Epidemiology of Venous Thromboembolism

WILLIAM W. COON, M.D.

From the Department of Surgery, University of Michigan Medical Center, Ann Arbor, Michigan

This review of the epidemiology of venous thromboembolism includes estimates of incidence and prevalence of venous thrombosis and its sequelae, a discussion of geographical, annual and seasonal variations and data concerning possible risk factors. Selection of patients at increased risk for development of deep venous thrombosis or pulmonary embolism for specific diagnostic screening or for prophylactic therapy with low-dose heparin may be a more effective approach to lowering morbidity and mortality from this disease.

THE DISCIPLINE OF EPIDEMIOLOGY deals with the incidence and prevalence of a disease, its impact upon the health of a nation or society in general, and those conditions which influence the frequency of appearance of the disease in a given location or population. By defining factors which appear to affect the risk of development of a disease, one may develop leads to possible etiology or pathogenesis and, in some cases, design a more rational or cost-effective program for prevention.

An increasing interest in the development of safer measures for the prevention of venous thromboembolic complications has made a knowledge of the epidemiology of thromboembolism of practical importance to the physician in the selection of those patients in whom he wishes to institute specific prophylactic procedures.

Incidence and Prevalence of Venous Thromboembolism and its Sequelae

Unfortunately, the difficulties in clinical diagnosis of both deep venous thrombosis and pulmonary embolism limit the accuracy of previous and current estimates. In addition, since fatal pulmonary embolism in hospitalized patients usually occurs as a sequel to the primary disease for which the patient was admitted, vital statistics derived from coded death certificates present a gross underestimate of true frequency. Rossman, in a sample of death certificates from New York City, has shown that less than one in six deaths primarily ascribed to pulmonary embolism was appropriately coded (International Classification of Diseases: ICD Category 450).[145] Also, there is the contrary problem that not all sudden deaths which are attributed to pulmonary embolism, but lack confirmation by autopsy, represent the correct diagnosis.

For these reasons, perhaps the most accurate, although still very imperfect, values for the frequency of fatal pulmonary embolism are derived from extrapolations based upon autopsy data. Several estimates, in which pulmonary embolism was judged to be either the sole cause of death or a major contributory cause, are in the range of 140,000–200,000 deaths per year in the United States.[31,84] Even these figures may underestimate true frequency since Morrell and Dunnill[124] have shown that meticulous section of the lung in one centimeter segments will markedly increase the frequency of detection of recent and organizing pulmonary emboli and their presumed sequelae (fibrous webs, intimal fibrosis). Smith et al.[157] have demonstrated that utilization of a technique for demonstration of pulmonary embolism at autopsy by barium angiography may more than double the frequency usually reported with conventional methods; on the basis of their studies, they have called pulmonary embolism "the most common lethal pulmonary disease in adults seen at necropsy in the general hospital population" and "the third most common cause of death in this hospital."

Not all pulmonary emboli found at autopsy are "clinically significant" with respect to contributing to mortality. The judgment as to clinical significance is somewhat subjective, being based on the nature of the terminal episode, size and number of emboli, severity of associated disease, etc. Nevertheless, in our studies of 10 year autopsy samples 20 years apart, the number of significant emboli remained in the range of 7 to 9% of all subjects.[28,32] However, because of the nature of the primary disease, only about one-half of those individuals with major embolism would have had an extended life expectancy had pulmonary embolism not occurred. Other investigators, using similar criteria, have also concluded that in approximately one-half of

Submitted for publication: October 18, 1976.

patients with pulmonary embolism at necropsy, the emboli are the immediate cause of death and that in this sub-group, about one-half of these would have been expected to have survived for a considerable period had the embolism not resulted in death.[124] All of the above issues must be considered in attempting to assess the true impact of pulmonary embolism upon mortality.

An accurate estimate of the frequency of non-fatal pulmonary embolism is even more difficult to obtain because autopsy data are an inappropriate source and the clinical recognition of pulmonary embolism is notoriously inadequate.[28,32,54] Since, in our experience, less than 10% of all autopsy-proven pulmonary emboli are diagnosed prior to death, an assessment of incidence is purely speculative. Since there is some clinicopathologic support for the premise that for every episode of fatal pulmonary embolism, there are two or more episodes of non-fatal embolism, this would place the estimate for non-fatal pulmonary embolism in the United States at approximately 300,000 per year or more. Hume et al.[84] have published an estimate of this order of magnitude.

Similar difficulties exist with respect to the clinical diagnosis of deep venous thrombosis. The only available incidence data are related to clinically recognized cases. Hume et al.,[84] extrapolating from ICD-coded diagnoses for a segment of the hospitalized population in 1966, estimated about 182,000 cases per year; recognizing the frequent failure to code this diagnosis and lack of inclusion of cases from nursing homes, etc., this probably represents another gross underestimate of even clinically diagnosed episodes. Coon et al.,[31] in a longitudinal study of the incidence of deep venous thrombosis in a community, extrapolated their data on the basis of 1970 census figures to the U.S. population as a whole and presented an estimate of 250,000 clinically recognized cases annually.

Data from the same community health study were utilized to estimate the prevalence of post-phlebitic sequelae in the U.S. population. The approximate frequency of stasis changes in the skin of the legs was in the range of 6–7,000,000 persons while 400,000 to 500,000 have or have had leg ulcers. Although a large extrapolation was made from data on 6389 persons to the entire U.S. population, these figures may be somewhat more accurate since one is dealing with a normal population sample (rather than solely hospitalized patients), and stasis changes and leg ulcers are readily recognized by physical examination. These figures for the prevalence of post-phlebitic changes in the skin of the legs would represent an age-adjusted frequency in the U.S. adult population of about 5%, about twice the estimate obtained by Gjores in a study of 1453 Swedish adults 20 years ago.[62] The calculated frequency of leg ulcers alone of approximately five per 1000 U.S. adults is similar to the estimate made by Boyd et al. from English data.[14]

Geographic and Racial Variability

The meager information on geographic differences has been summarized recently.[17,84,148] Accurate data might provide important leads as to a possible etiology. However, many reports are clinical and anecdotal. Three studies comparing frequency of thromboembolism at autopsy in patients age 40 and greater appear to provide the most reliable information. One of these investigations reports the prevalence of venous thromboembolism to be 2% in Uganda, compared to 24% in Caucasians and 22% in Negroes in St. Louis (tending to rule out an ethnic factor).[165] However, most Ugandans died from diseases thought to be associated with a low frequency of thromboembolism; heart disease was very rare, and only 11% of deaths were due to cancer. The second study compared the prevalence of pulmonary embolism in Boston (23.8%) and Kyushu, Japan (0.8%); more importantly, when frequencies were contrasted in patients with heart disease, cancer or operation, the marked differences persisted.[64] A collaborative study under the auspices of the World Health Organization has reported a necropsy frequency of pulmonary embolism of 14% in Prague, 6% in Malmo and 2% in Yalta.[100] These three studies, and particularly the latter, provide information which might indicate that something other than ethnic background and known risk factors is responsible for the differing prevalence. The possible pathogenic factors which have been most frequently offered as an explanation for these differences include altered fibrinolytic activity,[117] dietary elements[17] and variations in degree of physical activity, even during serious illness.

When racial differences in postoperative venous thrombosis detectable by labelled fibrinogen are considered, results are conflicting. Several studies involving Asian[38] and Sudanese[73] patients have reported an apparently lower frequency of thrombosis; on the other hand the best controlled trial, carried out in a South African hospital with appropriate matching for age, sex, weight and type of operation, showed no difference in prevalence of thrombosis between European, Bantu, "coloured" and Indian patients.[93]

Annual and Seasonal Variations in Frequency

The available data from which assumptions can be made on the possibility of a changing frequency of venous thromboembolism are derived from studies of autopsy-proven pulmonary embolism. Even under this

circumstance there are potential variations: in technique of autopsy, increased awareness possibly leading to a greater diligence in search for emboli, a changing spectrum of primary diseases and therapeutic modalities affecting the extent of operative procedures, duration of bed rest, etc. The reports of an apparently lower prevalence of fatal pulmonary embolism during the early decades of this century may be related to one or more of the above-mentioned factors.

More recently, several investigators have presented figures suggesting a progressively rising frequency of pulmonary embolism. One study, involving Registrar-General's reports from England and Wales, shows estimated crude death rates from pulmonary embolism rising from 15 to 19 per million in 1941–45 to 94 per million in 1966.[84] These data, however, are based upon "vital statistics"; presumably, most of the diagnoses of "cause of death" were not confirmed by autopsy. Morrell, Truelove, and Barr have reported a five-fold increase in number of patients with necropsy-documented pulmonary embolism in Oxford between 1952 and 1961; the actual prevalence varied between two and 7% in the earlier portion of the period and 8–10% in later years.[123]

To examine whether a similar apparent increase in prevalence was occurring in the United States Coon recently reported a 10 year survey of autopsied patients with the same analytic techniques used in the study of a sample from the same hospital 20 years before.[32] In the period between 1945 and 1955 the frequency of pulmonary embolism was 13.6% while in the 1964–1974 period the figure was 12.3% (not significantly different). However, in both periods under study, there was a considerable variation in annual prevalence (e.g., 7.4% to 15.2% in the latter period) which appeared to be statistically significant.

A number of European observers have noted decreases in autopsy-proven pulmonary embolism during wartime which they attribute to nutritional factors.[149,163,198] Although nutrition may play a role in pathogenesis when frequency of pulmonary embolism is plotted over many decades, wide variations in frequency have been noted in peacetime as well.[149,198] In addition, it seems unlikely that the differences in annual prevalence in a well-fed U.S. sample[32] can be explained by yearly differences in nutritional status. Apparent variations in frequency of clinically diagnosed venous thromboembolism have been attributed to all of the common meteorologic variables: extremes of humidity,[161] changes in barometric pressure[68] and temperature fluctuations.[42] Marked quarterly differences in prevalence (from 3% to 23%) in two studies were shown to be random and not statistically significant.[29,32]

Variations Due to Methods of Diagnosis and to Selection

The accuracy of data concerning incidence, prevalence and relative risk of development of venous thromboembolism is limited by the precision of techniques of detection and restricted to the subset of the population under study. This is especially true when statistics are derived for a geographic area since the predominant method of diagnosis is clinical. Numerous investigators have shown that the great majority of cases of deep venous thrombosis and pulmonary embolism are never clinically diagnosed. However, to a leser degree, the same limitations in diagnostic accuracy apply to other methods of detection. The frequency of recognition of pulmonary emoblism at autopsy is directly related to the technique used for detection and the care with which the necropsy is performed; specialized techniques or no more than meticulous sectioning of the lungs, has led to a two-fold or greater increase in prevalence.[124,157] In the United States, the necropsy performance of complete leg vein dissections in a search for thrombi is extremely rare because of the special consent required and the vigorous objections of undertakers (since this interferes with the usual methods for embalming). When complete leg vein dissections have been performed in other countries on a randomly selected general hospital population, recent thrombi have been detected in 50 to 60% of adults.[61,164]

Although a number of special procedures have been developed which increase the frequency of detection of venous thromboembolism, all have limitations (related either to cost, accuracy or morbidity) when considered for sequential mass screening of individuals. At present, perhaps the most attractive method for screening of hospitalized patients for deep venous thrombosis involves the use of I^{125}-fibrinogen; still unsettled, however, is the major conceptual problem of whether the many thrombi confined to veins below the knee represent a significant clinical entity with respect to ultimate morbidity from embolism or postphlebitic sequelae. British investigators consider below-knee thrombi relatively innocuous[101] and only treat those patients who on repetitive screening show propagation of thrombus to the popliteal vein or above. Two other techniques which could be used for mass screening, impedance phlebography and ultrasound, detect only those occlusive processes at or above the knee, but in most hands there appear to be more false positive and false negative measurements. Similarly, perfusion scans of the lungs are frequently inaccurate, especially in the postoperative patient; repeated scanning for screening purposes would be unacceptable from the

point of view of radiation exposure and, although combined ventilation-perfusion scanning would be more accurate, the same objection applies.

Another important consideration in the assessment of epidemiologic factors in thromboembolism must be the recognition that any calculation of frequency or comparative risk applies only to a population comparable to that from which the statistics were derived. Most estimates of risk have been obtained from a hospital population. Since the conditions and diseases which appear to affect the frequency of venous thromboembolism are multiple, the selection of entirely suitable control groups is extremely difficult, if not impossible. When autopsy-proven pulmonary embolism is used as a criterion for diagnosis, a bias in selection of patients for necropsy must be considered. These and other problems of selection bias make risk estimates qualitative rather than quantitative.

Possible Risk Factors in Venous Thromboembolism

Although venous thrombosis and pulmonary embolism are seen with greater frequency in association with certain diseases and conditions, this association does not necessarily imply a pathogenetic relationship. The linkage may be entirely coincidental, or perhaps more frequently, several of the diseases or conditions may be associated with a common underlying physiologic abnormality which may be the more important causal relationship. From the pathogenetic standpoint, most discussions of risk factors return to a classification based upon the Virchow-Aschoff postulates concerning the elements affecting the development of venous thrombosis: 1) trauma to the vein wall; 2) a decrease in rate of blood flow in veins; 3) changes in coagulability of the blood; 4) changes in the corporeal elements of the blood. Nevertheless, a knowledge of those conditions which may be associated with an increased risk could lead to a more selective approach to prevention or detection of venous thromboembolic disease.

Sex

Data for sex distribution are conflicting.[114] Accepting the fact that all vital statistics represent gross underreporting, U.S. vital statistics for 1970 show a death rate from pulmonary embolism of 5.4 (per 100,000) for males and 5.0 for females.[178] On the other hand, Hume et al.[84] have calculated crude death rates in England and Wales for 1966 at 7.7 and 11.0, respectively.

In a community study of the frequency of thromboembolic disease, the rates for incidence and prevalence of deep venous thrombosis were much higher for females.[31] The differential was particularly striking under age 40; venous thrombosis was recognized in females with as much as a ten-fold greater frequency. About one-half of the episodes in younger women were related to thrombosis associated with pregnancy.

In hospitalized patients, the difference in sex distribution disappears. In our large sample of patients treated with anticoagulants for venous thromboembolism, the numbers of males and females are equivalent. In addition, the percentages of males and females with detectable pulmonary emboli at autopsy are almost identical.[29,33]

A possible explanation for these differing figures is that deep venous thromboses, many related to pregnancy, are more frequent in young women, but few result in death from pulmonary embolism. Venous thromboembolism in a general hospital population is associated with many other epidemiologic factors which are more evenly distributed between the sexes, resulting in an equivalent sex incidence in this environment.

Age

The influence of age upon the frequency of occurrence of pulmonary embolism has been consistently observed in major analyses of the problem in the U.S. and the British Isles. The observation of an age relationship is confirmed by World Health Organization data encompassing Japan, Australia, Israel and Germany.[51] In many studies the prevalence of pulmonary embolism appears to increase almost linearly with advancing age. Others have suggested various age break-points for a changing frequency. Our data support the premise that an increased frequency after age 30 can be chiefly attributed to the presence of heart disease or cancer since, if patients with these associated conditions are excluded, the prevalence of pulmonary embolism reaches a plateau after this age.[29] A higher frequency of ^{125}I-fibrinogen-detectable thrombi has been reported in postoperative patients age 60 or over (45%) as compared to those between 40 and 59 years of age (24%).[102]

Venous thromboembolism is considerably less frequent in children. The clinical prevalence of venous thrombosis has been estimated at 1.2 per 10,000 admissions to a children's hospital;[192] a recent suggestion has been made that this low figure may represent a failure of recognition which could be improved by utilization of one of the newer diagnostic measures.[94] The frequency of pulmonary embolism detectable at autopsy varies from series to series. In a sample of approximately 2000 autopsies in children, 25 fatal pulmonary emboli were found.[50] In several other studies the

prevalence varied from about 3% in children under age 10 to approximately 8% in the 10–19 year age group.[29,33] Although "spontaneous" deep venous thrombosis (not associated with any known risk factors) is occasionally observed in adults,[41,62] it is extremely rare in children; almost all cases of venous thromboembolism occur in children with infection, trauma, heart disease, nephrosis, malignancy, cerebral thrombosis or hemorrhage, or ventriculojugular shunts.[95,96]

Familial venous thromboembolism. Almost every clinician who deals with large numbers of patients with venous thromboembolism has encountered occasional patients with a family history (two or more affected family members). In single families with a strong history of familial venous thrombosis, several clotting factor abnormalities have been reported,[47,48,69,113,143] but in the majority of cases no hemostatic aberration can be demonstrated. A number of years ago Jordan and Nandorff[99] summarized 22 familial cases from the world's literature and reported 21 cases of their own; however, these were anecdotal reports from which it is impossible to separate those families in which superficial thrombophlebitis in varicose veins may have been the major familial association.

Blood groups. Mourant et al.[126] have recently collated and summarized data concerning the relative deficiency of blood group O in subjects with venous thromboembolism. This association has been expressed as the "relative incidence" or relative excess of group A in individuals with thromboembolic disease (controls by this calculation = 1.0). Summarizing data from multiple sources, the relative frequency of group A was estimated as follows: 1) women taking oral contraceptives who develop thromboembolism: 3.12; 2) thromboembolism in pregnant or puerperal women: 1.85; 3) thromboembolism in postoperative patients: 1.23; 4) patients dying of pulmonary embolism: 1.26; 5) mean "incidence" in combined medical and surgical patients with thromboembolism: 1.4.

Jick et al.[92] have pointed out the interesting observations that levels of antihemophilic factor activity appear to be higher in individuals with group A as opposed to group O[140] and that patients who have group O are more likely to bleed from a peptic ulcer.[106]

Estrogen—oral contraceptives. Although case reports concerning the development of several forms of vascular disease in women receiving oral contraceptives began appearing about 1961, the retrospective controlled investigations of Vessey and colleagues in England[86,173] and Sartwell et al.[150] in the United States in the latter part of the decade convinced most physicians that a relationship did exist. While some critical objections regarding statistical methods have been made, the mass of data which have accumulated since these initial studies are overwhelmingly supportive of the conclusion that estrogens increase the risk of development of venous thromboembolism. The more recent evidence in favor of the influence of estrogens on the risk of developing myocardial infarction[35] and stroke[26] as well will not be discussed here. In the above-mentioned and subsequent British studies the risk of development of venous thromboembolism was increased about seven-fold while Sartwell et al.[150] estimated the relative risk in a U.S. sample to be 4.4. The estimated increase in annual death rate in oral contraceptive users was also about 7-fold, averaging about three per 100,000 per year; the death rate was about twice as high in women age 35–44 when compared to women of ages 20–34. The risk remains constant as long as oral contraceptives are used and for several weeks after discontinuation.[150]

The influence of dose of estrogen is also documented.[87,162] A positive correlation has been found between dose and risk of venous thromboembolism. Vessey and Inman[175] have estimated that, if the relative risk of thromboembolism is 1.0 for a woman ingesting a contraceptive containing 50 micrograms of estrogen, the risk is 3.2 at a dose of 100 micrograms and 5.9 at a dose of 150 micrograms.

Further evidence that estrogen is the thrombogenic component of oral contraceptives is provided by the reports of a higher frequency of venous and arterial thromboembolism in patients receiving estrogens alone for the management of cardiovascular disease,[35,131] prostatic carcinoma[177] or suppression of lactation.[40,91]

In a recent comparison of estrogenic therapy of prostatic carcinoma, the use of diethylstilbestrol was associated with a significantly higher frequency of thromboembolic complications than that observed with other estrogenic compounds (chlorotrianisene and ethinyl estradiol[121]).

The observations regarding estrogen suppression of lactation are particularly impressive. Venous thromboembolism is increased about three-fold by suppression of lactation by diethylstilbestrol. The risk is even higher in low-parity women over age 25 and in women over 25 requiring operative delivery.[167]

Although retrospective studies attempted to eliminate women with other predisposing factors, there is some evidence that the effect of oral contraceptives and other risk factors may be cumulative. There is a potentiation of risk in women of blood types A, AB and B who are receiving oral contraceptives.[92] In women taking oral contraceptives during the month prior to operation or other trauma, the risk of thromboembolism appears to be increased by four to 6-fold.[66,174] An increased frequency of ^{125}I-fibrinogen-detectable leg vein thrombi

in women taking oral contraceptives and undergoing operations has been reported.[146,188] These data support the recommendation that women scheduled for hospitalization, and particularly for operation, terminate oral contraceptive use three to four weeks prior to hospitalization; although coagulative changes take place within several days after initiation of oral contraceptive medication,[180] return to normal may require up to three weeks after termination of use.[179]

Interestingly, some recent data indicate that the risk of recurrence of thromboembolism is four times greater in women with previous venous thrombosis not related to oral contraceptives (except for recurrences occurring during pregnancy or the puerperium, in which no difference was noted).[6]

Estrogenic influence upon the pathogenesis of venous thrombosis may be pluricausal. Intimal proliferative lesions have been described in both arteries and veins in women taking oral contraceptives and in pregnant and postpartum women.[89,90] An increase in permeability of vascular endothelium induced by estrogen has also been implicated.[2] Both pregnancy and oral contraceptives significantly decrease venous tone and mean linear velocity of blood flow in the calf of the leg.[63] Multiple effects upon the clotting mechanism have been described. The most consistent change noted by a number of observers is an increase in Factors VII and X;[180] others have also reported an increase in Factors II[4] and VIII,[46,180] a decrease in antithrombin III,[199] and concomitant increase in rate of thrombin generation.[180] Plasma soluble fibrin concentration is increased,[136] and red cell filterability (which might lead to stasis in the microcirculation) is decreased.[132] Blood platelet adhesiveness is increased.[12,23] These effects appear to be related to the effects of the estrogenic component of the oral contraceptive since administration of a progestin alone produces no significant changes in clotting factors or platelet function.[12,119,139] While women receiving low-dose oral contraceptives appear to have a lesser frequency of detectable thromboembolism, the estrogenic effect upon clotting factor activity may not be dose-dependent.[138] Although little information is available concerning increased risk of thromboembolism in women receiving "natural estrogens" for relief of menopausal symptoms, equine estrogens have been shown to increase levels of Factors VII and X[34] and decrease antithrombin III.[181]

Pregnancy and the puerperium. The relative risk of venous thrombosis or pulmonary embolism in women who are pregnant or postpartum is 5.5 times that expected in non-pregnant, non-puerperal women who are not taking oral contraceptives. During the period 1961–1966 in England and Wales, pulmonary embolism ranked as the second leading cause (after abortion) of maternal mortality.[59] In a U.S. investigation of 85 maternal deaths from vascular causes, 21 were due to pulmonary embolism,[130] second only to amniotic fluid embolism as a cause of fatal vascular accidents in pregnant women.

A study of prevalence of disease in a community has shown that approximately one-half of all venous thromboembolic events occurring in women below age 40 were related to pregnancy or the puerperium.[31] This was the most important factor contributing to a much higher frequency of thromboembolic disease in young women when compared to men of similar age. Deep venous thrombosis or pulmonary embolism was recognized about once in every 200 pregnancies (rate 5.9/1000). This range of prevalence has been reported by others.[1,40,59,91] Postpartum thrombosis is three to 6 times as frequent as antepartum thrombosis.[1,85,151]

Venous flow is known to decrease as pregnancy progresses, being slowest after engagement of the fetal head.[194] Changes in blood coagulation during pregnancy and the puerperium are similar to those seen after administration of oral contraceptives.[168,180] Platelet factor 3 activity also seems to be increased.[197] These changes increase further during delivery and persist in the early postpartum period; in addition, the platelet count shows a pronounced rise,[13] a possible explanation for the increased thromboembolic risk during the puerperium. Chromatographic measurements of fibrinogen-fibrin products, utilized as an index of hypercoagulability, show a frequency of abnormalities of 15% in pregnant women in the first trimester, 30% in the second trimester, 40% at 8 months and 80% in the early postpartum period.[18]

Hiilsmaa found a frequency of thromboembolism in a Finnish hospital of 10.7/1000 after normal delivery but 22.1/1000 after caesarean section.[75] Aaro and Juergens report that more than one-fourth of patients with deep venous thrombosis after delivery have had some type of obstetrical complication, and one-third of patients have had a prior history of thromboembolic disease.[1] Documented deaths from puerperal thromboembolism appear to be in the range of one to two per 100,000, the higher figure reported in women of age 35 and over.[173] There is some evidence to suggest that in recent years a real decrease in mortality from puerperal pulmonary embolism has occurred as a result of better obstetrical care.[176]

Obesity. Several autopsy studies have shown that the risk of pulmonary embolism in obese subjects is one and one-half to two times that observed in the non-obese.[29,33] A similar augmentation in risk of development of deep venous thrombosis has been reported in studies utilizing ^{125}I-fibrinogen scanning.[102,129] The additive risk of obesity in the development of post-

operative pulmonary embolism was noted by Snell 50 years ago[159] and confirmed later by Barker et al.[8] who noted a two-fold increase in risk of pulmonary embolism in obsese women after hysterectomy. A decrease in blood fibrinolytic activity has been reported in obese patients.[10]

Heart disease. The relatively high frequency of deep venous thrombosis and pulmonary embolism in hospitalized patients with heart disease has been well documented.[21,29,33,69,143,182,190] When the prevalence of pulmonary embolism at autopsy is compared between all patients over age 30 without heart disease or cancer and all patients over age 30 with heart disease, the frequency of pulmonary embolism is about 3½ times as great in the subjects with heart disease.[29,33] When risk is considered with respect to specific pathologic types of heart disease, patients with all forms of heart disease except for hypertensive heart disease, and congenital heart disease in individuals under age 10, have a significantly increased risk for development of pulmonary embolism.[33] The hazard of embolism is even greater if atrial fibrillation or congestive heart failure is present.[29,33,43,143] Although pulmonary embolism does not appear to be significantly more frequent in autopsied patients with acute myocardial infarction than in individuals with other forms of heart disease,[33,122] a sub-class of "severely ill" patients with acute myocardial infarction has been shown to have a higher frequency of ^{125}I-fibrinogen-detectable leg vein thrombi than the patients with less extensive infarcts.[70,103,154] The frequency of deep venous thrombosis in non-anticoagulated patients with acute myocardial infarction is 30 to 40%[70,103,115] More than one-half of the thrombi develop within 72 hours of the acute infarction.[115] Advanced age, a prior history of thromboembolism and the presence of varicose veins augment the risk of development of deep venous thrombosis in patients with an acute myocardial infarct.[49,115]

While mural thrombi in the right heart have been thought to be a major source of pulmonary embolism in patients with heart disease, right mural thrombi are found in only 10–20% of cardiac patients who develop autopsy-proven pulmonary embolism,[32,33] an indication that the leg veins are the major source of emboli in cardiac patients as well. Another observation in support of this premise is that patients found to have a mural thrombus only in the left side of the heart have a prevalence of pulmonary embolism equal to that of subjects with right cardiac mural thrombi.[33]

One might interpret these data as suggestive that the critical influences on frequency of thromboembolism in cardiac patients are severity of the heart disease and disturbances in cardiac rhythm which may influence cardiac output, venous return or the extent of immobilization of the patient (which also affects rate of venous flow). Although many reports have attempted to incriminate a "hypercoagulability" of the blood as a major pathogenetic element, there is no definitive demonstration that the myriad coagulative changes which have been found have any causal relationship to the development of the thromboses.

Cancer. The relation between malignant neoplasms and venous thrombosis has been known for more than 100 years.[170] Although unusual and extensive thrombotic conditions, such as migratory thrombophlebitis[44] and phlegmasia cerulea dolens,[116] have been described in conjunction with extensive cancer (especially related to cancers of the pancreas,[160] lung[19] and stomach[170]), the frequency of venous thromboembolism is increased in patients with many other types of neoplasm as well. The risk of pulmonary embolism is increased two-to three-fold in all patients with cancer.[29,33,182] Apart from carcinoma of the pancreas, in which approximately one-third or more of patients who die have autopsy-proven pulmonary embolism, other types of cancer are also associated with a high embolic risk: genito-urinary neoplasms, stomach, lung, colon and breast; in patients with other types of malignant tumors, the frequency of embolism is considerably lower.[29,33] Although speculations have been made that the high frequency of thrombosis in patients with carcinoma of the pancreas is related to mucin production by the tumor,[137,160] Lafler and Hinerman[105] found no correlation between concentration of stainable mucin and the presence of thrombosis but a good correlation with the presence of glandular epithelium ("differentiating ductal carcinoma").

In postoperative patients studied with labelled fibrinogen, the presence of carcinoma increased the risk of development of leg vein thrombosis about one and one-half fold when compared to all patients without cancer, regardless of other risk factors; 40.6% of patients with cancer developed evidence of deep leg vein thrombosis.[102] Others have reported a three-fold increase in risk of postoperative thrombosis in cancer patients.[137] The frequency of thromboembolism after abdominal hysterectomy is increased two and one-half fold if the operation is for cancer.[9]

Tumor cells are not usually found in the venous thrombus. Numerous observations regarding alterations in blood viscosity, clotting factors and platelet number or function have been made,[5,16,107,109,118,120,166] but none of these abnormalities has been shown to be of pathogenetic significance. The role of ancillary predisposing conditions (older age, prolonged bed rest, major operations, heart disease) may be of importance.

Past history of venous thromboembolism. A history

of prior deep venous thrombosis and pulmonary embolism has been recognized for many years as a major epidemiologic factor influencing the development of further thromboembolic disease. This is especially true when another risk factor, such as operation, is also present. Thirty-five years ago Barker et al.[9] documented the magnitude of the risk, reporting that of 46 women with a prior history of thromboembolism undergoing hysterectomy, 31 developed postoperative pulmonary embolism, and 15 died from embolism. More recently, Kakkar et al.[102] found a 68.4% prevalence of leg vein thrombi in postoperative patients with a prior history of thromboembolism; Nicholaides and Irving[129] have reported a frequency of thrombosis of 61% (as compared to 26% in patients without a prior history). In a retrospective review, Turnbull discovered that a past history increased the risk of recurrent thromboembolism three-fold in postoperative gynecologic patients.[172]

Varicose veins. Many authors have cited varicose veins as a risk factor in surgical patients. An element which has not been adequately considered is whether the patients with varicose veins who develop postoperative deep venous thrombosis or pulmonary embolism are a subcategory of individuals who have developed varices secondary to a prior unrecognized deep venous occlusion.[110] In a study of the frequency of venous thromboembolism post abdominal hysterectomy, patients with "peripheral vein disease" were defined as those having either varicose veins or a past history of venous thrombosis; this group had a three-fold increase in frequency of thromboembolic disease when compared to patients without known predisposing factors.[9] Several studies utilizing labelled fibrinogen have presented data supporting a two-fold increase in risk in all postoperative patients if varicose veins are present.[102,129]

Accidental trauma. Most of the important elements in the relationship of injury to thromboembolism were defined in the classic autopsy studies of Sevitt and Gallagher.[153] The estimated prevalence of fatal pulmonary embolism in injured patients admitted to the hospital appears to be about 1% and the overall frequency of both fatal and non-fatal emboli about 2%. Most of the instances of deep venous thrombosis are "silent" (without clinical signs). The frequency of venous thrombosis increases with advancing age and with duration of bed-rest. When complete leg vein dissections are performed, deep venous thrombi are found in from 40% to 86% of subjects, the lower figure in patients with head and chest injuries and the higher in subjects with femoral fractures. In spite of a unilateral limb injury, thrombosis is usually bilateral. As Sevitt and Gallagher stress, and Coon has recently confirmed,[33] all patients with trauma, regardless of the site of injury or the age of the patient, are at increased risk of developing thromboembolic disease. The risk of pulmonary embolism rises from that observed in head and chest injuries (2%–5%), to burns (5%–8%), spinal fractures (14%), pelvic fractures (27%), to the highest frequency of 45–60% in tibial and femoral fractures.

Numerous investigators have provided data in support of one or more of the above observations. Freeark et al.[58] found a prevalence of venographically proven leg vein thrombi in 35% of patients with various forms of trauma; the thrombi were frequently bilateral, and only one-third were detected clinically. In another venographic study, 45% of patients with tibial fractures had deep venous thrombi; while patients under age 25 had a 12% frequency of thrombi, the prevalence was in the 50 to 60% range for several age categories between 25 and 75 years.[79]

The fact that lower extremity injuries, and particularly femoral fractures, are the chief contributor to fatal pulmonary embolism after trauma has been known for more than 40 years.[111] The greatest attention in trauma-related thromboembolic disease has been devoted to fracture of the hip because this complication has been considered the most common cause of death after this injury.[53,54,193] When autopsies were conducted on 161 of 247 patients dying after hip fractures, the cause of death was attributed to pulmonary embolism in 38% of patients; in the remaining patients, in whom necropsy was not performed, only 2% were thought clinically to have had a pulmonary embolus.[54] In another study, 50% of all deaths after hip fracture were due to pulmonary embolism.[53] Studies with labelled fibrinogen has shown a frequency of deep venous thrombosis of over 50% in the injured limb; thrombi were also demonstrated in the uninjured limb in 34%.[52] The pathogenic role of accidental trauma often cannot be distinguished from the superimposed influence of operative treatment of the injury. Data referable to risk of thromboembolism after orthopedic operations will be discussed separately.

Several investigators have suggested that trauma per se may be of lesser importance as a pathogenetic agent than the immobilization following the injury since the frequency of thrombi and emboli increases with the duration of bed-rest;[33,152,153] the frequent bilaterality of leg vein thrombi also supports this premise.

The role of direct venous trauma in the initiation of thrombosis is self-evident. Admonitions against administration of fluid in leg veins have existed in most hospitals for many years because of the known risk of induction of a superficial venous thrombus which may secondarily involve the deep veins. Less well recognized is the very real thrombogenic and embolic risk

of central venous catheterization via the subclavian or jugular veins;[83] Muller has recently reported eight cases of fatal pulmonary embolism from this source observed in a university hospital during a one-year period.[127]

A lesser degree of injury is presumed to be responsible for the so-called "effort thrombosis" which follows unusual or persistent muscular activity or sudden muscular strain. Although recognized as a frequent mechanism of initiation of axillary and subclavian vein thrombosis,[30] it has also been linked to the development of leg vein thrombosis.[36]

Operation. The role of operation in contributing to the risk of venous thromboembolism is difficult to differentiate from the risk contributed by the patient's primary disease and associated conditions, his age, his preoperative immobilization in bed, etc. Although operation per se is probably a significant risk factor, the hazard of venous thrombosis and pulmonary embolism is greatly increased if other predisposing conditions are also present. Many studies utilizing labelled fibrinogen, usually confined to patients age 40 and over undergoing major operations, have shown an overall frequency of deep venous thrombosis of 15 to 50%.[7,78,88,102,103,129] Not all ^{125}I-fibrinogen-detectable thrombi are thought to carry a high risk of embolism; the 10–30% of venous thrombi which originate or propagate into the popliteal vein or above are the group associated with a high risk of pulmonary embolism.[101] Although some observers have proposed that at least one-half of the thrombi develop on the day of operation or within the first several postoperative days,[55,72] a careful evaluation of immobilized preoperative patients has only recently been conducted. Heatley et al.[74] evaluated a group of patients with gastrointestinal disease admitted to the hospital more than four days prior to operation and found that 62% of phlebographically-confirmed thrombi developed before operation; patients with cancer and those receiving parenteral alimentation were particularly susceptible.

The magnitude of the operative procedure appears to have a greater effect upon the frequency of both thrombosis and embolism than does the site of operation (except for orthopedic operations, especially those involving the hip).[8,33,71,102,129,171] For example, the frequency of detection of leg vein thrombi with labelled fibrinogen is 50% in patients after retropubic prostatectomy versus 4% after transurethral resection of the prostate gland, and 24% after transabdominal gynecologic procedures as compared to 9% after vaginal operations.[103] Leg amputations are also associated with a high frequency of thromboembolism.[27,39,185,191] As in cases of accidental trauma, the pathogenetic influence related to magnitude of operation may be the increase in duration of immobilization in bed; autopsy-proven pulmonary embolism in postoperative patients increases in frequency with duration of bed-rest.[33]

A cumulative increase in risk of development of venous thrombosis and pulmonary embolism in postoperative patients occurs in the presence of other risk factors: increasing age, obesity, varicose veins, past history of thromboembolism, carcinoma, cardiac disease, severe infection.[9,33,102,129] Although estimates of the additional risk contributed by these other factors are not definitive, it appears that the hazard of thromboembolism is increased by about 50% in patients with obesity and as much as 300% in subjects with cardiac disease or a past history of deep venous thrombosis (with the other risk estimates falling between these two extremes.[9,129]

Paralysis, prolonged bed-rest and other forms of immobility. Paralyzed patients and others who are totally immobilized have been of considerable epidemiological interest as a natural experiment concerning the role of venous stasis in the pathogenesis of venous thrombosis. Warlow et al.,[184] using labelled fibrinogen, found a 60% prevalence of thrombosis in the paralyzed legs of 30 patients within 10 days of the onset of their cerebrovascular accidents; only two patients had venous thrombosis in both legs. Pulmonary embolism occurred in four patients. Others have also observed an apparent increase in frequency of pulmonary embolism in patients with strokes.[15,20] Of 30 patients with Guillain-Barre syndrome, three had autopsy-proven pulmonary emboli and an additional 7 had the clinical diagnosis of pulmonary embolism.[141] An apparent increase in frequency of signs of thrombosis or evidence of postphlebitic sequelae has also been noted in subjects with catatonia or severe cerebral arteriosclerosis.[82]

Acute paraplegia is associated with a high frequency of venous thromboembolism.[33,169,183,186] Sixty-six instances of thromboembolic disease were detected in 500 patients with acute paraplegia; 15 deaths from massive pulmonary embolism occurred between four and 85 days after onset of paraplegia.[183] Patients with chronic paraplegia are at lesser risk of developing nonfatal and fatal pulmonary embolism.[169]

Other forms of immobilization, such as the treatment of tetanus[104] or the management of chronic respiratory insufficiency in an intensive care unit,[134] have also been linked with an increased risk of pulmonary embolism. A recent prospective study has demonstrated that clinically recognized deep venous thrombosis is almost twice as common in patients admitted as emergencies as compared to electively admitted patients;[125] although many factors may contribute to this difference, the degree of immobility con-

tributed by the acute illness may be a factor. Lesser degrees of confinement to bed, such as in the pre-antibiotic period of management of pulmonary tuberculosis, are not associated with a high frequency of thromboembolism;[57] however, when tuberculous patients are seriously ill, and more immobile for that reason, the prevalence of pulmonary embolism is as high as that found in a general hospital population.[29,97]

When the duration of confinement to bed during a terminal illness is related to the prevalence of deep venous thrombosis and pulmonary embolism found at autopsy, the peak frequency of venous thromboembolism is achieved after one week of immobilization.[61,153] These observations concur with isotopic measures of venous flow in the leg which have shown a progressive decrease in rate of venous flow in bedridden medical and postoperative patients, the maximum decrease being observed after the first week of confinement to bed.[98,195,196] Venous flow is markedly decreased in a paralyzed limb.[196]

The role of immobility in the pathogenesis of deep venous thrombosis is not limited to hospitalized patients. Recognition of the deleterious effect of transient but rather rigid confinement in air raid shelters surfaced in the early days of World War II; the sudden increase in frequency of fatal pulmonary embolism following the restriction of elderly patients to deck chairs in shelters is vividly described by Simpson.[155] Subsequently, Homans reported the development of deep venous thrombosis in individuals after long confining rides in airplanes or automobiles or prolonged sitting for other reasons.[81] On a somewhat similar basis, "spontaneous" leg vein thrombosis has been noted in tall men,[128] presumably as a result of the awkward sitting position necessitated by furniture of inappropriate size.

Hematologic problems. The hematologic diseases or conditions which clearly increase the risk of venous thromboembolism have not yet been fully defined. The best available data in support of an increase in thromboembolic risk relates to several of the myeloproliferative disorders: primary thrombocythemia,[133] polycythemia rubra vera[24,135] and agnogenic myeloid metaplasia.[80] Some investigators feel that a persistent elevation of the platelet count, including postsplenectomy thrombocytosis, is a predisposing factor to the development of thrombosis;[11] others have not found a correlation between postsplenectomy platelet count and frequency of thrombosis.[147] One study demonstrated venous thromboemboli in 6 of 25 patients with elevated platelet counts but in none of 21 patients with normal platelet numbers.[77] The sub-group of patients with postoperative thrombocytosis at greatest risk of thrombosis may be those who also show abnormalities in platelet aggregation, bleeding time and platelet factor—3 activity,[200] or, as Hirsh et al. have proposed, may be those subjects who have persistent postoperative anemia.[76]

Thromboembolic disease is a major problem in patients with paroxysmal nocturnal hemoglobinuria. Cerebral and portal venous thrombosis are more common as a cause of death than pulmonary embolism.[37] A number of abnormalities of blood coagulation have been reported, but many of these observations are conflicting.[3]

Patients with cryofibrinogenemia are thought to have an increased frequency of thromboembolism, but this apparent relationship may be secondary to the association of cryofibrinogenemia with cancer or to an accompanying hyperfibrinogenemia, or the cryofibrinogens may develop as a result of the thrombotic process.[158]

Ulcerative colitis. A significantly higher frequency of venous thromboembolism has been found in patients with chronic ulcerative colitis studied at autopsy.[29,65] The increase in risk appears to be two to three-fold. Medically treated patients may be at greater risk than surgically treated patients.[65] An increased prevalence in women has been noted by several observers.[45,65] Conflicting reports complicate interpretation of the significance of possible coagulative abnormalities in this disease;[108] an increase in factor VIII and in fibrinogen concentration has been noted, but such changes are not unexpected in patients with chronic inflammatory conditions.

Other conditions. Many other diseases and conditions have been proposed to be predisposing to venous thromboembolic disease. In many instances the association has been poorly documented; in others, the disease in question is accompanied by a high frequency of other well-recognized risk factors (heart disease, prolonged immobilization, etc.).

Diabetes mellitus is frequently cited. A frequency of pulmonary embolism of 20% was found in 349 diabetics age 30 and older examined at necropsy;[33] however, of the 71 patients with pulmonary embolism, 52 had associated heart disease and another 12 had other risk factors (cancer, recent leg amputation, cerebrovascular accidents, etc.).

Certain forms of infection have also been incriminated. An almost two-fold increase in ^{125}I-fibrinogen-detectable leg vein thrombi was found in surgical patients who developed postoperative infection;[129] although the difference appears to be significant, whether the infection per se or the added immobilization is the important element is difficult to define. Venous thromboembolism is a common and well-recognized complication of gram-negative septicemia;[25] this asso-

ciation is not unexpected in a condition known to be linked with a hypercoagulable state and intravascular coagulation. Subclinical endotoxemia may also be accompanied by a higher frequency of venous thrombosis and a more extensive thrombotic process; Fossard et al.[56] found that 29% of postoperative patients with a positive Limulus assay developed leg vein thrombi as compared to a 19% incidence in a control group; half of the thrombi associated with endotoxemia were "major" (above the knee).

A recent report has described 7 of 19 consecutive patients with Cushing's syndrome who developed thromboembolic complications before or after adrenalectomy.[156]

A high frequency of venous thrombosis has been linked with homocystinuria, an inborn error of metabolism.[22] An increased platelet "stickiness" has been demonstrated in these patients; normal platelets develop similar properties when incubated with homocystine *in vitro*.[112] In addition, homocystine is able to activate factor XII in an *in vitro* system.[142]

Another rare condition, Behcet's syndrome (aphthous stomatitis, uveitis, and genital ulceration) is also frequently accompanied by the presence of both superficial and deep venous thrombosis.[67,144]

Many other diseases and conditions have been proposed as risk factors: nutritional factors, alcohol, smoking, arthritis, chronic pulmonary disease, hyperlipidemia. Certain drugs other than oral contraceptives and estrogens have also been implicated, particularly adrenocorticosteroids, epsilon aminocaproic acid and several antibiotics. The data currently available are too conflicting and inconclusive to warrant their inclusion in this discussion.

Discussion

The current available information concerning the epidemiology of venous thromboembolism should be assessed with the recognition that it may be inaccurate, erroneous, or subject to misinterpretation. Many of the reports which have been cited are anecdotal. Most have not compared the frequency of a risk factor in patients with venous thromboembolism to its frequency in the total population from which the cases of venous thromboembolism were derived. Almost all of the data have been obtained from highly selected groups of patients. Diagnoses are based upon methodologies with varying levels of sensitivity and specificity. The risk of development of deep venous thrombosis in patients with a particular disease or condition may not be, and probably is not, synonymous with the risk of development of pulmonary embolism. Since so many possible risk factors have been proposed, the interrelationships, possible dependent variables, and likelihood of cumulative effects make estimates of risk ratios somewhat inaccurate.

Whenever so many elements thought to affect the frequency of development of venous thromboembolism exist, a justifiable presumption is that the true pathogenesis of the disease has remained undetected. An association does not necessarily mean causation. This discussion has attempted to point out the commonality of the Virchow-Aschoff postulates in the great majority of these proposed diseases and conditions. As one reviews the various proposed predisposing conditions, one or another of these factors is present. Perhaps the most frequent and best-documented association is with venous stasis. Advancing age and increased periods of immobilization appear to be of critical importance. As age increases, the soleal veins increase in number, size and tortuosity while calf muscle mass decreases, both contributing to a decrease in rate of venous return from the lower extremities. Decreased muscular activity and the antigravitational direction of flow in the soleal venous plexus in the recumbent position result in a further decrement in venous flow.

However, as Wessler has shown in experimental venous thrombosis,[187] stasis alone may not be sufficient for thrombus formation. In a given circumstance, the additional initiating factor may be direct venous trauma or endothelial injury produced by hypoxia; in other situations, a change in blood coagulability may contribute. If hypercoagulability of the blood is influential in thrombus development, the alterations in coagulation may be confined to the area of venous stasis and not be detectible in the systemic circulation. In spite of thousands of published papers on systemic changes in clotting factors as possible predictive tests for venous thrombosis, no definitive evidence has yet been presented. Measurement of levels of antithrombin III, which is probably identical to heparin cofactor and activated factor X inhibitor, is of greatest current interest; these studies have practical implications because the probable mechanism of action of low-dose heparin is through an increase in the rate at which antithrombin III combines with activated factor X.[189]

Although considerable skepticism is justified with respect to the role of epidemiological studies in further defining etiology or pathogenesis of venous thromboembolism, such investigations are of practical value in prediction of which patients are most likely to develop disability or to die from the sequelae of deep venous thrombosis. Epidemiologic data can be utilized to define "high-risk" groups of subjects most likely to benefit from specific prophylactic measures. The difficult and as yet unsolved problem is the determination of

the magnitude of the increase in risk produced by any given disease or condition and the possible cumulative effect upon risk when more than one risk factor is present. Currently, the individual physician must make this decision based upon the insufficient data which are now available. The more important risk factors which should be seriously considered in hospitalized patients are briefly listed in summary below; in many instances a cumulative increase in risk may be present when more than one risk factor is identified: 1) Past history of venous thromboembolism or physical signs of venous insufficiency. 2) Advancing age, when accompanied by immobilization for one week or longer. 3) Obesity (greater than 20% over ideal weight). 4) Acute paralysis or other conditions resulting in lack of usual mobility. 5) Heart disease. Risk is increased with severity of the heart disease and, particularly, in the presence of cardiac arrhythmia or congestive heart failure. 6) Cancer of lung, gastrointestinal and genitourinary tracts and, perhaps, of the breast. 7) Major operations, especially operations involving the lower one-half of the body, including intra-abdominal pelvic procedures and other operations resulting in extended periods of immobilization. 8) Postpartum patients with other risk factors, including estrogen suppression of lactation. 9) Women receiving oral contraceptives who are hospitalized and have other risk factors, particularly those scheduled for operation. 10) Accidental trauma to lower extremities, spine and pelvis. 11) Ulcerative colitis and (probably) Crohn's disease. 12) Infections with gram-negative organisms (possibly).

If a decision is made that a potential increase in risk warrants further measures, several alternatives are available. All patients at increased risk can be followed by one or more "screening" procedures thought to have greater sensitivity than clinical examination in the detection of venous thrombosis (e.g., ^{125}I-fibrinogen scanning, impedance phlebography, Doppler ultrasound examination, etc.). The validity of this approach to early detection of thrombosis depends upon the clinical acceptability of the test procedure, which should be proven to be simple, accurate and cost-effective. The other choices involve the utilization of a form of effective drug prophylaxis. At the present time, the measures proven to be of some value include conventional heparin or oral anticoagulant therapy, intravenous dextran, "low dose" heparin and, perhaps, under certain circumstances, intermittent mechanical compression or stimulation of the calf muscles. The choice of drug regimen depends upon physician preference and experience and a judgment concerning relative effectiveness in a given clinical situation, balanced against the risk of bleeding and other complications of therapy. Currently, a popular preventive measure for most surgical patients is low-dose heparin which, in a recent multicenter trial, has been shown to be both relatively safe and effective.[88]

This review of information concerning the epidemiology of venous thromboembolism is presented to provide an awareness of the magnitude of the problem and to provide data which the individual physician may utilize to be selective in his approach to prevention of this complication by restricting his efforts at early detection or prevention to those patients at greatest risk of morbidity or mortality.

Acknowledgment

Personal studies cited in this review were supported by the Michigan Heart Association.

References

1. Aaro, L. A. and Juergens, J. L.: Thrombophlebitis and Pulmonary Embolism as Complications of Pregnancy. Med. Clin. North Am., 58:829, 1974.
2. Almen, T., Hartel, M., Nylander, G. and Olivecrona, H.: The Effect of Estrogen on the Vascular Endothelium and its Possible Relation to Thrombosis. Surg. Gynecol. Obstet., 140: 938, 1975.
3. Amris, C. J. and Hansen, H. E.: Coagulation and Fibrinolytic Studies in Paroxysmal Nocturnal Hemoglobinuria. Acta Med. Scand., 184:551, 1968.
4. Amris, C. J. and Stourp, J.: The Coagulation Mechanism in Oral Contraception. Acta Obstet. Gynecol. Scand., 46:78, 1967.
5. Amundsen, M. A., Spittell, J. A., Jr., Thompson, J. H., Jr. and Owen, C. A., Jr.,: Hypercoagulability Associated with Malignant Disease and with the Postoperative State. Ann Intern. Med., 58:608, 1963.
6. Badaracco, M. A. and Vessey, M. P.: Recurrence of Venous Thromboembolic Disease and Use of Oral Contraceptives. Br. Med. J., 1:215, 1974.
7. Ballard, R. M., Bradley-Watson, P. J., Johnstone, F. D., et al. Low Dose of Subcutaneous Heparin in the Prevention of Deep Vein Thrombosis After Gynaecological Surgery. Br. J. Obstet. Gynaecol., 80:469, 1973.
8. Barker, N. W., Nygaard, K. K., Walters, W. and Priestly, J. T.: A Statistical Study of Postoperative Venous Thrombosis and Pulmonary Embolism. I. Incidence in Various Types of Operations. Mayo Clin. Proc., 15:769, 1940.
9. Barker, N. W., Nygaard, K. K., Walters, W. and Priestly, J. T.: A Statistical Study of Postoperative Venous Thrombosis and Pulmonary Embolism. II. Predisposing Factors. Mayo Clin. Proc., 16:1, 1941.
10. Bennett, N. B., Ogston, C. M., McAndrew, G. M. and Ogston, D.: Studies on the Fibrinolytic Enzyme System in Obesity. J. Clin. Pathol., 19:241, 1966.
11. Bensinger, T. A., Logue, G. L. and Rundles, R. W.: Hemorrhagic Thrombocythemia; Control of Postsplenectomy Thrombocytosis with Melphalan. Blood, 36:61, 1970.
12. Bolton, C. H., Hampton, J. R. and Mitchell, J. R. A.: Effects of Oral Contraceptive Agents on Platelets and Plasma-Phospholipids. Lancet, 1:1336, 1968.
13. Bonnar, J., McNicol, G. P. and Douglas, A. S.: Coagulation and Fibrinolytic Mechanisms During and After Normal Childbirth. Br. Med. J., 2:200, 1970.
14. Boyd, A. M., Jepson, R. P., Ratcliffe, A. H., and Rose S. S.:

The Logical Management of Chronic Ulcers of the Leg. Angiology, 3:207, 1952.
15. Brown, M. and Glassenberg, M.: Mortality Factors in Patients with Acute Stroke. JAMA, 224:1493, 1973.
16. Brugarolas, A., Mink, I. B., Elias, E. G. and Mittelman, A.: Correlation of Hyperfibrinogenemia with Major Thromboembolism in Patients with Cancer. Surg. Gynecol. Obstet., 136: 75, 1973.
17. Burkitt, D. P.: Varicose Veins, Deep Vein Thrombosis and Haemorrhoids: Epidemiology and Suggested Aetiology. Br. Med. J., 2:536, 1972.
18. Burstein, R., Alkjaersig, N. and Fletcher, A.: Thromboembolism During Pregnancy and the Postpartum State. J. Lab. Clin. Med., 78:838, 1971.
19. Byrd, R. E., Divertie, M. B. and Spittell, J. A., Jr.: Bronchogenic Carcinoma and Thromboembolic Disease. JAMA, 202:1019, 1967.
20. Byrne, J. J. and O'Neil, E. E.: Fatal Pulmonary Emboli: A Study of 130 Autopsy-Proven Fatal Emboli. Am. J. Surg., 83:47, 1952.
21. Carlotti, J., Hardy, I. B., Jr., Linton, R. R. and White, P. D.: Pulmonary Embolism in Medical Patients. JAMA, 134: 1447, 1947.
22. Carson, N. A. J., Dent, C. E., Field, C. M. B. and Gaull, G. E. Homocystinuria: Clinical and Pathological Review of Ten Cases. J. Pediatr., 66:565, 1965.
23. Caspary, E. A. and Peberdy, M. Oral Contraception and Blood-Platelet Adhesiveness. Lancet, 1:1142, 1965.
24. Chievitz, E. and Thiede, T.: Complications and Causes of Death in Polycythaemia Vera. Acta Med. Scand., 172:513, 1962.
25. Chow, A. W. and Guze, L. B.: Bacteroidaceae Bacteremia: Clinical Experience with 112 Patients. Medicine, 53:93, 1974.
26. Collaborative Group for the Study of Stroke in Young Women: An Epidemiologic Study of Oral Contraception and Cerebrovascular Disease. N. Engl. J. Med., 288:871, 1973.
27. Colt, J. D. and Lee, P. Y.: Mortality Rate of Above-Knee Amputation for Arteriosclerotic Gangrene: A Critical Evaluation. Angiology, 23:205, 1972.
28. Coon, W. W. and Coller, F. A.: Clinicopathologic Correlation in Thromboembolism. Surg., Gynecol. Obstet., 109:259, 1959.
29. Coon, W. W. and Coller, F. A.: Some Epidemiologic Considerations of Thromboembolism. Surg. Gynecol. Obstet., 109:487, 1959.
30. Coon, W. W. and Willis, P. W., III.: Thrombosis of the Deep Veins of the Arm. Surgery, 64:990, 1968.
31. Coon, W. W., Willis, P. W., III and Keller, J. B.: Venous Thromboembolism and Other Venous Disease in the Tecumseh Community Health Study. Circulation, 48:839, 1973.
32. Coon, W. W.: The Spectrum of Pulmonary Embolism - Twenty Years Later. Arch. Surg., 111:398, 1976.
33. Coon, W. W.: Risk Factors in Pulmonary Embolism. Surg., Gynecol. Obstet., 143:385, 1976.
34. Coope, J., Thomson, J. M. and Poller, L.: Effects of "Natural Estrogen" Replacement Therapy on Menopausal Symptoms and Blood Clotting. Br. Med. J., 4:139, 1975.
35. Coronary Drug Project. Initial Findings Leading to Modifications in Its Research Protocol. JAMA, 214: 1303, 1970.
36. Crane, C: Deep Venous Thrombosis in the Leg Following Effort or Strain. N. Engl. J. Med., 246:529, 1962.
37. Crosby, W. H.: Paroxysmal Nocturnal Hemoglobinuria. Relation of the Clinical Manifestations to Underlying Pathogenic Mechanism. Blood, 8:769, 1953.
38. Cunningham, I. G. E. and Yong, N. K.: The Incidence of Postoperative Deep Vein Thrombosis in Malaysia. Br. J. Surg., 61:482, 1974.
39. Daly, W. A. and Capps, W., Jr.: Major Leg and Thigh Amputations. Surgery, 46:333, 1959.
40. Daniel, D. G., Campbell, H., Turnbull, A. C.: Puerperal Thromboembolism and Suppression of Lactation. Lancet, 2: 287, 1967.
41. DeCamp, P., Landry, R., Ochsner, A. and DeBakey, M. E.: Spontaneous Thrombophlebitis. Surgery, 31:43, 1952.
42. DeTakats, G., Mayne, A., and Peterson, W. F.: The Meteorologic Factor in Pulmonary Embolism. Surgery, 7:819, 1940.
43. Domenet, J. G., Evans, D. W. and Stephenson, H.: Anticoagulants in Congestive Heart Failure. Br. Med. J., 2:866, 1966.
44. Edwards, E. A.: Migrating Thrombophlebitis Associated with Carcinoma. N. Engl. J. Med., 240:1030, 1949.
45. Edwards, F. C. and Truelove, S. C.: The Course and Prognosis of Ulcerative Colitis III. Complications. Gut, 5:1, 1964.
46. Egeberg, O. and Owren, P. A.: Oral Contraception and Blood Coagulability. Br. Med. J., 1:220, 1963.
47. Egeberg, O.: Inherited Antithrombin Deficiency Causing Thrombophilia. Thromb. Diath. Haemorrh., 13:516, 1965.
48. Egeberg, O.: Inherited Fibrinogen Abnormality Causing Thrombophilia. Thromb. Diath. Haemorrh., 17:176, 1967.
49. Emerson, P. A., Teather, D. and Handley, A. J.: The Application of Decision Theory to the Prevention of Deep Vein Thrombosis Following Myocardial Infarction. Q. J. Med., 43: 389, 1974.
50. Emery, J. L.: Pulmonary Embolism in Children. Arch Dis. Child., 37:591, 1962.
51. Fejfar, Z., Badger, D. and Crais, M.: Epidemiological Aspects of Thrombosis and Vascular Disease. Throm. Diath. Haemorrh., suppl. 21:5, 1966.
52. Field, E. S., Kakkar, V. V., Nicolaides, A. N. and Renney, J. T. G.: Deep Vein Thrombosis in Patients with Fractured Neck of Femur. Br. J. Surg., 58:873, 1971, (Abst.).
53. Fisher, M., Michele, A. and McCann, W.: Thrombophlebitis and Pulmonary Infarction Associated with Fractured Hip. Clin. Res., 11:407, 1963.
54. Fitts, W. T., Jr., Lehr, H. B., Bitner, R. L. and Spelman, J. W.: An Analysis of 950 Fatal Injuries. Surgery, 56:663, 1964.
55. Flanc, C., Kakkar, V. V. and Clarke, M. B.: The Detection of Venous Thrombosis of the Legs Using ^{125}I-Labelled Fibrinogen. Br. J. Surg., 55:742, 1968.
56. Fossard, D. P., Kakkar, V. V. and Higgins, J.: Infection and Postoperative Thrombosis. Br. J. Surg., 61:919, 1974. (Abst.)
57. Fox, T. T., Robitzek, E. H., Bernstein, I. and Bobb, A. L.: Bed Rest and Thromboembolization in Tuberculosis. Am. Rev. Tuberc., 57:485, 1948.
58. Freeark, R. J., Boswick, J. and Fardin, R.: Posttraumatic Venous Thrombosis. Arch. Surg., 95:567, 1967.
59. Friend, J. R. and Kakkar, V. V.: Deep Vein Thrombosis in Obstetric and Gynaecologic Patients, *In* Thromboembolism: Diagnosis and Treatment, V. V. Kakkar and A. J. Jouhar, eds., Edinburgh-London, Churchill Livingstone, 1972, pg. 131.
60. Gaston, L. W.: Studies on a Family with an Elevated Plasma Level of Factor V (Proaccelerin) and a Tendency to Thrombosis. J. Pediatr., 68:367, 1966.
61. Gibbs, N. M.: Venous Thrombosis of the Lower Limbs with Particular Reference to Bed Rest. Br. J. Surg., 45:209, 1957.
62. Gjores, J. E.: The Incidence of Venous Thrombosis and its Sequelae in Certain Districts of Sweden. Acta Chir. Scand.,: suppl. 206, 1956.
63. Goodrich, S. M. and Wood, J. E.: Peripheral Venous Distensibility and Velocity of Venous Blood Flow During Pregnancy or During Oral Contraceptive Therapy. Am. J. Obstet Gynecol., 90:740, 1964.
64. Gore, I., Hirst, A. E., and Tanaka, K.: Myocardial Infarction and Thromboembolism: A Comparative Study in Boston and Kyushu, Japan. Arch. Intern. Med., 113:323, 1964.
65. Graef, V., Baggenstoss, A. H., Sauer, W. G. and Spittell, J. A., Jr.: Venous Thrombosis Occurring in Non-Specific Ulcerative Colitis. Arch. Intern. Med., 117:377, 1966.
66. Green, G. R. and Sartwell, P. E.: Oral Contraceptive Use in Patients with Thromboembolism Following Surgery, Trauma or Infection. Am J. Public Health, 62:680, 1972.
67. Haim, S., Sobel, J. D. and Friedman-Birnbaum, R.:

Thrombophlebitis, a Cardinal Symptom of Behcet's Syndrome. Acta Derm. Venereol., 54:299, 1974.
68. Halse, T., Jr. and Quennet, G.: Klimatische Einflusse en der Thrombogenese. Dtsch. Med. Wochenschr., 73:125, 1948.
69. Hampton, A. O. and Castleman, B.: Correlation of Postmortem Chest Teleroentgenograms with Autopsy Findings. Am. J. Roentgenol. Radium Ther. Nucl. Med., 43:305, 1940.
70. Handley, A. J., Emerson, P. A. and Fleming, P. R.: Heparin in the Prevention of Deep Vein Thrombosis After Myocardial Infarction. Br. Med. J., 7:436, 1972.
71. Harris, W., Salzman, E. and DeSanctis, R.: The Prevention of Thromboembolic Disease by Prophylactic Anticoagulation. J. Bone Joint Surg., 49A:81, 1967.
72. Hartsuck, J. M. and Greenfield, L. J.: Postoperative Thromboembolism. A Clinical Study with ^{125}I-Fibrinogen and Pulmonary Scanning. Arch. Surg., 107:733, 1973.
73. Hassan, M. A., Rahman, E. A. and Rahman, I. A.: Prostatectomy and Deep Vein Thrombosis in Sudanese Patients. Br. J. Surg., 61:650, 1974.
74. Heatley, R. V., Morgan, A., Hughes, L. E. and Okwonga, W.: Preoperative or Postoperative Deep Vein Thrombosis? Lancet, 1:437, 1976.
75. Hiilesmaa, V.: Occurrence and Anticoagulant Treatment of Thromboembolism in Gravidas, Parturients and Gynecologic Patients. Acta Obstet. Gynecol. Scand., 39 (suppl 2):5, 1960.
76. Hirsh, J. and Dacie, J. V.: Persistent Postsplenectomy Thrombocytosis and Thromboembolism: A Consequence of Continued Anemia. Br. J. Haematol., 12:44, 1966.
77. Hirsh, J., McBride, J. A. and Dacie, J. V.: Thromboembolism and Increased Platelet Adhesiveness in Postsplenectomy Thrombocytosis. Aust. NZ. J. Med., 15:122, 1966.
78. Hirsh, J.: Venous Thromboembolism: Diagnosis, Treatment, Prevention. Hosp. Practice, 10:53, 1975.
79. Hjelmstedt, A. and Bergvall, U.: Incidence of Thrombosis in Patients with Tibial Fractures. Acta Chir. Scand., 134:209, 1968.
80. Hoagland, H. C. and Perry, M. C.: Thrombocythemia (Thrombocytosis). JAMA, 235:2330, 1976.
81. Homans, J.: Thrombosis of the Deep Leg Veins Due to Prolonged Sitting. N. Engl. J. Med., 250:148, 1954.
82. Horwitz, O., Devon, D. W., Sebring, H. D., et al.: Venous Thrombosis in Catatonic Patients. Circulation, 26:733, 1962 (Abst.)
83. Hoshal, V. L., Ause, R. G. and Hoskins, P. A.: Fibrin Sleeve Formation on Indwelling Subclavian Central Venous Catheters. Arch. Surg., 102:353, 1971.
84. Hume, M., Sevitt, S. and Thomas, D. P.: Venous Thrombosis and Pulmonary Embolism. Cambridge, Commonwealth Fund/Harvard University Press, 1970, pg. 4.
85. Husni, E. A., Pena, L. I. and Lenhert, A. E.: Thrombophlebitis in Pregnancy. Am. J. Obstet. Gynecol., 97:901, 1967.
86. Inman, W. H. W. and Vessey, M. P.: Investigation of Deaths from Pulmonary, Coronary and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age. Br. Med. J., 2:193, 1968.
87. Inman, W. H. W., Vessey, M. P., Westerholm, B. and Engelund, A.: Thromboembolic Disease and the Steroidal Content of Oral Contraceptives; A Report to the Committee on Safety of Drugs. Br. Med. J., 2:203, 1970.
88. International Multicentre Trial. Prevention of Fatal Postoperative Pulmonary Embolism by Low Doses of Heparin. Lancet, 2:45, 1975.
89. Irey, N. S., Manion, W. C. and Taylor, H. B.: Vascular Lesions in Women Taking Oral Contraceptives. Arch. Pathol., 89:1, 1970.
90. Irey, N. S. and Norris, H. J.: Intimal Vascular Lesions Associated with Female Reporductive Steroids. Arch. Pathol., 96:227, 1973.
91. Jeffcoate, T. N. A., Miller, J., Roos, R. F., and Tindall, V. R.: Puerperal Thromboembolism in Relation to the Inhibition of Lactation by Oestrogen Therapy. Br. Med. J., 4:19, 1968.
92. Jick, H., Slone, D., Westerholm, B., et al.: Venous Thromboembolic Disease and ABO Blood type. Lancet, 1:539, 1969.
93. Joffe, S. W.: Racial Incidence of Postoperative Deep Vein Thrombosis in South Africa. Br. J. Surg., 61:982, 1974.
94. Joffe, S. W.: Postoperative Deep Vein Thrombosis in Children. J. Pediatr. Surg., 10:539, 1975.
95. Jones, D. R. B. and MacIntyre, I. M. C.: Venous Thromboembolism in Infancy and Childhood. Arch. Dis. Child., 50: 153, 1975.
96. Jones, R. H. and Sabiston, D. C., Jr.: Pulmonary Embolism in Childhood. Monogr. Surg. Sci., 3:35, 1966.
97. Jones, R. S., Black, T. C. and Span, H. A.: Incidence and Significance of Thromboembolism in Pulmonary Tuberculosis. Am. Rev. Tuberc., 61:826, 1950.
98. Jonsson, G.: Venous Circulation in the Lower Half of the Body. Acta Chir. Scand., suppl. 161:1, 1951.
99. Jordan, F. L. J. and Nandorff, A.: The Familial Tendency in Thromboembolic Disease. Acta Med. Scand., 156:267, 1959.
100. Kagan, A.: Information on Thrombosis as a Cause of Death, from Studies Promoted by the World Health Organization. *In* Thrombosis, S. Sherry, (Ed.), Washington, D.C., National Academy of Sciences, 1969, p. 9.
101. Kakkar, V. V., Howe, C. T., Flanc, C. and Clarke, M. B.: Natural History of Postoperative Deep-Vein Thrombosis. Lancet, 2:230, 1969.
102. Kakkar, V. V., Howe, C. T., Nicolaides, A. N., et al.: Deep Vein Thrombosis of Leg. Is There a "High Risk" Group? Am. J. Surg., 120:527, 1970.
103. Kakkar, V. V.: The Diagnosis of Deep Vein Thrombosis using the ^{125}I-Fibrinogen Test. Arch. Surg., 104:152, 1972.
104. Kerr, J. H., Corbett, J. L., Prys-Roberts, C., et al.: Involvement of the Sympathetic Nervous System in Tetanus. Lancet, 2:236, 1968.
105. Lafler, C. J. and Hinerman, D. L.: A Morphologic Study of Pancreatic Carcinoma with Reference to Multiple Thrombosis. Cancer, 14:944, 1961.
106. Langman, M. J. S. and Doll, R.: ABO Blood Group and Secretor Status in Relation to Clinical Characteristics of Peptic Ulcers. Gut, 6:270, 1965.
107. Lawrence, E. A., Bowman, D. E., Moore, D. B. and Bernstein, G. I.: A Thromboplastic Property of Neoplasms. Surg. Forum, 3:694, 1952.
108. Lee, J. C. L., Spittell, J. A., Jr., Sauer, W. G., et al.: Hypercoagulability Associated with Chronic Ulcerative Colitis: Changes in Blood Coagulation Factors. Gastroenterology, 54: 76, 1968.
109. Levin, J. and Conley, C. L.: Thrombocytosis in Cancer. Arch. Intern. Med., 114:497, 1964.
110. Løfgren, E. P., Coates, H. L. C. and O'Brien, P. E.: Clinically Suspect Pulmonary Embolism After Vein Stripping. Mayo Clin. Proc., 57:77, 1976.
111. McCartney, J. S.: Pulmonary Embolism Following Trauma. Am. J. Pathol., 10:709, 1934.
112. McDonald, J., Bray, C., Field, C., et al.: Homocystinuria, Thrombosis and the Blood Platelets. Lancet, 1:745, 1964.
113. Marciniak, E., Farley, C. H. and DeSimone, P. A. Familial Thrombosis Due to Antithrombin III Deficiency. Blood, 43: 219, 1974.
114. Masi, A. T.: Endocrine Factors and Risk of Venous Thrombosis. Milbank Mem. Fund Q., 50 (part 2):46, 1972.
115. Mauer, B. J., Wray, R. and Shillingford, J. P.: Frequency of Deep Venous Thrombosis After Myocardial Infarction. Lancet, 2:1385, 1971.
116. Meek, J. R. and Maurer, J. J.: Phlegmasia Cerulea Dolens. Am. J. Surg., 97:104, 1959.
117. Mibashan, R., Nossel, H. L. and Moodie, A.: Blood Coagulation and Fibrinolysis in Relation to Coronary Heart Disease; A Comparative Study of Normal White Men, White Men with Overt Coronary Heart Disease, and Normal Bantu Men. Br. Med. J., 1:219, 1960.
118. Miller, S. P., Sanchez-Avalos, J., Stefanski, T. and Zuckerman,

L.: Coagulation Disorders in Cancer. I. Clinical and Laboratory Studies. Cancer, 20:1452, 1967.
119. Mink, I. B., Covery, N. G., Moore, R. H., et al.: Progestational Agents and Blood Coagulation. IV. Changes Induced by Progestogen Alone. Am. J. Obstet. Gynecol., 113:739, 1972.
120. Moolten, S. E., Vroman, L., Vroman, G. M. S. and Goodman, B.: Role of Blood Platelets in Thromboembolism. Arch. Intern. Med., 84:667, 1949.
121. Morales, A. and Pujari, B.: The Choice of Estrogen Preparations in the Treatment of Prostatic Cancer. Can. Med. Assoc. J., 113:865, 1975.
122. Moran, T. J.: Autopsy Incidence of Pulmonary Embolism in Coronary Heart Disease. Ann. Intern. Med., 32:949, 1950.
123. Morrell, M. T., Truelove, S. C. and Barr, A.: Pulmonary Embolism. Br. Med. J., 2:830, 1963.
124. Morrell, M. T. and Dunhill, M. S.: The Postmortem Incidence of Pulmonary Embolism in a Hospital Population. Br. J. Surg., 55:347, 1968.
125. Morrell, M. T.: Acute Illness—An Important Cause of Venous Thrombosis and Pulmonary Embolism. Br. J. Surg., 63:162, 1976.
126. Mourant, A. E., Kopec, A. C. and Domaniewska-Sobcznak, K.: Blood-Groups and Blood-Clotting. Lancet, 1:223, 1971.
127. Muller, K. M.: Tödliche Thromboembolische Komplicationen Nach Zentralen Venenkatheter. Dtsch. Med. Wochenschr, 101:411, 1976.
128. Naide, M.: Venous Thrombosis in Tall Men. JAMA, 148: 1202, 1952.
129. Nicolaides, A. N. and Irving, D.: Clinical Factors and the Risk of Deep Venous Thrombosis. *In* Thromboembolism, A. N. Nicolaides, (Ed), Baltimore, University Park Press, 1975, pg. 194.
130. Nishiyama, R. H., Anderson, D. G., Brody, G. L., et al.: Vascular Causes of Death in Pregnancy. Mich. Med. 66:1419, 1967.
131. Oliver, M. F.: Thrombosis and Estrogens. Lancet, 2:57, 1967.
132. Oski, F. A., Lubin, B. and Buckert, E. D.: Reduced Red Cell Filterability with Oral Contraceptive Agents. Ann. Intern. Med., 77:417, 1972.
133. Ozer, F. L., Truax, W. E., Miesch, D. C. and Levin, W. C.: Primary Hemorrhagic Thrombocythemia. Am. J. Med., 28: 807, 1960.
134. Pariente, R., Bignon, J., Roche, J. and Brouet, G.: Frequence et Particularities Cliniques des Thromboembolies Pulmonaires en Reanimation Respiratoire et Polyvalente. Rev. Tuberc. (Paris) 33:619, 1969.
135. Perkins, J., Israels, M. C. G. and Wilkinson, J. F.: Polycythaemia Vera: Clinical Studies on a Series of 127 Patients Managed Without Radiation Therapy. Q. J. Med., 33:499, 1964.
136. Pilgeram, L. O., Ellison, J. and von dem Bussche, G.: Oral Contraceptives and Increased Formation of Soluble Fibrin. Br. Med. J., 3:556, 1974.
137. Pineo, G. F., Brain, M. C., Gallus, A. S., et al.: Tumors, Mucus Production and Hypercoagulability. Ann N.Y. Acad, Sci., 230:262, 1974.
138. Poller, L., Tabiowo, A. and Thomson, J. M.: Effects of Low-Dose Oral Contraceptives on Blood Coagulation. Br. Med. J., 3:218, 1968.
139. Poller, L., Thomson, J. M. and Thomas, P. W.: Effects of Progestogen Oral Contraception with Norethisterone on Blood Clotting and Platelets. Br. Med. J., 4:391, 1972.
140. Preston, A. E. and Barr, A.: The Plasma Concentration of Factor VIII in the Normal Population. II. The Effects of Age, Sex and Blood Group. Br. J. Haematol., 10:238, 1964.
141. Ramon, T. K., Blake, J. A. and Harris, T. M.: Pulmonary Embolism in Landry-Guillain-Barre-Strohl Syndrome. Chest, 60:555, 1971.
142. Ratnoff, O. C.: Activation of Hageman Factor by L-Homocystine. Science, 162:1007, 1968.
143. Rosenthal, S. R.: Thrombosis and Embolism: An Analysis of 1000 Autopsies. J. Lab. Clin. Med., 16:107, 1930.
144. Rosenthal, T., Halkin, H., Shani, M. and Deutsch, V.: Occlusion of the Great Veins in the Behcet Syndrome. Angiology, 23:600, 1972.
145. Rossman, I.: True Incidence of Pulmonary Embolization and Vital Statistics, JAMA, 230:1677, 1974.
146. Sagar, S., Stamatakis, J. D., Thomas, D. P. and Kakkar, V. V.: Oral Contraceptives, Antithrombin-III Activity, and Postoperative Deep-Vein Thrombosis. Lancet, 1:509, 1976.
147. Salter, P. P. and Sherlock, E. C.: Splenectomy, Thrombocytosis, and Venous Thrombosis. Am. Surg., 23:549, 1957.
148. Sandritter, W. and Felix, H.: Geographical Pathology of Fatal Lung Embolism. Pathol. et Microbiol., 30:742, 1967.
149. Sandritter, W., Thomas, C. and Kirsten, W. H.: Color Atlas and Textbook of Macropathology. Chicago, Yearbook Medical Publishers, Inc., 1972, pg. 70.
150. Sartwell, P. E., Masi, A. T., Arthes, F. G., et al.: Thromboembolism and Oral Contraceptives: An Epidemiological Case-Control Study. Am. J. Epidemiol., 90:365, 1969.
151. Seigel, D. G.: Pregnancy, the Puerperium and the Steroid Contraceptive. Milbank Mem. Fund Q., 50 (part 2): 15, 1972.
152. Sevitt, S.: Fatal Road Accidents: Injuries, Complications and Causes of Death in 250 Subjects. Br. J. Surg., 55:48, 1968.
153. Sevitt, S. and Gallagher, N.: Venous Thrombosis and Pulmonary Embolism. A Clinicopathologic Study in Injured and Burned Patients. Br. J. Surg., 48:475, 1971.
154. Simmons, A. V., Sheppard, M. A. and Cox, A. F.: Deep Venous Thrombosis after Myocardial Infarction. Predisposing Factors. Br. Heart J., 35:623, 1973.
155. Simpson, K.: Shelter Deaths from Pulmonary Embolism. Lancet, 2:744, 1940.
156. Sjoberg, H. E., Blomback, M. and Granberg, P. O.: Thromboembolic Complications, Heparin Treatment and Increase in Coagulation Factors in Cushing's Syndrome. Acta Med. Scand., 199:95, 1976.
157. Smith, G. T., Dammin, G. J. and Dexter, L.: Postmortem Arteriographic Studies of the Human Lung in Pulmonary Embolization. JAMA, 188:143, 1964.
158. Smith, S. B. and Arkin, C.: Cryofibrinogenemia: Incidence, Clinical Correlations and a Review of the Literature. Am. J. Clin. Pathol., 58:524, 1972.
159. Snell, A. M.: The Relation of Obesity to Fatal Postoperative Pulmonary Embolism. Arch. Surg., 15:237, 1927.
160. Sproul, E. E.: Carcinoma and Venous Thrombosis: Frequency of Association of Carcinoma in Body or Tail of Pancreas with Multiple Venous Thrombosis. Am J. Cancer, 34:566, 1938.
161. Stahli, W.: Thrombose und Lungenembolie in ihren Beziehungen zu Witterungsvorgangen für die Hohenlage von Davos. Schweiz. Med. Wochenschr., 72:321, 1942.
162. Stolley, P. D., Tonascia, J. A., Tochman, M. S., et al.: Thrombosis with Low-Estrogen Oral Contraceptives. Am. J. Epidemiol., 102:197, 1975.
163. Strukov, A. I. and Vasilieva, N. N.: Contributions to the Pathological Anatomy of Thrombosis and Embolism. Khirurgiia, 34:86, 1958 (Abst. JAMA, 169:1246, 1959).
164. Teviotdale, B. M. and Gwynne, J. F.: Deep Calf Vein Thrombosis and Pulmonary Embolism—A Necropsy Study. NZ Med. J., 66:530, 1967.
165. Thomas, W. A., Davies, J. N. P., O'Neal, R. M. and Dimakulangan, A. A.: Incidence of Myocardial Infarction Correlated with Venous and Pulmonary Thrombosis and Embolism: A Geographic Study Based on Autopsies in Uganda, East Africa and St. Louis, U.S.A. Am. J. Cardiol. 5:41, 1960.
166. Tietien, G. W., Chien, S., Scholz, P. M., et al.: Changes in Blood Viscosity and Plasma Proteins in Carcinoma. Surg. Forum, 26:166, 1975.
167. Tindall, V. R.: Factors Influencing Puerperal Thromboembolism. Br. J. Obstet. Gynaecol., 75:1324, 1968.
168. Todd, M. E., Thompson, J. J., Bowie, E. J. W. and

Owen, C. A.: Changes in Blood Coagulation During Pregnancy. Mayo Clin Proc., 40:370, 1965.
169. Tribe, C. R.: Causes of Death in the Early and Late Stages of Paraplegia. Paraplegia, 1:19, 1963.
170. Trousseau, A.: Phlegmasia Alba Dolens. Clinique Medicale de l'Hotel-Dieu de Paris, Vol. 3, Paris, Balliere, 1865, p. 94 and 654.
171. Tubiana, R. and Duparc, J.: Prevention of Thromboembolic Complications in Orthopedic and Accident Surgery. J. Bone Joint Surg., 43B:7, 1961.
172. Turnbull, A. C.: Prophylaxis by Anticoagulants after Gynaecologic Operations. *In* Thrombosis and Anticoagulant Therapy, W. Walker, (Ed.), London, E. S. Livingstone, Ltd., 1960, pg. 60.
173. Vessey, M. P. and Doll, R.: Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. Br. Med. J., 2:199, 1968.
174. Vessey, M. P., Doll, R., Fairbairn, A. S., and Glover, G.: Postoperative Thromboembolism and the Use of Oral Contraceptives. Br. Med. J., 3:123, 1970.
175. Vessey, M. P. and Inman, W. H. W.: Speculations about Mortality Trends from Venous Thromboembolic Disease in England and Wales and Their Relation to the Pattern of Oral Contraceptive Usage. Br. J. Obstet. Gynaecol., 80:562, 1973.
176. Vessey, M. P.: The Epidemiology of Venous Thromboembolism. *In* Recent Advances in Thrombosis, L. Poller, (Ed.), Edinburgh,-London, Churchill Livingstone, 1973, pg. 39.
177. Veterans Administration Cooperative Urologic Research Group. Treatment and Survival of Patients with Cancer of the Prostate. Surg., Gynecol. Obstet., 124:1011, 1967.
178. Vital Statistics of the United States, 1970, Vol II—Mortality, Washington, D.C. U.S. Govt. Printing Office, 1975, pg. 1–124.
179. Von Kaulla, K. N.: Bed Rest, Elective Surgery, and Oral Contraceptives. JAMA, 218:888, 1971.
180. Von Kaulla, E., Droegemueller, W., Aoki, N., and Von Kaulla, K. N.: Antithrombin III Depression and Thrombin Generation Acceleration in Women Taking Oral Contraceptives. Am. J. Obstet. Gynecol., 109:868, 1971.
181. Von Kaulla, E., Droegemueller, W. and Von Kaulla, K. N.: Conjugated Estrogens and Hypercoagulability. Am. J. Obstet. Gynecol., 122:688, 1975.
182. Walker, R. M. and Parry, E. W.: Some Clinical Features in the Etiology of Thrombosis and Embolism. Gynecol. Invest., 138: 140, 1954.
183. Walsh, J. J. and Tribe, C. R.: Phlebothrombosis and Pulmonary Embolism in Paraplegia. Paraplegia, 3:209, 1965.
184. Warlow, C., Ogston, D. and Douglas, A. S.: Venous Thrombosis Following Strokes. Lancet, 1:1350, 1972.
185. Warren, R. and Kihn, R. B.: A Survey of Lower Extremity Amputations for Ischemia. Surgery, 63:107, 1968.
186. Watson, N.: Venous Thrombosis and Pulmonary Embolism in Spinal Cord Injury. Paraplegia, 6:113, 1968.
187. Wessler, S., Reimer, S. M. and Sheps, M. C.: Biologic Assay of a Thrombosis-Inducing Activity in Human Serum. J. Appl. Physiol., 14:943, 1959.
188. Wessler, S.: Small Doses of Heparin and a New Concept of Hypercoagulability. Throm. Diath. Haemorrh., 33:81, 1974.
189. Wessler, S.: Prevention of Venous Thromboembolism by Low-Dose Heparin. Mod. Concepts. Cardiovasc. Dis., 45:105, 1976.
190. White, P. D., Pulmonary Embolism and Heart Disease. A Review of Twenty Years of Personal Experience. Am. J. Med. Sci., 200:577, 1940.
191. Williams, J. W., Britt, L. G., Eades, T. and Sherman, R. T.: Pulmonary Embolism After Amputations of the Lower Extremity. Surg., Gynecol. Obstet., 140:246, 1975.
192. Wise, R. C. and Todd, J. K.: Spontaneous Lower-Extremity Thrombosis in Children. Am. J. Dis. Child., 126:766, 1973.
193. Wood, E. H., Prentice, C. R. M. and McNicol, G. P.: Association of Fibrinogen—Fibrin Related Antigen (F. R.—Antigen) with Postoperative Deep Vein Thrombosis and Systemic Complications. Lancet, 1:166, 1972.
194. Wright, H. P., Osborn, S. B. and Edmonds, D. G.: Changes in the Rate of Flow of Venous Blood in the Leg During Pregnancy, Measured by Radioactive Sodium. Surg. Gynecol. Obstet., 90:481, 1950.
195. Wright, H. P., Osborn, S. B. and Edmonds, D. G.: Effects of Postoperative Bed Rest and Early Ambulation on the Rate of Venous Blood Flow. Lancet, 1:22, 1951.
196. Wright, H. P., Osborn, S. B. and Hayden, M.: Venous Velocity in Bedridden Medical Patients. Lancet, 2:699, 1952.
197. Zahir, M.: Platelet Function in Pregnancy. Clin. Res., 17:603, 1969.
198. Zeitlhofer, J. and Reiffenstuhl, G.: Untersuchungen über fulminante, tödliche Lungenembolien an Obduktionsmaterial der Jahre 1941 bis 1951. Wien. Klin. Wochenschr. 64:446, 1952.
199. Zuck, T. F., Bergin, J. J., Raymond, J., and MandDwyre, W. R.: Implications of Depressed Antithrombin—III Activity Associated with Oral Contraceptives. Surg. Gynecol Obstet., 133:609, 1971.
200. Zucker, S. and Mielke, C. H.: Classification of Thrombocytosis Based on Platelet Function Tests: Correlation with Hemorrhagic and Thrombotic Complications. J. Lab. Clin. Med., 80: 385, 1972.