THROMBO-EMBOLISM

AN ANALYSIS OF CASES AT THE CHARITY HOSPITAL IN NEW ORLEANS OVER A 12-YEAR PERIOD*

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FOR A NUMBER OF YEARS many investigators, including ourselves, have been interested in and concerned with thrombo-embolism. Considerable work has been done to discover the cause of this disabling, and, all too frequently, fatal complication. Various therapeutic measures have been advocated to prevent its development and to control it once it has developed. In spite of all this, as previously demonstrated by us, the incidence of venous thrombosis and its attendant sequelae has increased progressively. We believed that much could be accomplished as regards prophylaxis and that diagnosis of an existing thrombus was not difficult if its existence was considered and looked for. With increasing experience, however, and by careful analysis of the cases of thrombo-embolism in the Charity Hospital in New Orleans, it has become obvious to us that prevention of venous thrombosis is difficult and that the diagnosis of phlebothrombosis, at least, is extremely difficult and at times may be impossible. In the Charity Hospital, where the staff has been cognizant of the frequency and seriousness of thrombo-embolism and has maintained a constant vigilance for the detection of venous thrombosis, in approximately one-half the cases of fatal pulmonary embolism no clinical evidence of an antecedent thrombus could be demonstrated.

The present report is based on a study of the cases of thrombo-embolism in the Charity Hospital in New Orleans from July 1, 1938, to June 30, 1950. The Charity Hospital is a large general hospital to which the white and colored races are admitted with about equal frequency and, therefore, this study is of significance not only because of the large number of cases, but also because both races are involved. During the period of study there were admitted to the Charity Hospital, 647,868 patients, of whom 32,254 died. Stillbirths were not included in the latter group. Ten thousand nine hundred and forty-seven (33.9 per cent) of the 32,254 deaths had autopsies. This is a low autopsy rate, which was due to local conditions that were not correctable until recently. One hundred and eighty-six thousand, two hundred and seventy-nine operations were performed, not including those on the Eye, Ear, Nose and Throat Services. The eye and otolaryngologic operations were omitted because they were of such a character that they were seldom associated with sufficient trauma to give rise to the danger of thrombo-embolism. Thrombo-embolism was diagnosed in 1223 cases (0.19 per cent).

A diagnosis of fatal pulmonary embolism was made in 476 instances, of which 383 were confirmed by autopsy. Had one hundred per cent autopsies been performed, the expected incidence of fatal pulmonary emboli would have been 1130. The fre-

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quency of fatal emboli based on the actual cases is 0.073 per cent, whereas the expected frequency based on 100 per cent autopsies is 0.174 per cent. Of the 186,279 patients operated upon, 106 had a fatal pulmonary embolus, of which 72 were confirmed by autopsy. Had autopsies been performed in all cases the expected incidence of postoperative emboli would be 212. The frequency of postoperative pulmonary emboli is, therefore, actually 0.057 per cent, and expected 0.114 per cent.

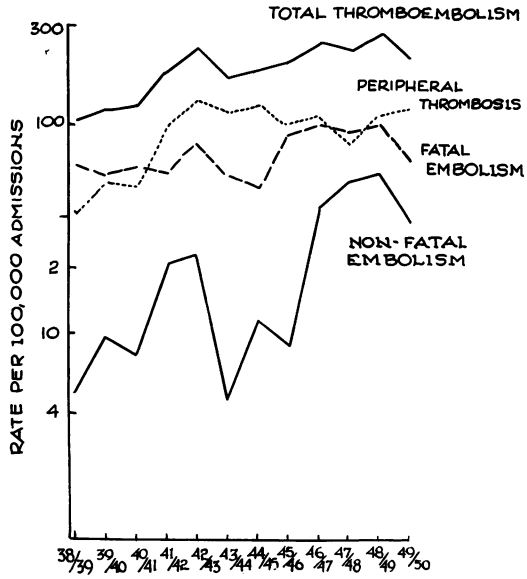


FIG. 1.—Comparative incidence of thrombo-embolism by years.

As mentioned previously, the distressing phase of the problem is that in the present series, in spite of everything that has been done to prevent the development of thrombo-embolism and also to prevent the fatal outcome as a result of pulmonary embolism, there has been a progressive increase in the incidence of thrombo-embolism as a whole, peripheral thromboses, fatal embolism, and non-fatal embolism, until in the past year, when there has been a decrease in all of these except peripheral thromboses (Fig. 1). The decrease in the incidence of fatal and non-fatal pulmonary emboli in the past year may be due in part to the more constant vigilance in all patients who are candidates for venous thromboses and to the institution of measures to prevent a detachment of a clot. If one considers the series according to three different time periods, *i.e.*, from 1938 to 1942, from 1942 to 1946, and from 1946 to 1950, there is a progressive increase in the incidence of all cases of thrombo-embolism and also of fatal pulmonary emboli, the increase in the former being from 131 per hundred thousand admissions* in the first period to 241 in the last period. These respective figures in the fatal pulmonary emboli are 61 and 89 (Fig. 2).

* Unless otherwise noted all incidence figures throughout this report are given as rates per hundred thousand admissions.

Thrombo-embolism occurs somewhat more frequently in the white than in the colored race. Two hundred and sixty-six cases per hundred thousand occurred in the white as compared with the 244 in the Negro race. On the other hand, there was a slightly higher incidence of fatal pulmonary embolism in the Negro as compared with the white patients, 106 and 87, respectively. Peripheral thromboses without embolism were higher in the white (141) than in the Negro patients (110) (Fig. 3). Thrombo-embolism occurs more frequently in men (281) than in women (238). Fatal pulmonary embolism was twice as frequent in men (140), as in women (70). On the other hand, peripheral thromboses occurred more frequently in women (139) than in men (98) (Fig. 4). The higher incidence of fatal pulmonary embolism in men is undoubtedly due to the fact that men are more frequently afflicted with coronary thrombosis and other types of heart disease which may be complicated by pulmonary embolism. Peripheral thromboses, on the other hand, occur more frequently in women because of the relatively higher incidence of peripheral thrombosis in obstetrical patients.

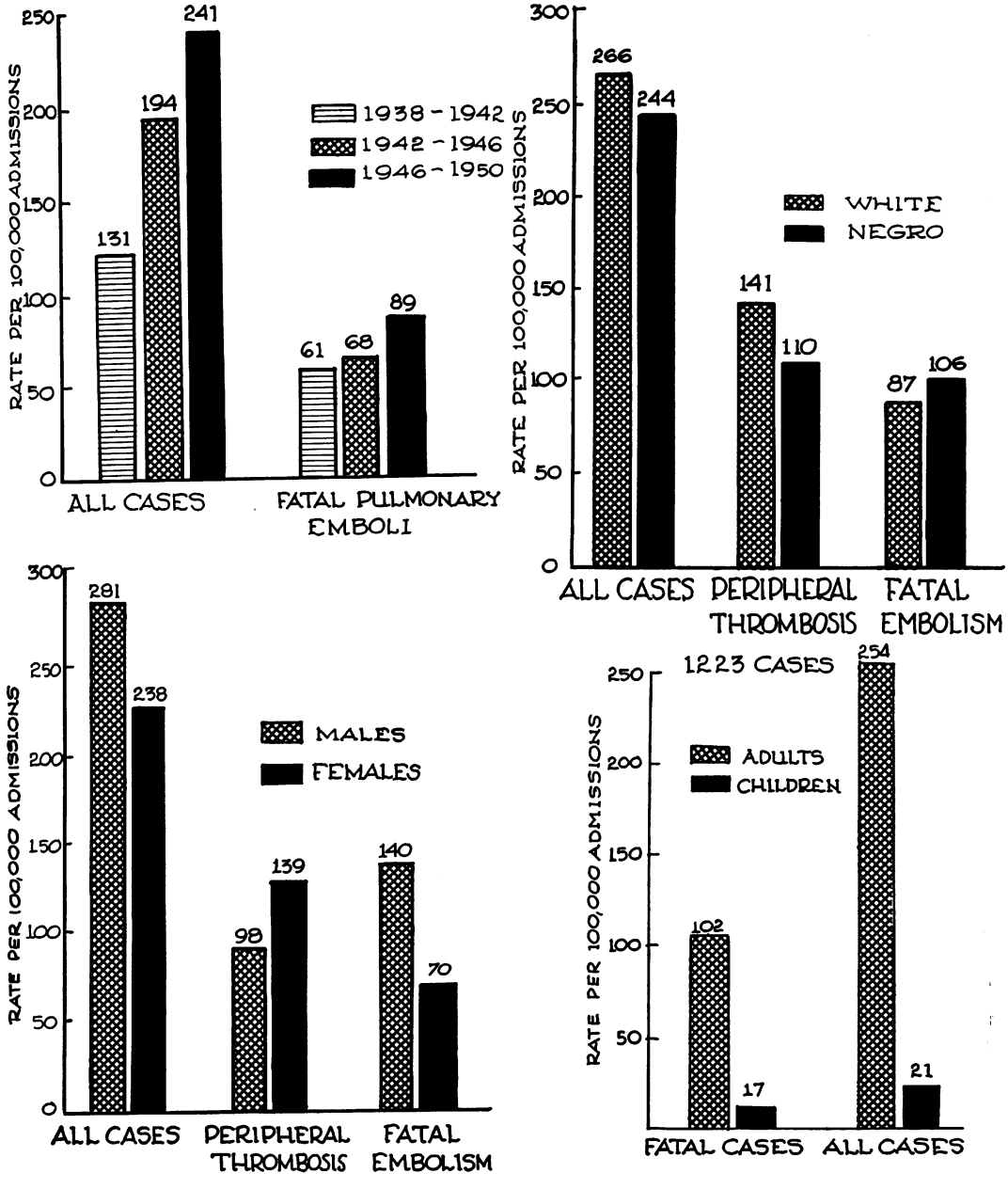


FIG. 2.—Incidence of thrombo-embolism by periods.
FIG. 3.—Adult race incidence of thrombo-embolism.
FIG. 4.—Adult sex incidence of thrombo-embolism.
FIG. 5.—Incidence of thrombo-embolism in adults and children.

Until relatively recently, thrombo-embolism was considered a relatively rare complication in children. Although thrombo-embolism occurs much less frequently in children than in adults, it must be considered. In the present study, 467,350 adults and 180,300 children were admitted to the Charity Hospital, of whom 1186 adults and 37 children developed thrombo-embolism. The respective rates per hundred thousand

admissions were 254 and 21. Four hundred and seventy-five (rate of 102) of the adults and 31 (rate of 17) of the children died (Fig. 5). Thus although the incidence of thrombo-embolism is higher in adults and even though the total number of fatal cases is higher in adults than in children, there is a relatively higher proportion of fatal cases in children. This is undoubtedly due to the fact that these children are so ill

It has been suggested that one of the factors responsible for the development of venous thrombosis is change which occurs in the vascular system as a result of seasonal variation. Although it must be admitted that in New Orleans the weather variations in the different seasons are not great, certainly in the present series there was no difference in the seasonal incidence (Fig. 7).

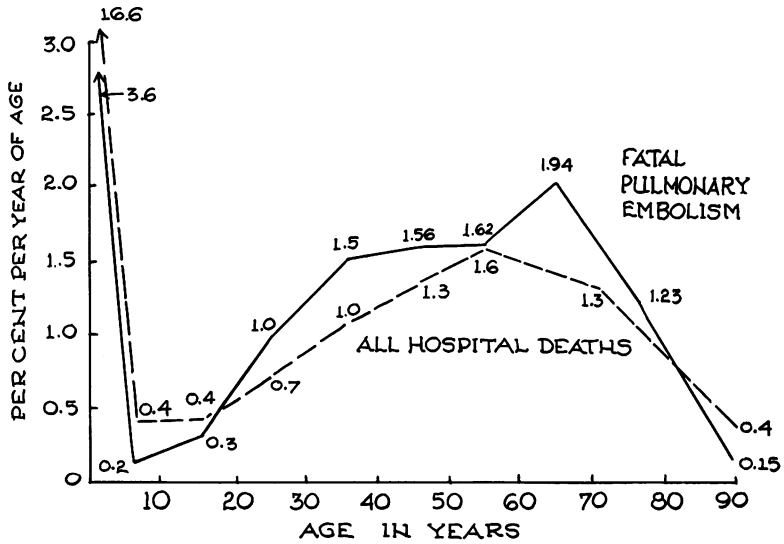


FIG. 6.—Age incidence of thrombo-embolism.

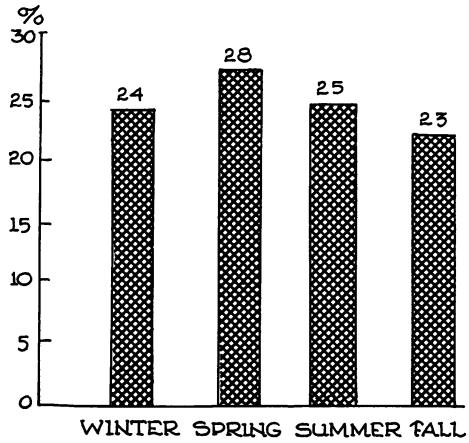
from other conditions and more frequently die from peripheral suppurative phlebitis of the cavernous sinus, lateral sinus, etc. The mortality rate in the first year of life is high, 3.6 per cent of all the cases of fatal thrombo-embolism. This, however, is not remarkable, because 16.6 per cent of all the hospital deaths occurred in the first year of life. In fact, there is a definite parallelism in the incidences of the fatal pulmonary embolism and all hospital deaths (Fig. 6). Up to 15 years of age the incidence of all hospital deaths is higher than the incidence of fatal pulmonary embolism but after 15 the incidence of the former is lower than that of the latter. The greatest incidence of fatal pulmonary embolism in adults occurred at the age of 65.

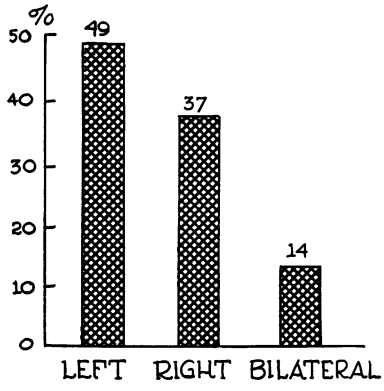
Venous thrombosis occurs much more frequently in the veins of the lower part of the body than elsewhere. Eighty-one per cent of cases of peripheral venous thrombosis involved the veins of the lower extremity; an additional 10 per cent involved the pelvis. Undoubtedly in many of the former there was a concomitant involvement of the pelvic veins. Of 871 cases of peripheral vein thrombosis, 789 involved the veins of the lower extremity and the pelvis (90 per cent); in 5 per cent the intracranial veins were involved; in 2 per cent the upper extremity veins were involved, and in an additional 2 per cent other miscellaneous veins were involved (Fig. 8). In the cases in which the veins of the lower extremity were involved, the left (49 per

cent) was involved more frequently than the right (37 per cent) and in 14 per cent the lesion was bilateral (Fig. 9).

The higher incidence of involvement of the veins of the left lower extremity is probably due to the greater amount of stasis in the veins of that extremity, which favors venous thrombosis. In many cases, thrombophlebitis of the pelvic veins is of the suppurative type, particularly in patients with puerperal sepsis following criminal abortion. In the present study the incidence of suppurative pelvic thrombophlebitis increased up to 1946 and has remained stationary since that time. On the other hand, suppurative thrombophlebitis in other sites has definitely decreased since 1946 (Fig. 10).

In the present study are included not only cases of thrombo-embolism developing on the surgical and surgical specialty services, but also on all other services. A relatively high incidence of thrombo-embolism occurs on the gynecologic and surgical services, the lowest incidence being on the obstetrical service. The number of cases per hundred thousand admissions for the various services were as follows: gynecology, 348; surgery, 269; medicine, 261; urology, 220; obstetrics, 106 (Fig. 11). Whereas an incidence rate of 261 cases of thrombo-embolism occurred on the medical service, only 75 of these were peripheral thromboses. The respective numbers of peripheral thromboses were as follows: gynecology, 195; surgery, 152; urology, 123; obstetrics, 87; and medicine, 75. On the other hand, the highest incidence of pulmonary emboli occurred on the medical service. Of pulmonary emboli per hundred





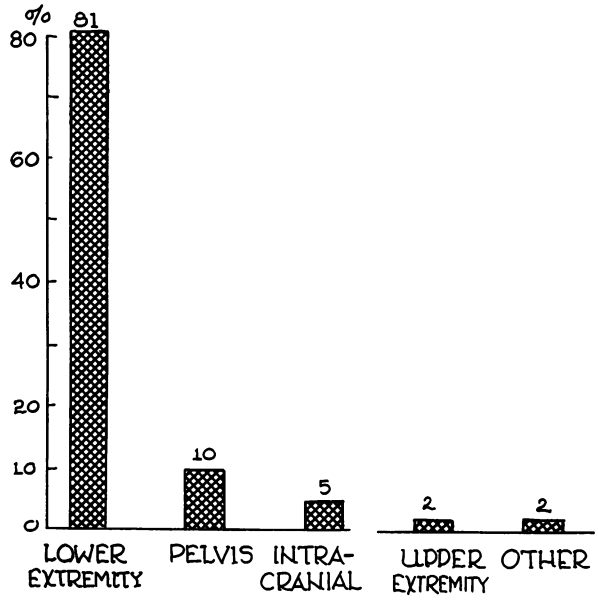


FIG. 7.—Seasonal incidence of thrombo-embolism.

FIG. 8.—This shows the division of 871 sites of peripheral venous thrombosis.

FIG. 9.—This shows the involvement of the lower extremities.

thousand admissions on the medical service, 174 were fatal and 34 non-fatal (Fig. 12). The highest incidence of fatal pulmonary emboli as compared with all the fatal emboli occurred on the pediatric and urologic services. Of 89 in children, 86 were fatal and of 96 pulmonary emboli occurring

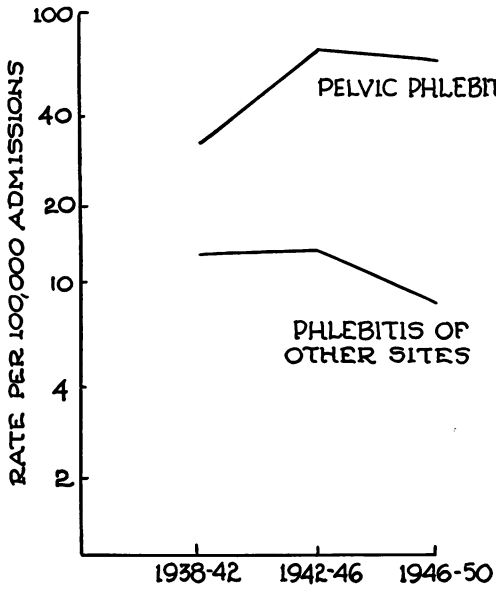


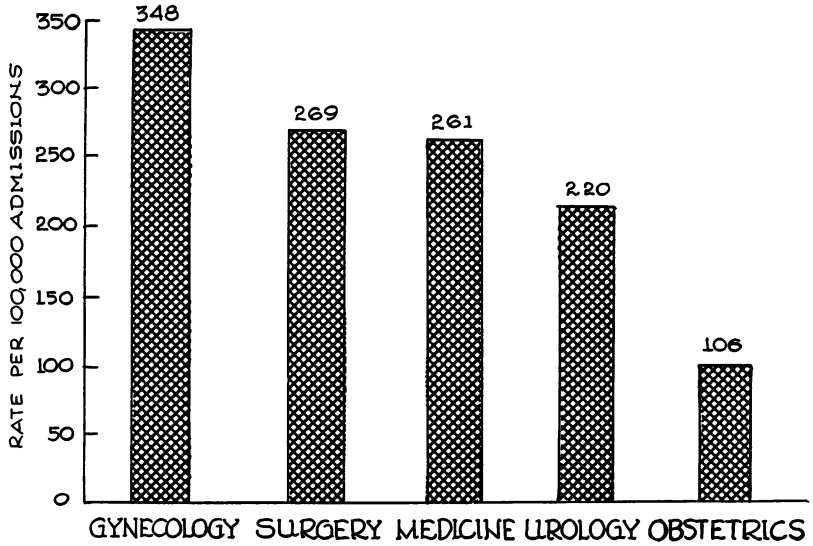
FIG. 10.—This shows the incidence of septic phlebitis by periods.

on the urologic service, 87 were fatal. The lowest incidence of pulmonary embolism occurred on the obstetrical service. Only 19 cases per hundred thousand admissions to the obstetrical service had pulmonary embolism, of which ten ended fatally. The relatively low incidence of pulmonary embolism on the obstetrical service is undoubtedly due to the fact that thromboembolism complicating obstetrics is almost invariably of the non-suppurative thrombophlebitic type in which the clot is firmly attached to the vein wall and does not become detached to give rise to pulmonary embolism.

A comparison of the ratio of the fatal pulmonary embolism to all hospital deaths according to the various services is of interest. There is, with few exceptions, a definite parallelism between the two, *i.e.*, 54 per cent of fatal pulmonary embolism and 52 per cent of all hospital deaths were on the medical service (Fig. 13). Two obvious discrepancies, however, exist. One is a high incidence of fatal embolism (11 per cent) on the gynecologic service as compared with a relatively low incidence of the hospital deaths (2.5 per cent). This is due to the fact that patients with puerperal sepsis following criminal abortion are admitted to the gynecologic service. They have a high incidence of suppurative pelvic thrombophlebitis and, until relatively recently, the mortality rate was extremely high. At the present time, however, as will be demonstrated later, there is a decrease in the mortality rate due to the prompt ligation of the vena cava and ovarian veins on the cardiac side of the thrombophlebitic involvement. Another discrepancy which is difficult to explain is the relative immunity of patients with tuberculosis to fatal pulmonary embolism. Whereas, 11 per cent of all the hospital deaths occurred on the tuberculosis service, only 1.3 per cent of the fatal pulmonary emboli occurred on this service. This phenomenon has been observed by others and has not been explained.

The relative proportion of the fatal pulmonary emboli to all the cases of thromboembolism according to the various services is of interest (Fig. 14). Thirty-four per cent of all the cases of thrombo-embolism occurred on the surgical service, but only 23 per cent of the fatal pulmonary emboli occurred on this service. This is probably due to the constant vigilance that is maintained on the surgical service and due to the institution of therapy to prevent the detachment of a clot in cases of phlebothrombosis. On the other hand, only 32 per cent of all cases of thrombo-embolism, and 55 per cent of the fatal pulmonary emboli, were on the medical service. This is undoubtedly due to the frequency with which pulmonary embolism complicates coronary thrombosis

and the severe types of heart disease. A relatively low incidence of fatal pulmonary embolism was observed on the obstetrical service, as has been mentioned previously. medical, surgical, and urologic services throughout the years, there has been a decrease in the incidence of total thrombo-embolism on the gynecologic service in the



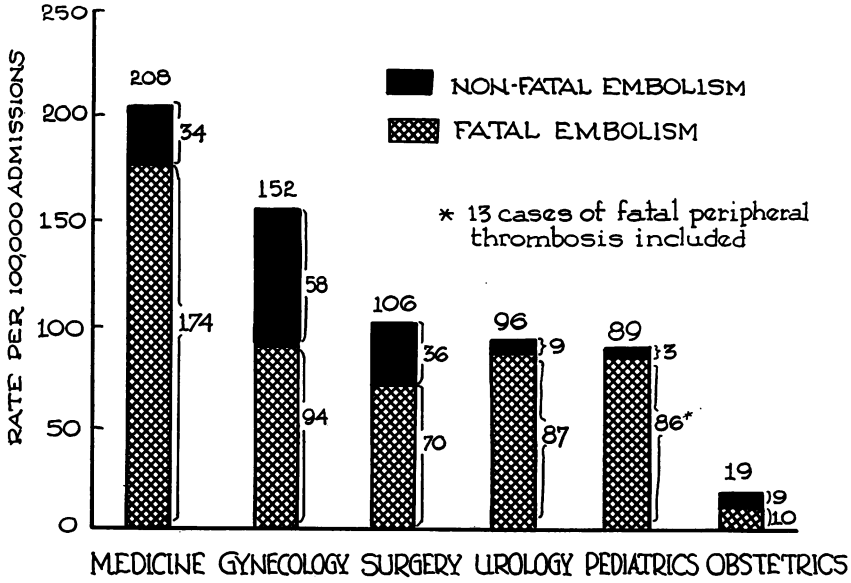


FIG. 11.—The incidence of cases according to hospital services.
FIG. 12.—Incidence of pulmonary embolism according to hospital services.

The incidence of thrombo-embolism, according to the various services, has varied from time to time throughout the years. Whereas there has been an increase in the incidence of total thrombo-embolism on the most recent period from 1946 to 1950. On the obstetrical service there was no increase in the incidence of thrombo-embolism; as a matter of fact, there has been some decrease (Fig. 15). The incidence of

FIG. 13

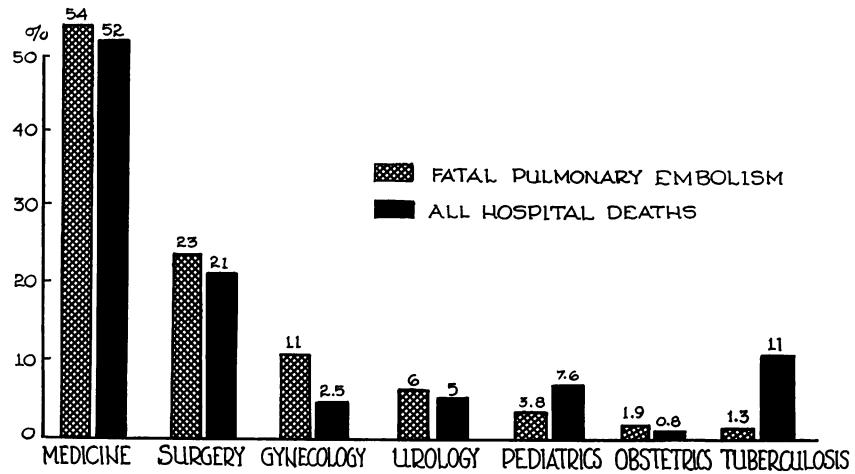
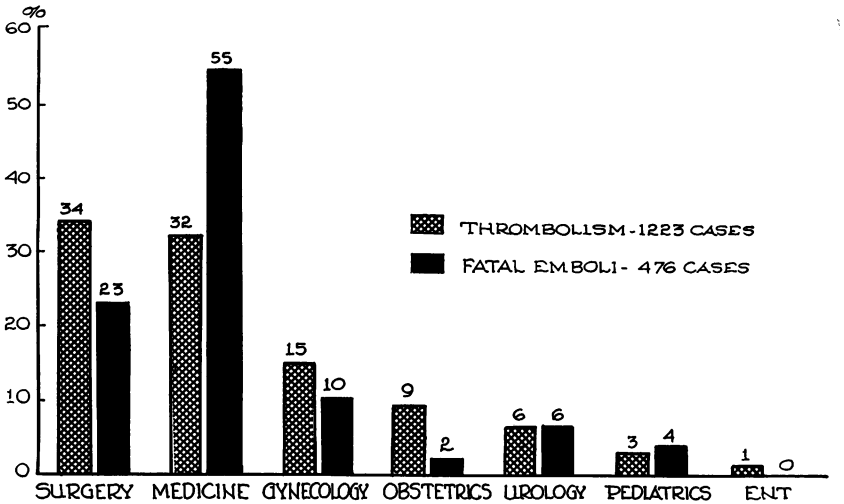


FIG. 14



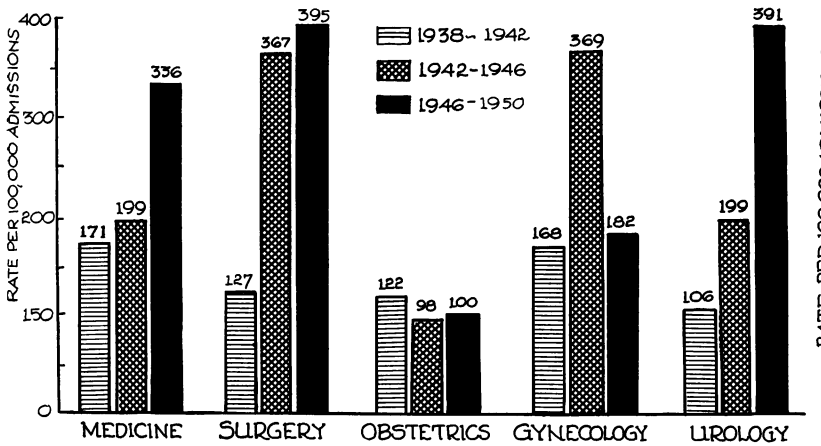


FIG. 15

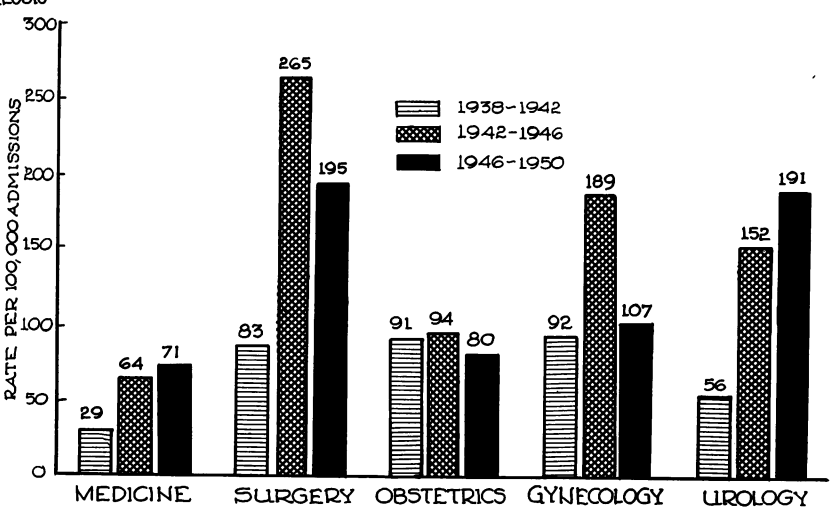


FIG. 16

(For legend see opposite page.)

peripheral thromboses, exclusive of pulmonary embolism, has increased on the medical service and on the gynecologic service. Whereas there was an increase on the surgical service in the period from 1938 to 1942 to the period 1942 to 1946, there has been a decrease in the period 1946 to 1950. Similar decreases have been observed on the gynecologic and obstetrical services (Fig. 16). The number of non-fatal pulmonary emboli has increased throughout the years on all services except the obstetrical service (Fig. 17), and the number of fatal pulmonary emboli have increased on all services except the gynecologic and the obstetrical (Fig. 18). The significant decrease in the number of fatal pulmonary emboli on the gynecologic service in the period from 1946 to 1950 as compared with the previous periods is undoubtedly due to the fact that patients with suppurative thrombophlebitis of the pelvic veins which previously were treated conservatively are now treated by ligation of the ovarian veins and vena cava on the cardiac side of the thrombophlebitic process, which prevents the detachment of the septic pulmonary emboli. Additional factors are the liberal use of antibiotics and blood transfusion.

Thrombo-embolism is a serious complication, and is associated with a high mortality rate. Of the 1223 cases at the Charity Hospital, 489 (40 per cent) ended fatally. The highest fatality incidence was on the pediatric service (84 per cent) (Fig. 19). The other fatality incidences were as follows: medical service, 67 per cent; urology, 40 per cent; gynecology, 27 per cent; surgery, 26 per cent; and obstetrics, 8 per cent. The relatively low mortality rate on the surgical service is, we believe, due to the fact that in many patients, fatality is prevented because of the recognition of the lesion and prompt ligation of the vessel.

Heart disease is associated with a higher incidence of fatal pulmonary embolism than any other disease (Fig. 20). Twenty-five per cent of all the cases of thrombo-embolism occurred in patients with heart disease, but 41 per cent of the pulmonary emboli occurred in these cases. There was a distinct parallelism between the number of cases of thrombo-embolism and pulmonary embolism in the non-operative and operative surgical cases.

As mentioned before, we previously believed that much could be accomplished prophylactically by overcoming the factors which are responsible for the development of venous thrombosis and thus prevent clot formation. Although thrombophlebitis is undoubtedly due to an inflammatory process resulting from perivenous lymphangitis, with the secondary changes in the vascular endothelium causing thrombosis, phlebothrombosis is the result of alterations in the blood constituents which favor clotting, combined with circulatory stasis, which is responsible for the localization of most phlebothromboses in the veins of the lower extremity. The changes in the blood coagulation favoring thrombosis, which are protective to prevent death from hemorrhage, are unquestionably the result of tissue injury, and apparently occur regardless of the type of injury. It apparently makes little difference whether the trauma is accidental, the result of an operation, or whether there is destruction of tissue as a result of invasion by neoplastic disease or infection. The changes are apparently proportionate to the degree of trauma, and it is for this reason that infection and invasion by neoplastic disease are particularly likely to be associated with an increased clotting tendency. Although there are many changes which have been thought to be responsible for the increased clotting tendency, we

FIG. 13.—Distribution of fatal cases according to hospital services.
FIG. 14.—Distribution of cases according to hospital services.
FIG. 15.—Incidence by periods according to hospital services.
FIG. 16.—Incidence of peripheral thrombosis by periods according to hospital services.

have an increasing belief that a prominent factor is a decrease in the antithrombin content of the plasma.

In the past, we have believed that relatively little could be done to prevent the increased clotting tendency as a result of tissue injury. However, except for the prevention of excessive trauma and infection, most of our efforts have been directed toward overcoming the precipitating factor, circulatory stasis. We hoped to accomplish this by facilitating the venous return blood from the lower extremities in the following way: Application of compression bandages to obliterate the superficial veins and thus speed the blood flow through the deep veins; having the patient take deep breaths to increase the negative pressure within the thorax, which favors venous return; having the patient contract the leg and thigh muscles actively against a resistance in order to pump the blood out of the veins; and early ambulation. In addition to these measures which have been instituted in an attempt to prevent the precipitation of a venous clot, we have examined carefully all patients who are likely candidates for venous thrombosis in order to detect any clinical evidence of thrombosis. The extremities of the patients have been examined carefully twice daily for vein tenderness and for the presence of a positive Homans' sign. An elevation of pulse rate has been considered significant, and whenever a patient has complained of an impending disaster, renewed and additional efforts to determine the presence or absence of a venous clot have been made.

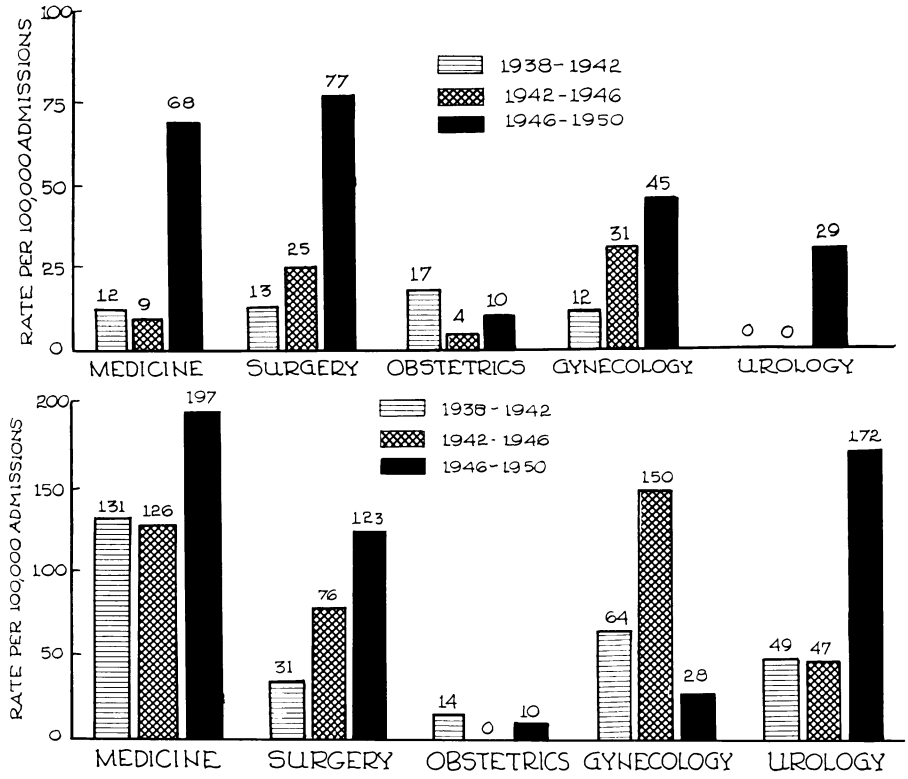


FIG. 17.—Incidence of non-fatal pulmonary embolism by periods according to hospital services.

FIG. 18.—Incidence of fatal pulmonary embolism by periods according to hospital services.

Because of the constant vigilance which has been maintained in the Charity Hospital to prevent venous thrombosis and to detect it once it occurs, it is of significance that in a large number of cases of fatal pulmonary emboli, there was no clinical evidence of a venous thrombosis before the fatality occurred (Fig. 21). We divided the cases into septic and non-septic groups. An analysis of the records of the patients with fatal pulmonary emboli showed that only 26 per cent of the non-septic cases had an elevation of pulse rate which might be suggestive of venous thrombosis. In only 24 per cent of the septic cases and 17 per cent of the non-septic cases was there any clinical evidence of involvement of the veins of the leg as determined by examination of the legs. In 54 per cent of the septic cases and 38 per cent of the non-septic cases was

FIG. 19

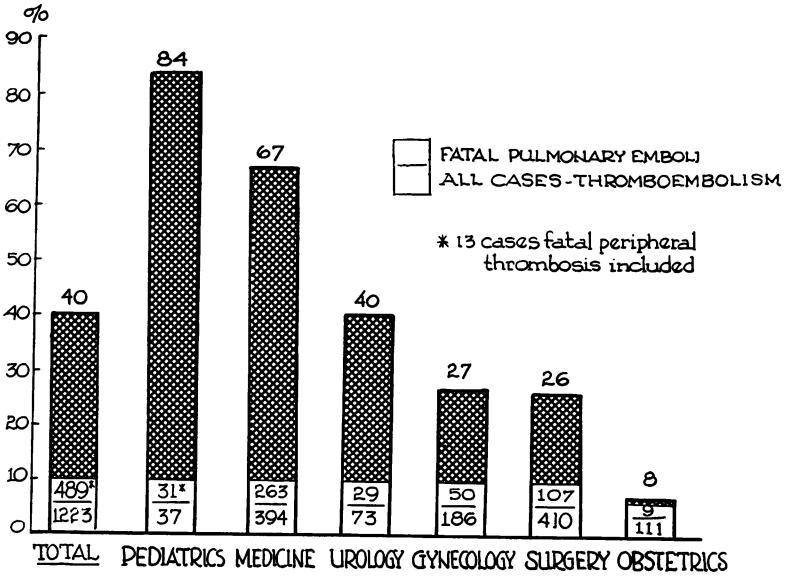


FIG. 20

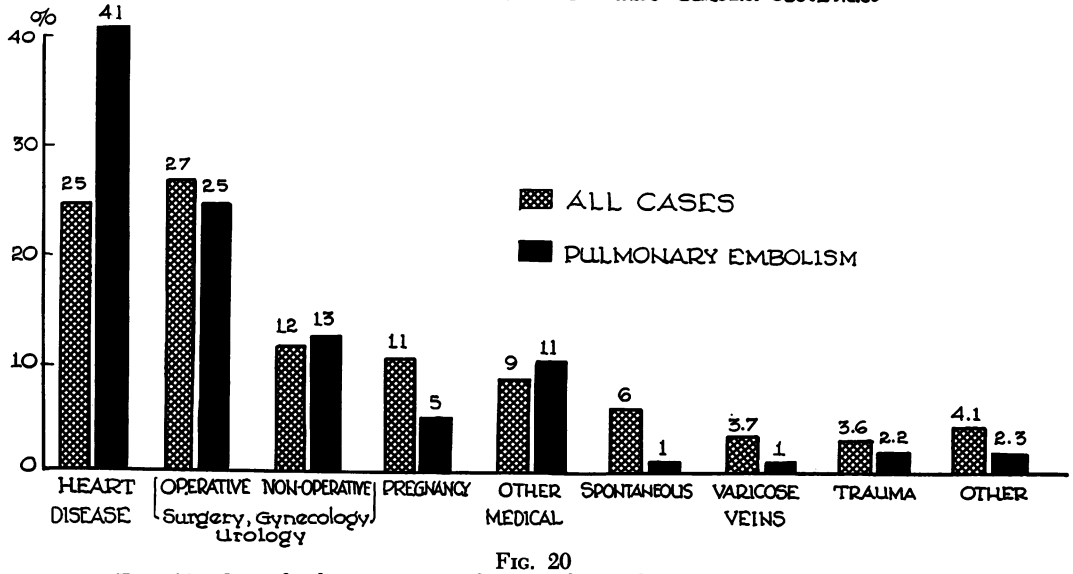


FIG. 19.—Case fatality rate according to hospital services.
FIG. 20.—Distribution of cases according to associated conditions.

there clinical evidence of a preceding pulmonary infarction, which suggested the existence of a clot somewhere from which emboli could originate. Combining all of these, in only 62 per cent of the septic cases and 56 per cent of the non-septic cases was there any previous clinical evidence of venous thrombosis which would suggest the presence of clot in the cases of fatal pulmonary embolism. This is extremely significant, because these statistics have been obtained in an institution in which considerable emphasis has been placed upon thrombo-embolism and its sequelae for a number of years. In spite of this attempt to prevent not only the development of the thrombus but also the disabling or fatal sequelae, we were unable to find any clinical evidence of an antecedent thrombus in approximately 40 per cent of the fatal cases.

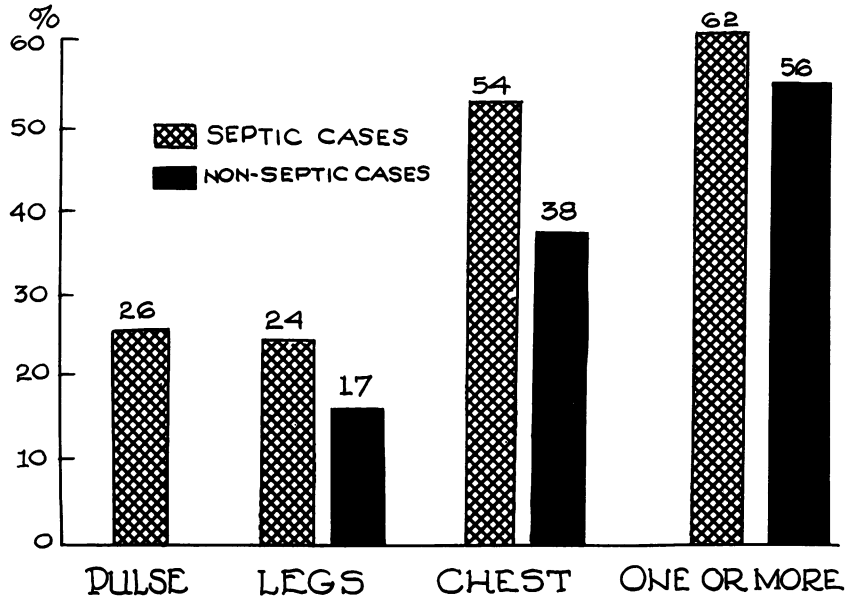


FIG. 21.—Fatal pulmonary embolism; incidence of clinical evidence of infarction or thrombosis.

Since the cases included in this series were treated by a large number of individuals on several teaching services, many types of therapy were employed. The largest group, of 871 patients, received no specific therapy to prevent the extension of thrombosis. Of this number, 18 had phlebothrombosis and 347 non-suppurative thrombophlebitis without evidence of pulmonary embolism. There were 28 cases of suppurative thrombophlebitis with 17 (61 per cent) fatalities. In 478 patients pulmonary embolism occurred, with a fatal outcome in 422, or 88 per cent. In a minority of these cases the pulmonary emboli were of secondary importance.

Interruption of veins proximal to venous thrombosis was employed in 201 individuals. No emboli developed in 71 individuals with phlebothrombosis or in 33 patients with non-suppurative thrombophlebitis, following appropriate vein ligation. In 27 individuals with septic thrombophlebitis, emboli failed to develop following vein ligation. However the disease progressed to fatal termination in two individuals with cavernous sinus thrombosis and one patient with lateral sinus thrombosis in spite of jugular vein interruption. This procedure did arrest the disease in six instances of lateral sinus thrombosis. Of 70 individuals with venous thrombosis associated with

pulmonary embolism, vein ligation was applied too late in three, and an ovarian vein was missed at operation in a fourth, resulting in a fatal outcome. In eight instances, vein ligation applied as conceived failed to prevent emboli which led to a fatal outcome. In two cases femoral ligations were performed in individuals in whom the emboli arose in the heart. In two instances bilateral superficial femoral ligations were performed and subsequently emboli arose from the pelvic veins. In three cases, inadequate surgery was performed. In one instance a unilateral femoral vein ligation, and in two instances of suppurative pelvic thrombophlebitis, emboli occurred in one subsequent to bilateral ovarian vein ligation, and in the other, following ligation of the common iliacs. In one additional case, thrombosis and emboli developed proximal to the point of superficial femoral vein ligation. The incidence of failure of vein ligation is 11.4 per cent in those cases in whom embolus had already occurred. The incidence in all potentially dangerous cases of phlebothrombosis, suppurative thrombophlebitis and pulmonary embolism is 4.8 per cent.

Anticoagulant therapy, consisting usually of heparin and Dicumarol, was admnistered to 109 patients: five peripheral phlebothrombosis, 43 non-suppurative thrombophlebitis, one suppurative thrombophlebitis and 60 with pulmonary embolism. Moderately severe hemorrhage resulted in four instances (3.7 per cent) and in seven individuals who had been adequately treated, fatal embolism subsequently developed. In some additional instances the therapy was begun too late to be effective, or inadequate therapy was given. Six of the seven individuals had been treated for pulmonary embolism associated with severe heart disease, and one developed a fatal embolus following a minor gynecologic procedure. That anticoagulant therapy may well be useful in advanced heart disease associated with severe congestive failure is evidenced by the fact that only 12 of 233 such patients survived without treatment, whereas 18 of 31 cardiacs survived following anticoagulant treatment. Anticoagulant

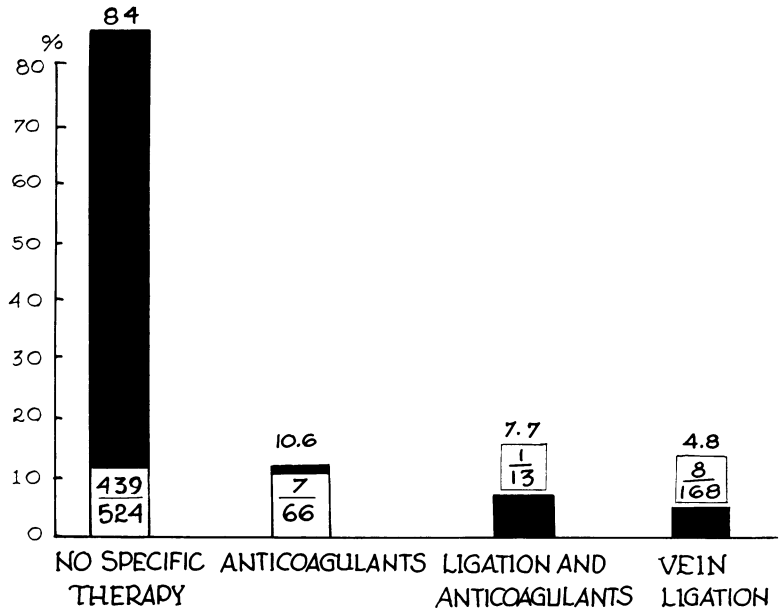


FIG. 22.—Treatment of dangerous venous thrombosis (phlebothrombosis, suppurative phlebitis, and embolism).

therapy failed in 11.7 per cent of 60 cases associated with pulmonary embolism. It failed in 10.6 per cent of the entire "dangerous" group of phlebothrombosis, suppurative thrombophlebitis and pulmonary embolism.

Venous ligation and anticoagulant therapy were both employed in 13 patients. In one case of lateral sinus thrombosis, anticoagulant and antibiotic therapy was ineffective. Following internal jugular vein ligation and the discontinuance of anticoagulants the condition rapidly resolved. In one individual with carcinomatosis arising from the pancreas, phlebothrombosis developed in one leg. Bilateral superficial femoral vein ligation was performed and a clot sucked out. He was placed on adequate doses of heparin and Dicumarol. In spite of this thrombosis recurred and extended up the inferior vena cava. Multiple emboli occurred and caused the patient's death.

Figure 22 summarizes the effectiveness of the various forms of management in reducing the high mortality of the untreated cases. Inaccuracy in locating the site of primary thrombosis caused four of the failures of vein ligation. Because the emboli in six of the eight fatalities following vein ligation originated in veins proximal to the site of ligation or from the pelvic veins, inferior vena caval ligation might have prevented the fatality in these instances. This suggests the advisability of inferior vena caval rather than superficial femoral vein ligation in extensive phlebothrombosis of the veins of the lower extremity, particularly when the possibility of pelvic involvement exists. Whereas we have previously not subscribed to this, we now believe that this is something that should be seriously considered. We are convinced that the sequelae following inferior caval ligation are not undesirable, in fact they are usually less than those following superficial femoral vein ligation, probably because of the rich collaterals in the pelvis.

In addition to the cases in which vein ligations were done as previously shown, over 40 per cent of the fatal cases of pulmonary embolism occurred in patients in whom there was no antecedent clinical evidence of venous thrombosis permitting even a presumptive diagnosis in order that a ligation might be done. It thus becomes obvious that if much is to be accomplished in the prevention and control of thrombo-embolism, a different attack must be used. Although undoubtedly we have prevented venous thrombosis many times as a result of prophylactic therapy employed and have prevented the detachment of thrombi in many instances which would have resulted fatally, the increasing incidence of thrombo-embolism makes it mandatory that additional therapeutic measures be used. Somewhat more than two years ago, we began attempting to decrease the incidence of thrombo-embolism by prevention of the decrease in the antithrombic content of the plasma in individuals subjected to trauma. Dr. John Kay, working in the experimental laboratory at Tulane, showed that patients subjected to major operative trauma in many instances develop a progressive fall in the antithrombic content of their plasma in the immediate postoperative period. Although a temporary decrease in the antithrombic content of plasma frequently is observed and is probably of little significance, a progressive fall in the antithrombic content of the plasma, which is less common, is a potential hazard in that probably when a sufficient disproportion between the prothrombin and antithrombin of the plasma exists, venous thrombosis can occur. Dr. Kay showed that alpha tocopherol, when combined with calcium, acted as an efficient antithrombin and for the past year and a half we have used alpha tocopherol and calcium prophylactically in a large number of patients who have been subjected to major surgical trauma. Only cases subjected to severe operative trauma are

included in the group, because it is this group of cases in which venous thrombosis is much more likely to occur.

Of 246 cases in the control group, 150 had antithrombin levels of 1:16 or greater. It is our belief that an antithrombin level of 1:16 or greater is sufficient to protect against a venous thrombosis. In this group of 150 there was one non-fatal pulmonary embolism five days postoperatively with an antithrombin level of 1:16 and a prothrombin time of 15 seconds. Ninety-six patients had antithrombin levels of less than 1:16, of whom 23 developed intravascular clotting, five had fatal pulmonary emboli, one other patient died of cerebral thrombosis with an antithrombin level of 1:4 and a prothrombin time of 39 seconds. None of these were treated with alpha tocopherol. There were 457 patients to whom alpha tocopherol and calcium were administered postoperatively, 442 of whom had antithrombin levels of 1:16 or above. Six had levels below 1:16 before treatment and nine had levels below 1:16 after treatment. In this group there were two cases with pulmonary embolism. In one the pulmonary embolism was the cause of death but it is likely that phlebothrombosis was present before operation and before therapy. The patient who had a pneumonectomy for bronchogenic carcinoma, on the third postoperative day coincident with discontinuance of oxygen therapy, developed dyspnea which was erroneously then considered to be due to the withdrawal of the oxygen. On the tenth postoperative day, she had a sudden massive pulmonary embolus and expired. Because the plasma and thrombic content was normal on the third postoperative day, phlebothrombosis and pulmonary infarction were not suspected. Had a venous ligation been performed at that time, the fatality probably could have been prevented.

In the other fatality, which occurred on the fifth day following repair of a gunshot wound of the abdomen with suture of the liver and stomach and ligation of the superior mesenteric vein, at autopsy a pulmonary embolism was found in the artery to right lower lobe but the cause of death was apparently peritonitis, small bowel obstruction and pulmonary congestion. There were five additional cases in which a presumptive diagnosis of phlebothrombosis was made, but in which no clots were found.

It is still too early to state just what will be accomplished ultimately by the administration of antithrombin and whether alpha tocopherol and calcium are the best substances or not. There is one objection to the use of alpha tocopherol and that is, it must be combined with calcium given intravenously. There are a number of patients who object to the unpleasant effects of the intravenous administration of calcium, and because of this, occasionally calcium administration is omitted in the therapy with the almost invariable result that there is a decrease in the antithrombin content of the plasma. At the present time we are investigating other antithrombic substances which might be used without the administration of an additional substance as calcium, and it is hoped that an efficient and yet safe antithrombin will be obtained which can be used routinely in all patients subject to operation and so prevent the high incidence of venous thrombosis.