Special Problems in Venous Thromboembolism *

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IN THIS antibiotic age venous thromboembolism remains one of the outstanding complications of major surgical procedures. Seven years ago it was decided that one of us (W. G. A.) should head a team that would attempt to see all patients with venous thromboembolism on the surgical and obstetrical services at Duke University Hospital. It was felt that up to that time the literature on venous thromboembolism was dominated by opinions derived from record library reviews rather than from personal experience. During this period approximately 453 patients with venous thromboembolism have been seen.

In this paper a routine review of this experience is not intended. It is hoped to focus attention on three special problems described in the literature either by isolated case reports or small series with conflicting opinions regarding etiology and management. These special problems are 1) severe arterial and arteriolar spasm accompanying deep venous thrombosis, 2) pulmonary embolism, and 3) the relationship between idiopathic venous thrombosis and hidden cancer.

SEVERE ARTERIAL AND ARTERIOLAR SPASM ACCOMPANYING DEEP VENOUS THROMBOSIS

The problem of the pathodynamics, recognition, and management of severe arterial spasm complicating venous thrombosis is one of the most confusing chapters in the field of peripheral vascular surgery. The historical account of the recognition of this clinical condition has been adequately recounted by many authors to supplement case reports or small series of cases. Suffice it to reiterate that according to Haimovici [9] the earliest reports were in the French and European literature. Tremolières and Veran [14] in 1929 are credited with the first clearcut description of this syndrome. The first report in the United States of two cases was by DeBakey and Ochsner [4] in 1949, and the largest single series reported was by Veal and his associates.[16] However, of the 11 cases reported by Veal, only five were spontaneous in origin; one case followed after the injection of sclerosing solution into a varicose vein, and the other five developed following vein ligations for deep venous thrombosis. Detailed historical reviews are available in the excellent articles by DeBakey and Ochsner [4] and Haimovici.[9]

The etiologic factors subscribed to have varied from author to author; no logical theory has been advanced in our opinion. Treatment has included conservative management with elevation and compresses, vena caval or femoral vein ligations, intra-arterial vasodilators, sympathetic blocks, anticoagulant therapy, and occasionally amputation.

CLINICAL MATERIAL

During the past seven years we have seen 19 cases of severe arterial and arteriolar spasm complicating deep venous thrombosis. These cases are summarized in Table I.

It is noted that there were eight males and 11 females in the group with ages ranging between 11 and 66 years. The arterial spasm involved more than one limb in three of the patients. In Case 18 there was involvement of the left hand and the lower

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TABLE I. *History of Cases*

No.	Patient	Date	Age	Race	Sex	Area of Thromboembolism	Accompanying Disease	Treatment	Result
1	M. S.	2/25/51	22	W	F	Left femoral	2 days antepartum—acquired hemolytic anemia—Hgb. 4 Gms.	Continuous caudal Heparin and Papaverine	Below knee amputation
2	E. H.	12/24/51	46	W	F	Rt. iliofemoral	Postop. cordotomy for intractable pain—Ca. of cervix	Continuous caudal Heparin and Dicumarol	Good immediate result. Has since expired
3	O. M.	3/4/52	28	W	M	Left iliofemoral	Postop. T. U. R. and partial cystectomy	Continuous caudal Heparia and Dicumarol	Good
4	A. B.	5/1/52	52	W	F	Left iliofemoral	Postop. insertion of nail in fractured hip	Paravertebral block; Heparin and Dicumarol	Good
5	W. C.	2/2/53	32	W	M	Left popliteal Pulm. embolus	Postop. rt. upper lobectomy for Tbc. Referred as possible arterial occlusion	Paravertebral block; Heparin and Tromexan®	Good
6	S. B.	2/22/53	11	W	F	Left iliofemoral	Dermatomyositis—on Cortisone Rx.	Heparin and Elevation	Good
7	D. E.	3/8/53	29	W	F	Left iliofemoral	Postpartum	Heparin and Elevation	Good
8	H. R.	7/27/53	65	W	F	Left femoral	Postop. hip nailing ? arterial embolus on admission	Artery explored Heparin and Elevation	Good
9	J. S.	3/29/54	15	W	F	Left femoral	Postpartum	Heparin and Elevation	Good
10	M. E.	4/15/54	62	W		Left iliofemoral	Idiopathic—Referred as arterial embolus	Heparin and Elevation	Good

TABLE I—*Continued*

No.	Patient	Date	Age	Race	Sex	Area of Ven Thromboembolism	Accompanying Disease	Treatment	Result
11	E. B.	6/2/54	65	W	F	Rt. femoral	Arteriosclerotic heart disease—Referred as arterial embolus	Heparin and Elevation	2+ postphlebitic syndrome Good
12	M. L.	2/21/55	53	W	M	Left femoral	Postop. irresectable Ca. of stomach	Heparin and Elevation	Good
13	C. K.	10/7/55	39	C	M	Vena Cava both legs	Idiopathic—? acute aortic occlusion or rupt. aneurysm	Explored abdomen Heparin and Elevation	Good
14	J. D.	12/28/55	66	W	M	Left ileofemoral Pulm. embolus	Idiopathic	Heparin and Elevation	2+ postphlebitic syndrome Good
15	J. P.	8/6/56	20	W	F	Left ileofemoral	Postpartum—Patent Ductus with reverse flow—Referred as arterial embolus	Heparin and Elevation	Good
16	J. M.	1/25/57	32	W	M	Bilat. femoral	Idiopathic	Heparin and Elevation	Good
17	G. B.	2/22/57	62	W	M	Left ileofemoral Pulm. embolus	Recurrent idiopathic venous thrombosis pulmonary embolism	Heparin and Elevation	Good
18	J. H.	2/27/57	64	C	M	Left hand Left femoral	Hypertensive vascular disease and congestive failure	Heparin and Elevation	Good
19	L. A.	4/22/57	55	C	F	Rt. iliofemoral	Referred 6 days after onset as acute arterial embolus with gangrene of foot. Had received Tromexan® only	Amputated	Below knee amputation

extremity of the left leg. In Case 13 and 16 there was involvement of both lower extremities. Case 13 is of special interest since he was originally thought to have a retroperitoneal rupture of an aortic aneurysm with secondary compression of the vena cava or a saddle embolus. On exploration he was noted to have thrombosis of the vena cava up to the level of the renal veins with a normal aorta. In retrospect he was a typical case of arterial spasm complicating deep venous thrombosis by the criteria listed below. One other patient (Case 8) was operated upon with the mistaken impression of acute femoral arterial occlusion: on exploration a normal artery was found lying beside a vein that was occluded by a fresh thrombus.

DIFFERENTIAL DIAGNOSIS

The most common error in diagnosis has been in the differentiation between acute arterial occlusion and arterial spasm complicating deep venous thrombosis. Eight of our 19 cases were referred to us with an initial impression of acute arterial occlusion, and two were erroneously explored for arterial occlusive disease.

We have found the following signs and symptoms helpful in differentiating acute arterial spasm complicating venous thrombosis from acute arterial occlusion.

1. *The swollen limb:* this indicates that the arterial inflow exceeds the venous outflow. Swelling does not occur in acute arterial occlusion.

2. *Patchy-blue discoloration of the skin:* this is due to increased amounts of reduced hemoglobin in the extremity. In primary arterial occlusion the limb is generally white.

3. *Prominent and distended superficial veins:* with the massive venous thrombosis of the deep system, there is congestion of the venous circuit. In acute arterial occlusion the superficial veins are generally collapsed.

4. *No definte sensory loss:* there is no loss of sensation in the same segmental level as in primary arterial occlusion. Any sensory deficit is patchy and not of the "stocking-glove" type.

5. *Presence of weak arterial pulses:* the arteries in spasm may be faintly palpable all the way down to the pedal vessels whereas in primary acute arterial occlusion the pulses are generally absent.

6. *Dissociation between level of coolness and lowest palpable pulse.* Whereas in acute arterial occlusion there is a definite correlation between the lowest palpable pulse and the level of coolness, no such correlation is prevalent in arterial spasm complicating deep venous thrombosis. For example, the limb may be cool up to the groin (due to arteriolar spasm), and yet there may be a fairly good femoral pulsation.

7. *An accessory consideration* may be the absence of underlying heart disease as the etiologic factor in the source of a primary arterial embolus.

Mistakes in differentiating between primary arterial occlusion and arterial spasm complicating deep venous thrombosis may be avoided by adhering to these criteria.

We have committed three errors. In two patients (Cases 8 and 13) these signs and symptoms were not appreciated preoperatively, and explorations were carried out for primary arterial occlusive disease. In a third patient (not listed in Table I) these diagnostic criteria were not adhered to, and an acute arterial thrombosis was initially thought to be an arterial spasm secondary to deep venous thrombosis. This latter patient did not respond to the measures listed below; the mistake was recognized, and at subsequent amputation the arterial system was occluded by a fresh thrombotic process whereas the venous system was patent throughout.

TREATMENT

Early in our experience we tended to follow the suggestions available in the lit-

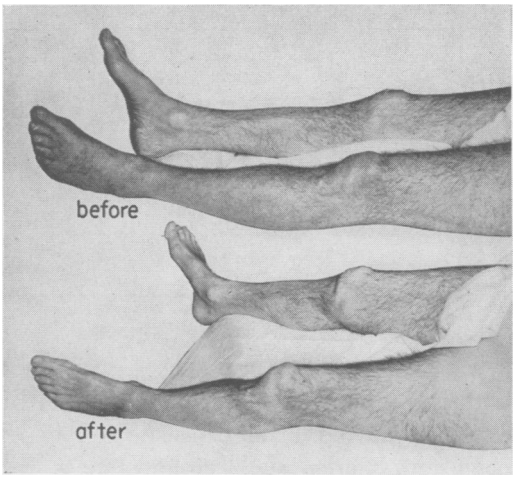

FIG. 1.

erature. An effort was made to establish adequate continuous spinal anesthesia; subsequently, the patients were started on anticoagulant drugs using heparin and dicumarol.

However, in Case 6 by mistake the intravenous heparin was administered prior to inserting a continuous spinal anesthesia catheter. Since the dangers of performing a spinal puncture on patients on heparin therapy were known, the sympathetic blockade was omitted. Much to our surprise within the hour the patient was relieved of his arterial spasm with heparin therapy only.

Subsequent patients were treated only with intravenous heparin, 50–75 mg. initially, followed by aqueous heparin, 50 mg. subcutaneously every four hours, with complete relief of the arterial spasm usually within a two-hour period. (See Figs. 1 to 4.) In addition to the heparin therapy the limbs were elevated in a modified Trendelenburg position. The hypothesis for the benefit from heparin therapy is discussed below.

There were only two limb losses. Case 1 was our first patient; she was in the seventh month of pregnancy with an acquired hemolytic anemia, and her hemoglobin was 4 Gm. per cent. The attending internist was evaluating the effect of steroid therapy on acquired hemolytic anemia and did not permit us to transfuse the patient; it was our feeling that the patient lost her limb due to the anemic anoxia superimposed on the arterial spasm. At below-knee amputation the major arteries were patent, whereas the venous system was filled with organizing thrombi. Our latest patient (Case 19) was referred to us as an aterial occlusion six days after the onset of her disease. She had been treated with Tromexan only. Her entire right lower extremity was markedly swollen, and her foot was gangrenous on arrival, presumably due to arterial compression by massive edema in tight fascial compartments.

DISCUSSION

The pathodynamics and etiology of the arterial spasm complicating deep venous thrombosis are not known. The numerous case reports are usually complemented by divers theories regarding etiology of the arterial spasm. Massive venous occlusion, venospasm, primary arterial spasm with secondary venous thrombosis, etc., have been mentioned in the literature.

Recently Smith and Smith [12] have reported that serotonin released from the breakdown of platelets may enhance the vasoconstriction of the pulmonary vascular bed over and above the mechanical occlusion of a pulmonary embolus to cause death. It is also interesting to note that heparin is a specific antagonist of serotonin. We are currently postulating that the cause of the arterial spasm may be serotonin released from the platelets in the thrombi in the venous system. The fact that the arterial spasm is rapidly counteracted by the administration of heparin supports this view.

The question may be raised as to why the serotonin which is available to the entire body would cause arterial constriction in one limb only. There is some evidence in our data to suggest that, whereas the arterial and arteriolar spasm may be most

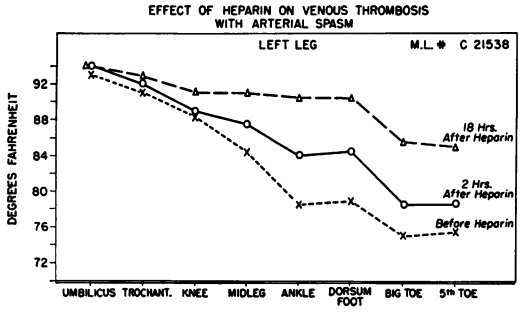

FIG. 2.

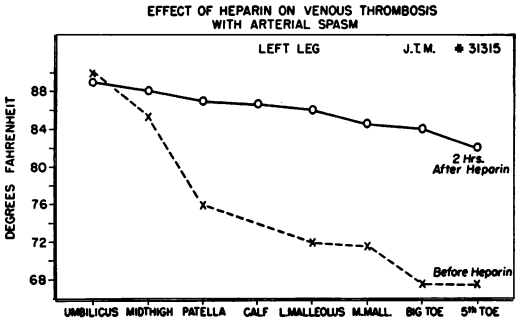

FIG. 4.

marked in the limb with deep venous thrombosis, there may be appreciable vasoconstriction in the other extremities (as in Cases 13, 16, and 18). These changes can be detected only if skin temperature and oscillometric studies are carried out routinely in all limbs. We are currently studying urinary levels of 5-hydroxy indol acetic acid (the breakdown product of serotonin) in patients with venous thrombosis.

In our experience paravertebral or spinal blocks have been found unnecessary. In fact, the possibility is raised as to whether they may be harmful by increasing the arterial inflow in a limb with a limited venous outflow.

There may be instances when a clearcut differentiation between arterial occlusive disease and arterial spasm secondary to deep venous thrombosis cannot be made. In such situations it may be desirable to insert a continuous spinal catheter first, followed by the administration of intravenous heparin. If there is no significant improvement within one hour, then the artery should be explored at the level of suspected acute occlusion. Under such circumstances the lesser mistake is to explore the artery rather than to delay until the onset of impending gangrene.

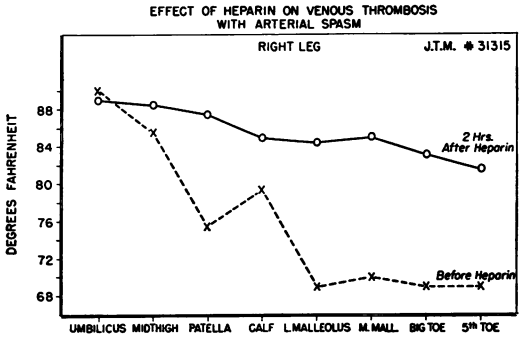

FIG. 3.

PULMONARY EMBOLISM

Pulmonary embolism occurring postoperatively or following delivery may manifest itself suddenly and unexpectedly: occasionally, it may cause immediate death in a patient who has otherwise had a smooth postoperative or postpartum course. It affects the young and the old; the age span in our 66 patients was between 19 and 77 years. A detailed analysis of our cases was published recently.[5] In this article we wish to emphasize some of the more obscure facets of this disease; in particular we should like to call attention to specific problems that we have learned to manage satisfactorily after many errors due either to the lack of information or to misconceptions in the literature.

Where do pulmonary emboli emanate from? Homans [10] had described pulmonary embolism as a complication of deep venous thrombosis which was a disease of the lower extremities, in particular, the veins in the calf of the leg.

More recently evidence has been presented to support the view that the majority of pulmonary emboli come from the pelvis and the iliac veins. McLachlin and Paterson [11] carried out detailed anatomic studies

on patients dying with pulmonary embolism: they concluded that 72 per cent of major emboli arose from the pelvis and the iliac veins. In our series of cases 50 per cent of the patients had no evidence whatsoever of peripheral deep venous thrombosis. Whereas they may have had so-called "bland" thromboses in the lower extremity, it is more likely that the emboli arose from the pelvis.

Etiology of Pulmonary Embolism. At the present time we accept the concept that following surgical procedures, trauma, or delivery there is a "hypercoagulant response" much like the "metabolic response." During this phase intimal damage or venous stasis may enhance the development of deep venous thromboses with subsequent pulmonary embolism. Whereas the nidus for the thrombus is formed at the height of the trauma, it takes two to 15 days for the formation of a thrombus large enough to manifest itself either as deep venous thrombosis or as a pulmonary embolus.

On the other hand, 13 or our 66 cases had no history of trauma, surgery, or delivery. These patients were all classified as having "idiopathic pulmonary embolism" and have been followed for periods of six months to two years with resolution of the pulmonary infarct and without evidence of any other underlying disease. It is of interest that on subsequent follow up it was noted that three of these patients who were all males between 68 and 72 years of age wore tight inguinal trusses for large herniae. Hence, the patient with idiopathic pulmonary embolism presents a problem in the differential diagnosis of the pulmonary lesion, especially when there is no evidence of peripheral venous thrombosis. When not treated adequately these patients may have repeated bouts of pulmonary embolism resulting in the gradual obliteration of the pulmonary vascular bed, pulmonary arterial hypertension, and terminally right-sided heart failure. There is some question in our minds as to whether some patients who have heretofore been thought to have "idiopathic pulmonary hypertension" have not in reality had repeated bouts of pulmonary embolism. Also, we have seen three patients with mitral stenosis who had experienced repeated episodes of pulmonary embolism with aggravation of the pulmonary arterial hypertension; in the absence of peripheral venous thrombosis, it was debated whether the emboli arose from the right heart or from the pelvis. Following vena caval ligation these patients ceased having pulmonary emboli and improved so markedly that mitral commissurotomy was carried out in the subsequent weeks without complication.

Inadequacy of Current Methods of Therapy. We have been disappointed with the use of coumarin drugs and vein ligations in the prevention of further embolism.

Erb and Schumann [6] pointed out that the incidence of venous thromboembolism was higher in femoral neck fractures after prophylactic superficial femoral vein ligations than in a control group of similar cases. In our series in this seven year period, six of eight patients who had femoral vein ligations had subsequent pulmonary emboli. Recently one patient underwent vena caval ligation because he had had repeated bouts of pulmonary embolism despite two courses of prolonged coumarin therapy. At operation his vena cava was soft and free of disease. Two days after vena caval ligation he had a definite but small pulmonary embolus. Heparin therapy was recommenced, and he recovered uneventfully. Hence, our last and heretofore dependable barrier to pulmonary embolism has proved to be fallible also.

Ten of our 66 patients with pulmonary embolism had subsequent emboli while on "therapeutic" doses of coumarin drugs with prothrombin levels ranging between 10 and 30 per cent. A more dismal picture of the efficacy of coumarins could be revealed if we had included our cases of peripheral venous thrombosis without embolism, who showed definite progression of their disease

while on the coumarin drugs. The empiric depression of blood levels of Factor VII and Prothrombin by coumarin drugs does not ensure the prevention of further embolism. Allen, Barker, and Hines [1] state that the untreated patient has a 30.5 per cent chance of having another pulmonary embolus and an 18.3 per cent chance of a fatal embolus. In our experience the patient treated with coumarins has a 15.2 per cent chance of having a second embolus; however, none of these second emboli has been fatal.

At the present time our patients with pulmonary emboli are treated as follows: as soon as the diagnosis is suspected, blood is drawn for a baseline Lee-White clotting time and a one-stage prothrombin level. With the same needle still in the vein, Aqueous Heparin 75 mg. is administered intravenously. After establishing the fact that the patient has a normal clotting time, he is given 50 mg. of aqueous heparin (usually within 20 minutes of the intravenous dose) subcutaneously every four hours. This heparin therapy is kept up for eight days. The clotting time is checked only once a day at a point three and one-half hours after a dose of heparin. If the clotting time in the third tube exceeds 25 minutes at this three and one-half-hour interval, then the dose of heparin is cut down to between 25–35 mg. every four hours. Our previous studies have shown that this regimen produces a peak clotting time between 30 and 60 minutes. There is a tendency in most patients for the clotting time peaks to become flattened out after the third day of heparin therapy and for the maintenance of a more even plateau. On the seventh day Dicumarol® is started; the initial dose (usually 300 mg.) is based on the control prothrombin level obtained before the administration of heparin, since well-heparinized blood is prone to give a falsely low prothrombin level by the one stage method. When the prothrombin level drops below 30 per cent of normal, the heparin is discontinued and the Dicumarol® therapy continued four to six weeks or longer until the patient returns to his normal activity.

Patients developing pulmonary embolism following prostatic resections have created a special problem. In our series there were fourteen patients with prostatic disease; Galleher [7] in our division of urology is currently reviewing the experience with venous thromboembolism in urologic patients. Anticoagulant drugs have been notorious in causing major hemorrhage in patients with venous thromboembolism following prostatic surgery. Presumably the clots on the prostatic bed are washed off by the urinary stream, and the anticoagulant drugs favor a state of prolonged bleeding.

Early in our experience we found out that the usual therapeutic doses of heparin and dicumarol resulted in a return of the patient to the operating room with a bladder full of blood clots and with the patient in shock. We were caught on a fine line between letting the patient die of pulmonary embolism secondary to a hypercoagulability state or from hemorrhage and shock from the anticoagulant drugs. We went through a phase of doing nothing to such patients except watchful waiting, accepting a 30.5 per cent chance of another embolus. More recently we have resorted to the following policy: 1) If the urethral catheter has been removed and the urine is free of blood at the time of onset of the pulmonary embolus, we advocate the administration of 20–25 mg. of aqueous heparin every four hours subcutaneously to prolong the clotting time just barely above control levels to around 20 minutes. All urines are saved and examined for blood. 2) If the patient still retains a urethral catheter with blood-tinged urine, vena caval ligation is recommended. Two patients are classified in this latter category and have both done well after vena caval ligation. It was necessary to perform a vena caval ligation on one other patient who did not have primary prostatic disease but in whom a urinary catheter had

been inserted on the medical service to keep the patient from straining to urinate; the heparin therapy produced uncontrollable bleeding from the prostatic bed which was ulcerated by the indwelling catheter.

Currently our indications for vena caval ligation in thromboembolic disease are as follows:

1) Recurrent pulmonary embolism despite two or more "adequate" courses of anticoagulant therapy

2) Presence of active bleeding contraindicating the use of heparin, e.g., following T. U. R.

3) Septic pelvic thrombophlebitis as advocated by Collins and his associates.[3]

In our experience 22 of 23 patients with vena caval ligation have not had any further pulmonary emboli. One patient described above had a small embolus after the vena caval ligation. It has been of interest that in two recent patients undergoing vena caval ligation, there was no rise in peripheral venous pressure in the legs, presumably due to previous adaptation to thrombotic occlusion of the iliac veins bilaterally; this has been proven by venography in one patient. We are in agreement with the impression in the literature that the early sequelae of vena caval ligation are proportional to the extent of thrombotic occlusion of the deep venous system. When the above indications for vena caval ligation exist, the operation should be carried out as a life-saving measure and any consideration of postphlebitic sequelae should be disregarded.

IDIOPATHIC VENOUS THROMBOSIS AND HIDDEN CANCER

Whereas Trousseau [15] in 1865 is credited with pointing out the possible relationship between venous thrombosis and intra-abdominal tumors, it was Sproul [13] in 1938 who set off the chain reaction of subsequent publications by many authors on the relationship between multiple venous thromboses and carcinoma of the pancreas. Her paper has been erroneously interpreted to justify and corroborate a small group of cases. A typical example is as follows: [8] "In 1938 Sproul analyzed 4,258 autopsies performed on patients with carcinoma, and found that multiple thromboses were present in 31.3 per cent of the cases of carcinoma of the body or tail of the pancreas. With lesions of the head of the pancreas, the incidence of multiple thrombophlebitis was 9.7 per cent."

Careful analysis of Sproul's paper reveals that these were 4,258 unselected consecutive autopsies at the Presbyterian Hospital in New York and not exclusively autopsies on cancer patients. The figures 31.3 per cent and 9.7 per cent are derived from five of sixteen autopsies of carcinoma of the body and tail and three of thirty-one autopsies of carcinoma of the head of the pancreas, respectively. Thus there was a net total of eight cases of multiple venous thrombosis found at autopsy at the end of a chronic debilitating disease. The average physician may, therefore, believe that in a large study group there is a high incidence of venous thrombosis. A corollary assumption has been that the incidence of hidden cancer is significant in patients with idiopathic thrombophlebitis.

We have previously reported a detailed analysis of our clinical cases of venous thromboembolism for possible relationship to underlying hidden cancer.[2] During the five year period, July, 1950, to June, 1955, there were 301 cases of acute or subacute venous thrombosis seen by our group. In the same five year period there were seen 792 patients in our tumor clinics with carcinoma of the pancreas, stomach, or bronchus.

Forty-four of the 301 patients with venous thromboembolism were in cancer patients, but all except five occurred in the postoperative period as in other unselected patients.

The five patients who had evidence of venous thromboembolism preoperatively

were as follows: one patient had a carcinoma of the stomach with dyspepsia for several months and a large palpable mass; two patients had obvious clinical evidence of inoperable bronchogenic carcinoma; the remaining two were problems in the differential diagnosis between pulmonary embolism and bronchogenic carcinoma; the diagnoses were established by bronchoscopic biopsy in one and a prescalene lymph-node biopsy in the other. The former proved to be irresectable at exploration, and the latter was clinically inoperable. None of our 179 patients with carcinoma of the pancreas during that five year period had venous thromboembolism preoperatively or as an isolated presenting symptom in a patient who is otherwise asymptomatic.

With regard to the corollary misconception in the literature that the patient with idiopathic venous thrombosis may have a hidden cancer, we have now had the opportunity of following twenty-six patients with idiopathic venous thrombosis for from six months to five years. These patients who were all asymptomatic except for the venous thromboembolism were submitted to a vigorous, detailed, and costly hospital examination with a battery of special studies. Early in our experience laparotomies were performed in three of these patients because of questionable signs of gastric or pancreatic tumors by gastro-intestinal x-ray survey. All three explorations were negative.

In the light of this experience we now feel that there is no need to fear a hidden cancer in a patient with idiopathic venous thromboembolism. We generally limit our diagnostic survey to a chest x-ray, three stool examinations for blood, and periodic follow ups unless they have symptoms specifically referable to certain organs.

It is our opinion also that venous thrombosis occurs in cancer patients preoperatively in moderate or far advanced cases of malignancy in which the tumor is readily demonstrable. The incidence of venous thrombosis in cancer patients is no higher than in individuals with other chronic debilitating diseases.

SUMMARY AND CONCLUSIONS

1. Over a seven year period 453 patients with venous thromboembolism have been seen by the authors at the Duke University Hospital. This experience tends to refute certain concepts and views currently entrenched in the literature. In particular, the three problems discussed are 1) severe arterial and arteriolar spasm accompanying deep venous thrombosis, 2) pulmonary embolism, 3) the relationship between idiopathic venous thrombosis and hidden cancer.

2. Nineteen cases of arterial spasm secondary to deep venous thrombosis (phlegmasia cerulea dolens) are presented. Signs and symptoms helpful in differentiating this syndrome from primary arterial occlusion are listed. Sympathetic blocks have been found unnecessary. Heparin and slight elevation of the legs have been found to relieve the syndrome markedly within two hours unless gangrene has developed prior to the initiation of treatment. Gangrene is usually due to massive edema in closed fascial compartments. The possibility that serotonin released from platelet breakdown in the massive venous thrombosis may be responsible for the arterial spasm is discussed.

3. Sixty-six cases of pulmonary embolism were seen. In 50 per cent of the patients there was no evidence of peripheral venous thrombosis. Rcurrent pulmonary embolism was noted in 15.2 per cent of patients on coumarin therapy, in six of eight patients after femoral vein ligations, and in one of 23 patients following vena caval ligation. Our current program of prolonged heparin therapy is outlined. Patients with thromboembolism following prostatic surgery constitute a special problem. Our indications for vena caval ligation are presented.

4. Contrary to the impression suggested in the literature, we have found no significant association between idiopathic venous thrombosis and hidden cancer.

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DR. HERRMANN: Our experience during the past 20 years has impressed upon us the importance of the mechanism of the clotting of blood in the process of peripheral venous thrombosis. We have found large quantities of a cold precipitable fibrinogen (Cryofibrinogen) in certain forms of acute or fulminating peripheral venous thrombosis, especially that type known as phlegmasia cerulea dolens.

We believe there is a defect in the mechanism of blood coagulation and this defect lies in the latter part of the coagulation cycle, rather than at the beginning of the cycle. This may partially explain the ineffectiveness of the antiprothrombic substances and the striking immediate effect from antithrombic substances, such as heparin. We also found, as Dr. Anlyan has just described to us, that not only was the arteriolar spasm of acute venous thrombosis eliminated but the progression of the thrombus was halted immediately. We recently have treated a young woman in whom intensive heparin therapy caused the process to subside promptly.

Our experience with a somewhat similar process of superficial venous thrombosis, which we believe is closely related to the Waterhouse-Frederichsen syndrome, also has convinced us that early heparinization of these patients will prevent serious or fatal complications. This study will be reported elsewhere.

I am happy that Dr. Anlyan has re-emphasized the early use of the antithrombins (heparin) rather than the antiprothrombins (Dicumarol®) in the management of acute or fulminating venous thrombosis.