPES OF ANESTHESIA UTILIZED IN THE DELIVERY OF 172 PATIENTS WHO DEVELOPED POSTPARTUM VENOUS THROMBOSIS

ANESTHESIA	NUMBER OF CASES
Ether with nitrous oxide	62
Ether	15
Spinal	37
Nitrous oxide	25
No anesthesia	17
Continuous caudal	11
Local (pudendal)	2
Cyclopropane	1
Chloroform	1
Pentothal and ether	1
Total	172

*Ambulation:* Opinions differ in the various studies which attempt to evaluate the physiological effect of early ambulation and leg exercises in the

prevention of venous thrombosis in surgical cases. Little has been written concerning this problem as it refers to the postpartum patient.

In the early years of this study of thrombosis in postpartum patients (1933-1940) the usual practice was to keep patients who were delivered vaginally in bed for ten to twelve days in the semi-Fowler or absolutely flat position. Those who had cesarean sections were kept in bed in these positions even longer, 12 to 15 days. Little attention was given to leg exercises during this time.

Gradually (1940-1946) earlier rising from bed was practiced—eight to ten days for the normal postpartum patient and some increased attention was given to leg exercises. During 1947 ambulation for patients delivered vaginally was started two to three days post partum and seven days post partum for the cesarean section patients. This was continued and the time was gradually reduced during the next two years (1948-1949), but early ambulation was irregularly practiced by the staff obstetricians.

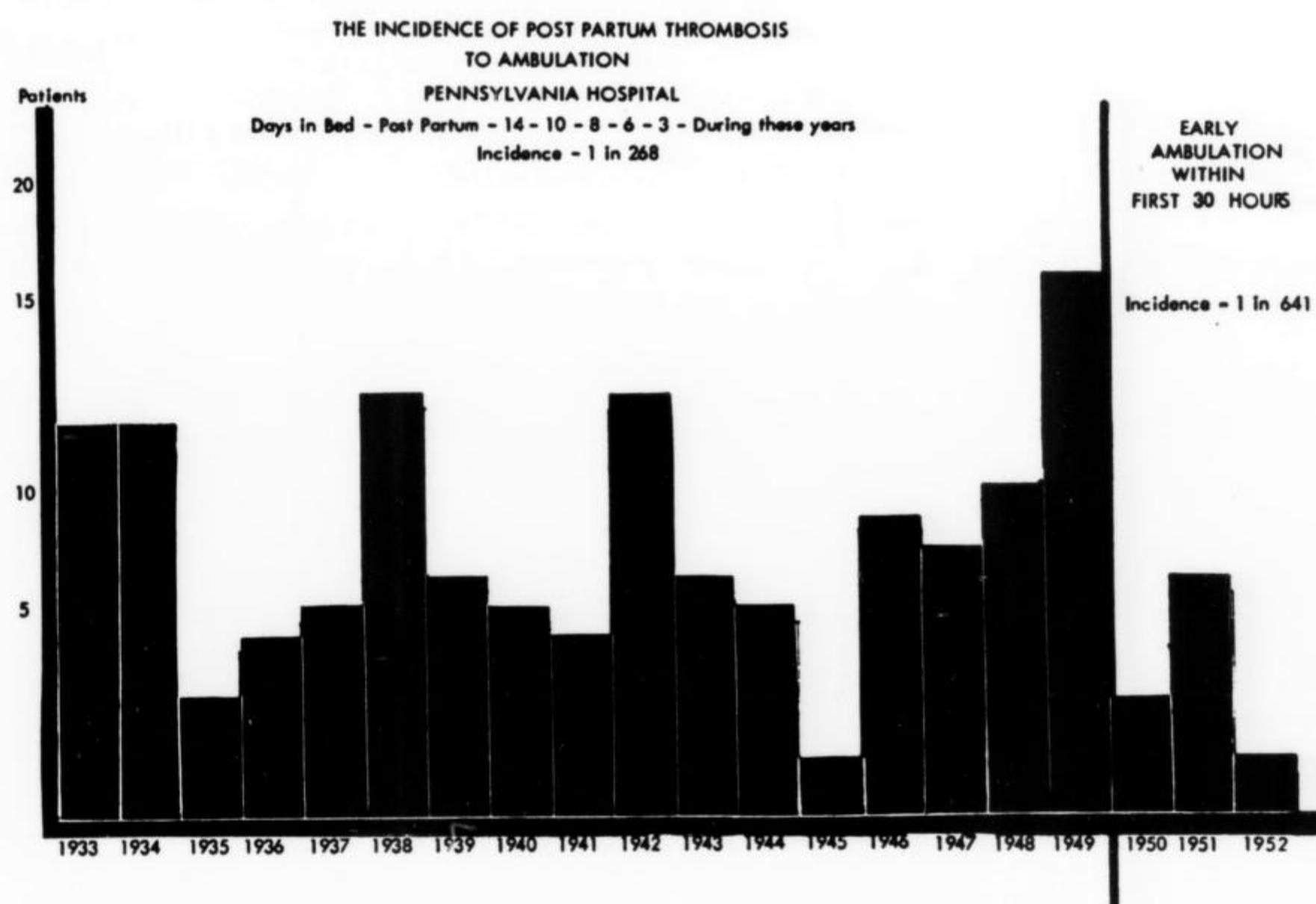


Fig. 5.—The ratio of postpartum venous thrombosis to ambulation, Pennsylvania Hospital, 1933-1953.

It was not until 1950 that early, more energetic ambulation of all postpartum patients was made the rule of the hospital and practiced on each patient unless some serious postpartum complication such as eclampsia or hemorrhage prevented. As a result, for the past three years almost all delivered patients have been encouraged to get out of bed within the first 24 hours or shortly thereafter.

In the analysis of the 172 patients with postpartum venous thrombosis, the average time for the onset of venous thrombosis in all patients was 7.6 days. For patients who were delivered by the vaginal route, it was 6.3 days, and for patients with cesarean section, 10.4 days. Thus, except for the last three years (1950-1953) the disease developed while the patients, for the most part, were confined to bed.

The relation of postpartum venous thrombosis to early ambulation is seen in Fig. 5. In the three years, 1950-1953, that early ambulation has been practiced, there were 14 patients in 8,983 who developed venous thrombosis, or an

incidence of 1 in 641. This is contrasted with the preceding 17 years of this study, 1933-1950, in which 158 patients in 41,349 developed thrombosis, an incidence of 1 in 268.

Although we have practiced early ambulation as a standardized regimen for only three years, and much more time must elapse before definite conclusions can be drawn, we feel that this procedure has great merit and may possibly diminish the incidence of postpartum venous thrombosis.

In order to accomplish this regimen, it is the obstetrician's responsibility to order the time, frequency, and amount of ambulation and leg exercises that are to be carried out by the patient. It is the obstetrician's responsibility also to see that the nursing staff is specifically instructed and that no laxity occurs. He should advise that the patients get out of bed at the earliest possible time after recovery from anesthesia, and at regular, frequent intervals thereafter.

Telling the patient of its value will greatly facilitate early ambulation. Offering calm, convincing reassurance that early rising from the puerperal bed and exercising the legs will do much to lessen the likelihood of blood clots in the veins of the legs will add much to the patient's confidence and desire to cooperate.

*Treatment of Postpartum Thrombosis:* The treatment prescribed for venous thrombosis for the 172 patients under our care is seen in Table VII. By "conservative" treatment is meant the use of heat, elevation, ice, or plastic bandages and sedatives. It is without anticoagulants or surgery. Conservative treatment was the usual method prior to anticoagulant therapy.

TABLE VII. TREATMENT PRESCRIBED IN THE CARE OF 172 PATIENTS WHO DEVELOPED POSTPARTUM VENOUS THROMBOSIS, AND ITS RELATION TO PULMONARY EMBOLI AND DEATH

TREATMENT	NUMBER OF CASES	DEVELOPED PULMONARY EMBOLI	FATAL
"Conservative"	112	21	7
Anticoagulants	46	8*	0
Surgical ligation of veins	8	0	0
Sympathetic nerve block	6	0	0
Total	172	29 (16.9%)	7 (4%)

\*Before treatment.

The 7 deaths that occurred were in the conservatively treated group—those who did not receive anticoagulants or vein ligation. There were no deaths in the group who received anticoagulant therapy, although 8 of these patients had pulmonary emboli after delivery prior to the administration of anticoagulants. The patients on whom venous ligations were performed did not develop pulmonary embolism, showing that ligation was done at the proper level or above the thrombosis.

### 2. Methods of Treatment.—

The treatment of postpartum venous thrombosis consists of: (a) prophylactic treatment, and (b) active treatment.

#### A. Prophylactic treatment:

1. Treatment of varicosities during pregnancy by injection, surgery, or elastic stockings.
2. Prevention of abnormal weight gain in the antenatal period.
3. Avoidance of infections whenever possible and prompt and adequate treatment when acquired.
4. Mature obstetrical judgment at delivery and elimination of operative and traumatic factors whenever possible.

5. Prevention of venous stasis in lower extremities during postpartum period by: (a) early, energetic ambulation; (b) avoidance of tight abdominal binders and dressings; (c) prevention of hemoconcentration from dehydration in cases of vomiting, diarrhea, fevers, prolonged labors; intravenous administration of glucose or saline solutions to maintain normal protein and hydration; (d) avoidance of chilling.

6. The use of anticoagulants in patients who had venous thrombosis in prior pregnancies. During this twenty-year period (1933-1953) 37 of our patients who had had thromboembolic disease in previous pregnancies received anticoagulant therapy. Under close regulation of clinical and laboratory studies, only one developed postpartum hemorrhage. This occurred in a patient in whom a portion of the placenta had been retained following delivery. Dilatation and evacuation of the uterus were performed without further hemorrhage.

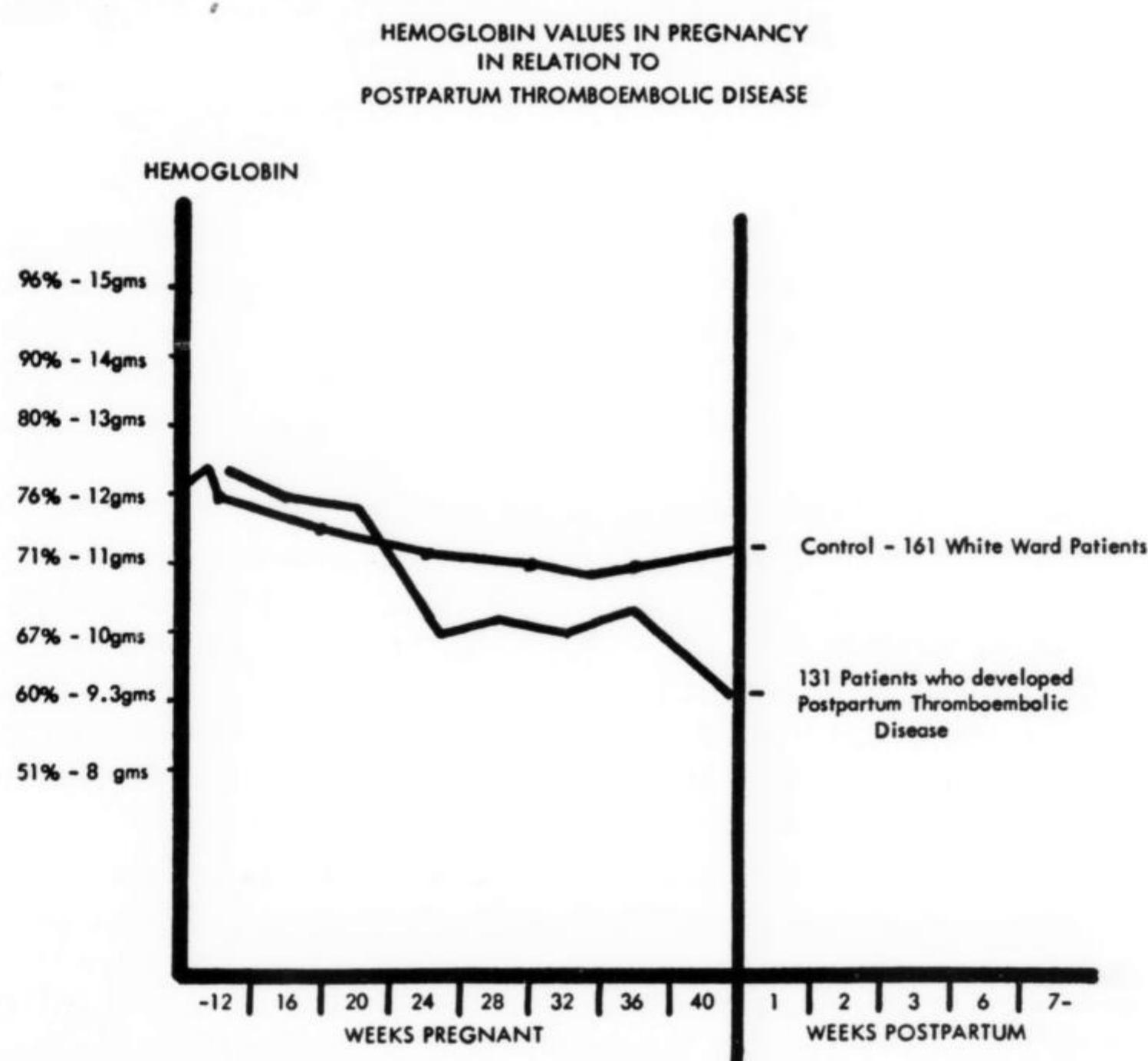


Fig. 6.—The relationship of anemia in pregnancy to postpartum thromboembolic disease.

7. Correction of anemia, by transfusion, if necessary. The correction of anemia as a prophylactic measure against thrombosis should receive special emphasis. Many physicians are aware that the incidence of venous thrombosis and pulmonary embolism is higher in anemic patients, but anemia has not been stressed as an important etiological factor. Shaw in 1924, while discussing a paper on pulmonary embolism presented by Glynn, called attention to the importance of anemia following hemorrhage as an important cause of thromboembolism, and Donald, at the same time, confirmed this view by citing additional data. In 1948, Hirschboeck again emphasized anemia as a cause of increased clot retraction and a factor in venous thrombosis. In support of this belief, Quick, in 1951, noted that massive pulmonary embolism is very uncommon or absent in polycythemia, although thromboses occur frequently. This can readily be explained by the poor clot retraction of such blood.

In this study of postpartum venous thrombosis, 132 patients had a sufficient number of determinations of hemoglobin and red blood cell count in pregnancy

to be of value in following their blood picture antenatally (Fig. 6). This is shown in relation to average hemoglobin values observed during pregnancy in 161 white ward patients at the Pennsylvania Hospital in a study by Weihl in 1950. The hemoglobin determinations made on these patients just prior to labor and delivery showed the average value to be 72 per cent or 11.2 Gm., whereas in the 132 patients who developed venous thrombosis in the puerperium, the hemoglobin value was 61 per cent, or 9.4 Gm. While no definite conclusions can be drawn from these values, they tend to support the belief mentioned that anemia is an important factor in pregnancy in the development of postpartum thromboembolic disease.

**B. Active treatment:** The so-called "conservative" therapy no longer has a place alone in the treatment of postpartum venous thrombosis, once the disease has been diagnosed. Certain measures, such as elevation of the affected extremity, heat, or elastic bandages may be used, but only in conjunction with anticoagulants or surgery.

1. Anticoagulant therapy should be the treatment of choice unless some contraindication exists. These contraindications include hemophilia, thrombocytopenic purpura, leukemia, open wounds or ulcerations, particularly of the gastrointestinal tract, impaired hepatic or renal function, severe hypertension, and subacute bacterial endocarditis. Anticoagulant therapy has largely replaced ligation as the active therapy in our patients. Heparin, given by the intermittent intravenous method, and/or Dicumarol by mouth have been the safest drugs in our hands. Rigid attention to controls and daily prothrombin determinations are essential if the drugs are to be used safely. It is desirable in most cases to give 50 mg. of heparin intravenously and to begin Dicumarol therapy at the same time. Three hundred milligrams is given orally, and this dosage is repeated in twenty-four hours. A *daily* prothrombin time determination is then used to control the Dicumarol therapy. In the postpartum patient it is usually safe to keep the prothrombin time close to 20 per cent of normal. Rapid subsidence of symptoms and signs has been the rule in our patients and usually they can be ambulatory in a few days. It is desirable to continue this therapy until they are quite active, usually ten to fourteen days.

2. Surgical ligation. Our experience with ligation of the veins has been limited to 8 cases. This is a natural result of the gratifying experiences with anticoagulants. It is well to remember that the only purpose of ligation of veins is to prevent pulmonary embolism. The ligation will prevent embolism only from that region which is distal to the ligature. Instances have been recorded of emboli originating from a region proximal to the ligature of one vein, or from a venous thrombosis which develops in the other leg later.

In contrast, anticoagulants are used for two purposes: to prevent pulmonary emboli from originating anywhere in the body, and to prevent extension of venous thrombosis. While it is impressive to prevent pulmonary embolism, the importance also of preventing occurrence or extension of venous thrombosis must be stressed. Anticoagulants also lessen venous insufficiency by preventing extension of the thrombosis, whereas ligation does not.

We recognize a role for ligation of veins, which at times becomes quite important. Cases of puerperal sepsis, or septic abortion, with multiple septic emboli, are best treated by iliac or vena cava ligation. In the type of cases considered in this presentation, however, we believe anticoagulant therapy is superior.

3. Lumbar sympathetic nerve block.
4. Continuous caudal analgesia.
5. Intravenous procaine.

The last three may be utilized in acute cases of thrombophlebitis with severe pain and swelling (vasospasm).

### Summary

Thromboembolic disease complicating pregnancy and the puerperium occupies a prominent place in obstetrics as a disabling or fatal condition.

A total of 50,332 pregnant women were registered antenatally and delivered at the Pennsylvania Hospital from 1933 to 1953, inclusive. Antepartum venous thrombosis occurred in 9 patients (0.018 per cent). One hundred thirty-five cases from the literature are reviewed, with the results of therapy. From this study evidence is accumulating that patients who develop venous thrombosis during pregnancy are best treated by anticoagulant therapy, provided meticulous control of the prothrombin time is maintained. Owing to the rarity of the condition it is difficult to be dogmatic as to treatment. It would be of great value if all cases were reported, as in this way a more accurate idea of the frequency of occurrence, mortality rate, and results of treatment could be ascertained.

During the same period (1933-1953) 172 patients developed venous thrombosis in the puerperium (0.34 per cent). Seven patients died as a result of this disease (4 per cent). Possible predisposing factors are discussed and the results of treatment are tabulated in relation to development of pulmonary embolism and fatal outcome.

The prevention of postpartum thromboembolic disease lies in better antenatal care, mature obstetrical judgment at delivery, and the avoidance of venous stasis. Early ambulation and treatment of infections are discussed. In our experience the prevention of fatalities of this disease, once it has occurred, is best accomplished by the use of anticoagulant therapy. Close cooperation between the cardiologist-internist, the vascular surgeon, and the obstetrician is essential for successful treatment.

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### Discussion

DR. CONRAD G. COLLINS, New Orleans, La.—In a four-year period from 1949 to 1952, the Tulane University service had 16,000 deliveries, in which there were 20 deaths, an average of 1.23 deaths per 1,000. We are not proud of that, but it is better than it used to be. What caused these deaths?

Embolism 7, hemorrhage 5, anesthesia 1, self-administered poison 1, sickle-cell crisis 1, pancreatitis 1, ruptured uterus with peritonitis on admission 1, toxemia 3.

So you see that 35 per cent of these maternal deaths were due to embolism. And embolism was due to: amniotic fluid embolism 3, air embolism 1, phlebothrombosis 2, tuberculosis and thrombophlebitis 1.

We mention this because in obstetrics and gynecology we have the most fertile field for embolism. Why do we mention air and why do we mention amniotic fluid embolism? Five years ago a report came from the Pathology Department of Charity Hospital that they had seen no amniotic fluid emboli. Yet in the following four years by careful search for the condition we found 3 such cases. Deaths in obstetrics are usually ascribed to pulmonary embolus, so unless one obtains a postmortem and looks carefully for the material from the amniotic fluid embolism, the diagnosis is missed. If an autopsy is not granted then blood should be aspirated from the heart, centrifuged, and a smear made from a layer between the red blood cells and serum. If amniotic fluid embolism has occurred, squamae and lanugo hair will be observed. Also cases of air embolism will be documented in this manner, as in air embolism frothy blood and/or air will be aspirated from the heart.

I do not agree with Dr. Ullery that anticoagulants are superior in most instances to vein ligation. I think the point he made this morning is that if we look for phlebothrombosis and if it is found and treated in a modern way by anticoagulants or ligation or a combination of both, we will prevent a lot of deaths due to pulmonary embolism from blood clot.

As you can see, in this four-year period embolism of one kind or another accounted for 35 per cent of the deaths, and we want to say that we think prophylaxis begins with the history. There is in Dr. Ullery's group a high incidence of patients with previous embolic episodes. All obstetric and gynecologic histories should have the information of previous vascular complications of any sort because those are the people who are more prone to have a recurrence. We do not use prophylactic vein ligation or anticoagulants except in pregnant women with a history of previous embolic episodes. When such a patient goes into labor, she is given anticoagulants.

Dr. Ullery has called to our attention that anticoagulants are safe to give during the period of gestation and in his cases no hemorrhage occurred.

In conclusion, we still pay attention to varicose veins and have them treated during pregnancy. We use lumbar block and ligation and occasionally anticoagulants, but we also use early ambulation. In the most severe cases where we get massive occlusion of the veins of the extremities with gangrene, "phlegmasia cerula dolens," the only thing that seems to be of benefit—whether we use block, anticoagulants, or ligation—is early flexion of the foot on the leg, flexion of the leg on the thigh, and the thigh on the abdomen, a pumping motion. It is necessary to have patients who are confined to bed move their legs every day, many times.

DR. WILLIAM E. STUDDIFORD, New York, N. Y.—Dr. Ullery mentioned in his review of the literature a case reported by Drs. Sachs and Labate in 1949 from the obstetrical and gynecological service of Bellevue Hospital. This represents one of the earliest cases of antepartum thrombophlebitis and pulmonary embolism treated with anticoagulants. Dicumarol was the drug used. The patient did very well but during the course of treatment the fetus died in utero. Some time after its death, normal delivery took place. Autopsy of the fetus revealed that, in spite of the macerated condition, quite extensive hemorrhages occurred in the mediastinum and subperitoneal tissues. Since then we have treated several cases of antepartum thrombophlebitis with anticoagulants but have not noted any accidents such as this. I would like to know if Dr. Ullery discovered any particularly high incidence of intrauterine death in the cases he reviewed.

DR. WILLIAM J. DIECKMANN, Chicago, Ill.—This subject is important to everyone and especially to obstetricians. Prior to Jan. 1, 1947, all obstetrical patients remained in bed for eight days, were permitted up on the ninth day, and discharged on the tenth day or later. On Jan. 1, 1947, we instituted early ambulation, meaning that the patients

could get out of bed within 24 hours after delivery if they so desired. They were not to go to the bathroom until the second day and outside of the room on the fourth day. Shower baths were not permitted until the fifth postpartum day. Various observations have been made both before and since this practice was instituted and we hope to report these within the year. We are especially interested in trying to decrease maternal deaths due to pulmonary embolism which is becoming an important cause of maternal deaths since the total number of such deaths from other causes has steadily decreased. In the period from May, 1931, to Dec. 31, 1946, there were 46,877 deliveries. There were 4 deaths due to pulmonary embolism proved by autopsy and a fifth in a cardiac patient whose clinical course supported the diagnosis. This gives an incidence of pulmonary embolism of 0.011 per cent. In the period from Jan. 1, 1947, to Dec. 31, 1953, there were 27,098 deliveries and 4 deaths proved to be due to pulmonary embolism, an incidence of 0.015 per cent. Obviously, early ambulation has not decreased the incidence of fatal pulmonary embolism when one considers the marked reductions in maternal deaths from other causes. It is disappointing that deaths from embolism not only still occur but are actually comprising a higher percentage of the total number of maternal deaths. It is of interest that in the first series two of the deaths were after cesarean section and in the latter series three of the deaths were after cesarean section.

Early ambulation has resulted in a clinical test which we would not have permitted had we been cognizant of it. Patients would develop pain in the leg or thigh and frequently wait two or more days before mentioning it. On examination there was obvious thrombosis. Initially, we placed these patients at bed rest but as we appreciated the clinical experiment, we have not restricted these patients and have permitted them to go home at a much earlier date than we originally did.

Anticoagulant therapy has been used in some of our patients but we have not been satisfied with the result. I cannot state that any patient actually died from this therapy but we have had some anxious moments while trying to control hemorrhage from the postpartum uterus and to replace the tremendous blood loss. We have also been concerned about the possibility of renal damage from the hemorrhage. In the majority of our cases where anticoagulant therapy was instituted, it was done primarily at the insistence of one of our medical or surgical colleagues who thought it would be a preventive procedure.

DR. JOHN C. ULLERY, Philadelphia, Pa. (Closing) (By invitation).—In answer to Dr. Studdiford's question concerning fetal deaths in antepartum patients with thromboembolic disease, so far as I could tell in the review of the literature, Dr. Sachs' was the only such case. As I recall in going over that report, the patient received an enormous amount of Dicumarol. It was difficult to control the pulmonary emboli prior to her delivery. She received much more of the drug over that period of time than any other patient of whom I have a record. Whether that was a factor I do not know.

As for Dr. Dieckmann's questions, we do not believe that early ambulation is the only preventive factor in this condition, but we do feel it may play an important role. Active leg exercises are important, too. Thirty-seven of our patients received prophylactic anticoagulant therapy after delivery and in this group there was no postdelivery hemorrhage except in one patient from whom there was excessive bleeding on the fourth day. Dilatation and evacuation revealed a portion of retained placenta, and with its removal there was no further bleeding. I have had no other experiences of hemorrhage in postpartum thromboembolic disease.