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Etiology of phlebitis

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Introduction

Phlebitis according to definition is an inflamation of a vein. Due to the fact that phlebitis is so commonly found to be accompanied by the formation of thrombi it is necessary that thrombo-phlebitis be included in this discussion. Since phlebitis clinically is so very common either as the primary condition or as the accompanying complication, one would think that the etiology would be well know. Such, however, is decidedly not the case. In fact very little study of the authorities on the subject is necessary to show one that the theories of the etiology of phlebitis are almost as numerous as the authorities writing on the subject.

Running as almost a constant in all the writings are three principal factors. These are first, any condition wherein the rate of flow of the blood stream is diminished to any great extent, second, changes in the walls of the blood vessels especially of the endothelial layer, third, certain changes which are frequently found in certain constituents of the blood stream.

In order that we may have a basis upon which to evaluate any of the above factors I believe it is fitting to give a brief discussion here of the modern theories of

the mechanism of the blood clotting. It is agreed, I believe, in practically all theories that the end product of the clotting process is fibrin. The method by which this substance is formed is the point of difference among authorities. The theory of Morawitz (25) is one of those quite widely accepted. According to him fibrin is the product of a protein which he calls fibrinogen and which is always in the plasma in combination with a ferment which he calls thrombin. This thrombin is due to the combination of thrombokinase, which is derived from the formed elements of the blood or other tissues, plus prothrombin which occurs in the plasma. This union is not understood but occurs only in the presence of a soluble salt of calcium. After the formation of the thrombin, calcium acts only as an accelerator of the clotting. What small amounts of the thrombokinase as may ordinarily be set loose in the blood stream are neutralized by anti-thrombin which is also shown to be present in the blood stream. The reaction of fibrinogen to fibrin is reversible. The type of reaction is not definitely known however it is likely that one is a hydrosol, the other a hydrojel.

Howell (25) explains the process somewhat differently. His theory is based upon the balance between antithrombin and prothrombin which neutralize eachother.

Injured cells or tissues liberate into the blood stream a substance which he called thromboplastin or thromboplastic substance which is a lipoid identical with kephalin. This thromboplastin neutralizes the antithrombin which in turn frees prothrombin so forming thrombin. The thrombin with the aid of calcium coagulates the fibrinogen forming the clot. Blood platelets, according to this author have not been shown to be definitely concerned with the process of clotting, although many authors do not agree to this. The platelets seem to be concerned in the formation of thrombi in that their agglutination precede the thrombi. These laminae of platelets catch leukocytes and liberate thromboplastic material so that the filaments of fibrin spread out to the next laminae. This catches red blood cells and finally a solid clot is formed. These red blood cells die, lose hemoglobin and wash out so that the color changes from red to grey.

These clots appear usually in veins or the auricular appendages. If in veins, they are more likely to be near a valve. The thrombus is inelastic, friable, and granular.

In discussing the cause of thrombi Mac Callum (25) emphasizes the fact that the wall of the vein is always

injuried. However he brings up the question,"Has the injury occured before or after the thrombus formation"? Eberth, Schimmelbusch and Welch say that it occurs before. Aschoff thinks it is due to slowing of the blood stream. The Author(25) thinks the thrombi are due to an inflamation which is the result of bacteria lodging at a venous valve which area has either died or been seriously injuried. He emphasizes injury to the endothelium as being more important than the other two factors. To prove this he cites the fact that ligating in two places does not give a clot, but that crushing does. As one can see the opinions vary so greatly that one would hesitate to draw conclusions from these various authors. I simply propose to review furthur some of the many ideas that I have found and have briefly stated above with some additions.

-Changes in the Blood-

There are many followers for each theory but let us first consider the blood changes in the various conditions and see the relationship to phlebitis and to thrombophlebitis. Borchard(6) believes the condition of the blood to be the chief factor.of the three common causes so often given. In speaking of thrombosis of the saphenous veins, which is one of the commonest sites for phlebitis, he says that he feels that it is too frequently said to be the cause of pulmonary embolism. Picot(28) thinks

that the coagulation phenomenon of the blood plays a very important role in the postoperative phlebitis and thrombosis. For that reason the writer never operates on a patient who does not have a normal coagulation time. He also maintains a normal time throughout the postoperative period in the hospital. He institutes treatment if it is accelerated, that is less that 17 minutes, or if it is delayed, being over 18 minutes. It generally requires 4 or 5 days to reduce the time from 25 to 18 minutes. The results which he obtained with this routine are quite remarkable. Of 1,050 cases observed the author operated 770. 167 of these were for hysterectomy and of all the cases there was only one case of embolism and none of clinical phlebitis. In 295 cases of appendicitis there was but one case of embolism and that was an old lady who was very corpulent and whose coagulation time was upto 24 minutes before treatment. In all the other cases there was only one case of embolism and that was in a man with appendicitis who refused to be treated preoperatively. In this group of patients there were some also who had had phlebitis previously, and had shown hyper-coagulation before the treatment to reduce the coagulation time was instituted. According to his statistics there was no doubt that the cases of uterine fibroids had the highest percentage of abnormal coagulation times.

Wildegans(37) also feels that the constituents of the blood stream are of major importance. He thinks that attemtion should be directed more in that direction than to the factors involving disturbances in the circulation, infection, or changes in the vessel wall. In a study of 18 patients of which all but two were over 40 it was found that there was more water, residual nitrogen and lactic acid in the saphenous veins than in the cubital veins. This was especially true in the cases of varicosities being present. In this study it was found however that there was no significant difference in the calcium or the thrombin content of the blood from the various locations in the body. This fact would lead one to look to the platelets for the difference in the blood in such cases.

It has been found that after operation, childbirth, and especially after Cesarean section the number of platelets begin to rise. This rise starts on about the 4th day and increases to a maximum in about 10 days.(12) The count then falls slowly to a normal level. As we know it is the usual thing to consider that a lowering of the platelet count is associated with an increase in the clotting time, and that a high platelet count means a decreased clotting time. The time relations of clinical thrombosis and embolism are similar to those of the plate-

let reaction. That is they are most frequent on about the 10th day after operation or childbirth.

Platelets show no change after simple hemorrhage, anesthesia, or staying in bed. Neither is there any constant variation in conditions of sepsis. The platelet reaction is excited however by fractures and even merely during the convalescence from an acute lobar pneumonia. These facts would suggest that the products of tissue breakdown are the causative factors in the exciting of the platelet reaction.

A case reported by Davies(11) leads one to wonder at the above. This was a case of septic anemia in which the patient died. At autopsy a portal thrombosis was found. The pathologist said," The phlebitis and thrombosis have presumably spread from the splenic pedicle along the splenic vein but no proof of infectionwas obtained." Here evidently there was no thrombosis of other origin than the blood itself, since infection was not present and there was no injury. However there usually is a lack of platelets in this condition which should lead to lessening of the clotting possibilities. Of course there was a large spleen that could have caused enough trauma to the veins in that area to cause phlebitis.. Again since there is some argument that the platelets are re-

sponsible for the clotting or have a direct relation to the clotting, it is possible that some other changes in the blood took place which we do not yet understand. And finally it is very possible that the pathologist could have missed a low grade infection being present.

-Slowing of the Blood Stream-

The slowing of the blood stream is given very frequently as an important factor in the cause of phlebitis and thrombophlebitis. It is found in practically all of the pathology text-books and is given by many of the writers on the clinical aspects of the subject. Wilensky(38) says,"The inflamatory process associated with any infection has as one of its prominent characteristics the slowing of the blood stream and the formation of a venous thrombus!"

Experiments have been made to show that the rate of flow of the blood stream has nothing to do with the formation of thrombi however.(1) It was found that in a case where a thrombus practically occluded a vessel, if the thrombus was not progressive, and there was room for only one erythrocyte to get passed, the blood continued to flow without clotting or causing a phlebitis. The experimenters concluded that the effect of slowing the blood stream was not perceptible. This was true when the blood flowed only intermittently also. No perivascular reaction to vascular occlusion could be

observed in the pia. All of this is contrary to the usual teachings on the subject. This experiment was performed by Armentrout and will be referred to again in connection with injury to the endothelium.

-Infection-

Infection as an important factor in the causation of phlebitis can hardly be denied by anyone, and in fact will in the last analysis probably be considered the chief factor. Lenormant and Mondor (20) think that all phlebitis, even that called "effort thrombosis" which it seems could not be due to infection, is due to infection.

Of all the types and varieties of phlebitis probably the commonest is pelvic thrombophlebitis which very often follows childbirth. Although it does not deal strictly with the etiology of phlebitis I believe it would be interesting to review here the the typical course of such a case. In the suppurative type there is a slightly febrile puerperium in which subacute uterine infection has been recognized. A rigor occurs on the 10th to the 15th day, and ushers in an abrupt elevation in the temperature, which as a rule soon falls to the normal. At intervals of a few hours or days the rigor and the high pyrexia recur, and the patient's condition gradually becomes worse, local signs being absent or insignificant; blood cultures are also almost invariably negative. The diagnosis of suppurative pelvic thrombo-

phlebitis is clinched by the appearance of a thoracic syndrome of dyspnea, cough and pain in the chest, due to a septic embolus. Death of the patient follows from pulmonary abscess, or abscesses, or from purulent pleurisy, the result of the first or succeeding emboli. Simple thrombophlebitis is also characterized by pyrexia, rigors, and even pulmonary symptoms; but apyrexial intervals are absent, rigors are less intense and pulmonary emboli, being aseptic, are dangerous only in their mechanical consequences. Lequeux (21) states that of late years necropsies in puerperal sepsis have shown a 20 to 50 percent incidence of pelvic thrombophlebitis, intravenous suppuration however not always being present.

Brown (7) in writing on the cause of postoperative phlebitis said that the direct cause was not obtained. However resections of the superficial veins showed marked inflamatory reaction in all the coats and contiguous tissue. The vessels were infiltrated with polymorphs and the thrombus was composed of leukocytes, fibrin, and red blood cells. The reaction was very intense and suggested very strongly an inflamatory process on an infective basis. Evidence also pointed to the infection leading to thrombus formation. This same picture is found to be present in the cases of varicose veins although here it is not so acute, being more of a latent

infection.(17)

Barrett (3) performed the following experiment to show that in addition to infection either necrosis or toxin is necessary for the formation of thrombi. The experiment consisted of seven parts:

1. A vein was crushed and no thrombi formed. The endothelium became thickened but it remained smooth.

2. The vein was crushed and staphyloccoci were introduced. Again no thrombus formed.

3. A sterile thread was allowed to be oscillating in the blood stream, and still no thrombus formed.

4. A sterile thread was again allowed to oscillate in the blood stream and this time with the introduction of either Colon bacilli or staphyloccoci a thrombus formed.

5. A sterile thread was put into the blood stream and allowed to go free. In this case the experimental animal developed no thrombus by the end of seven weeks.

6. A thread contaminated with Colon bacilli was freed in the blood stream and the animal died at the end of 3½ days of pulmonary thrombus.

7. When this was repeated but the Tubercle bacilli was used instead of the Colon bacilli, no thrombus developed at the end of seven or twelve weeks.

These experiments led the experimenter to conclude

that infection plus necrosis or a toxin are necessary to cause thrombosis. This would apply to tissues cut off by ligatures at operation and carrying a low grade infection, and so would explain many of the postoperative thrombophlebitis cases.

An experiment very much the same as the above experiment was done by Sato (32). To get the varying degrees of wall changes aseptic autotransplantations, homoiotransplantations, and heterotransplantations of arterial segments from one to four centimeters were made into the femoral or the carotid arteries of dogs. To determine the effect of infection, the suture material was contaminated with staphyloccoci in a series of experiments with similar transplants. The aseptic transplantations and the homoiotransplantations did not lead to thrombosis unless the narrowing of the lumen was extreme. In the heterotransplantation experiments necrosis of the transplant was associated with thrombosis, and necrosis of the vessel was believed to be the chief factor in causing the thrombosis. Infection was an important accessory factor, but in the abscence of necrosis required other conditions, such as slowing of the blood stream through a narrowed vessel, to establish thrombosis.

Phlebitis due to Staphyloccocus aureus has not

been reported very frequently and up until 1918 there had been no cases reported. At that time a case was reported (10) in a man 58 years old. His left leg began to swell without any previous history of rheumatism, gout, typhoid fever, or any local septic condition. About two weeks later the right leg also began to swell and pain. The superficial veins were hard, swollen, and tender. Twelve days later he also had symptoms of mesenteric thrombosis but this cleared up in a few days. About a week later a blood culture was done and Staphyloccocus aureus was obtained. This was repeated to rule out contamination and the same results were obtained. When he was given an autogenous vaccine his temperature which had remained up all this time promptly came down. He had received Colon vaccines previously which had had no effect on the temperature. A further complication of interest is that a short time later a carbuncle developed on the sacrum from which a positive culture for Staphyloccocus aureus was obtained. This fact together with the results obtained with the vaccine make the etiological question pretty certain. The causative organism must have been the Staphyloccocus aureus. Another case of Staphyloccocus aureus phlebitis will be considered later.

A group of cases are reported by Chlumsky (9)

which do not have a clear cut etiology but probably are on an infectious basis. These are cases of Chronic Phlebitis Migrans. They are observed in the summer or autumn and the hands and feet were first attacked; small swellings like the stings of gnats appearing but causing no discomfort aside from itching. These became painful in the course of time and the veins in the affected region became hard. The deeper venous trunks were slowly affected and the whole extremity slowly became swollen and painful. Fever not exceeding 101 degrees and redness of the skin were then noted. In most of the cases reported the condition gradually progressed and finally resulted in the death of the patient. Gout, syphilis, cancer, tuberculosis, rheumatism, and bacterial infection have never been found to cause these symptoms. One fact stands out in bold relief. They usually begin in the season when the gnats are the most numerous. The cases of Herzberg, Burger and Hess were Russian or Polish Jews and the author's material included two Jews. A knowledge of the sanitary conditions among such people justifies the belief that the peculiar affection just described is due to the bite of some insects, whether gnats, bugs, lice, or fleas. The insects undoubtedly make wounds in the superficial veins, and innoculate the patient with some unknown bacteria or poison which causes inflamation of the venous wall

and the subsequent more serious symptoms.

-Injury to the Vessel Wall-

In considering injury to the endothelium one is always confronted with the question as to whether the injury occured before the phlebitis or thrombosis or whether the injury was a result of the inflamatory process. There does seem to be very good evidence to support the theory that simple injury to the vein can result in a thrombophlebitis. In practically all of the cases which seem to show injury to the endothelium as the etiological factor one can not be sure that the infective process was not set up there due to the lowered resistance. In such an event it would be impossible to tell just how much of the process was the result of injury and how much was due to infection.

A good expamle of how hard it would be to evaluate the above factors is shown by a case (26) of a man admitted to the hospital with severe abdominal pain, vomiting and so forth. The appendix was ruled out and he was relieved by the vomiting, and by an enema. He had had a similar attact about a month previously. Before entrance he had had an attact in a dentist's office which so closely resembled an attact of renal colic that he was thoroughly gone over by a Urologist. Nothing was found. On entrance to the hospital consultation was

held and the diagnosis of mesenteric thrombosis was made. Operation showed the ileum to be dark blue, the mesentery red and congested, but there was no distention. The discolored area extended six to seven inches up from the ileocecal valve. By stripping the bowel through the fingers two pieces of wire were found 1 by 1½ inches in size. These had probably been swollowed with his food and had passed through the vasa intestinal tenuis. The patient completely recovered after the removal of the wire.

Another cases has been reported very similar to the one described above.(5) Here two pieces of wire were found also and had perforated the ileum. The mesentery had closed down over the site of perforation. The symptoms in this case were very much the same as in the preceding case.

Those cases seem to have been the result of the injury to the intestinal wall by the wire. However the abundance of infection that is present in the intestine would certainly contaminate any wound to the intestine. So one can never tell whether there would have been a phlebitis and thrombosis set up had there been only the wound to the intestine and no infection. It seems to me

only reasonable to think that such injuries in a sterile field would not be expected to cause such an extensive inflamatory process.

A peculiar reaction to the vascular endothelium has been reported as due to inflamatory processes.(16) The reaction is associated with more or less extensive thrombosis of the veins. It occurs in certain capillary vessels when the surrounding tissue is undergoing a congestive process with a chronic inflamation. The author describes the process as,"A new and hitherto undescribed form of productive thrombovasculitis". The endothelial cells grow as long and slender chains in the stationary or fluid blood and may even dispart the blood. The imprisoned red cells may become changed into a hyaline mass with the morphologic and tinctorial appearance of fibrin. The most pronounced changes of this kind have been observed in the urethral caruncles. The observer thinks there is a very close association between this process and that that takes place in the so called endovasculitis verrucosa found in typhoid fever, certain colon bacilli infections, and in sepsis. In these processes also hyaline thrombi arise through proliferation of the intima and fibrinoid changes of the nucleated red cells.

This process would help to explain many of the cases of thrombosis which seem to arise simply from a bruise. Here there would be an inflamation of the surrounding tissue but of course no infection would have been introduced. Still the infection would not be ruled out completely because the theory of the susceptibility of the point of lowered resistance to infection would cause one to wonder.

The above is well illustrated by the case of a man 49 years old who suffered a contusion of the right leg.(22) The swelling increased and the veins became tender firm cords. Four months later the left leg also became swollen, tender, and presented much the same symptoms. Finally thrombosis of the lower abdominal wall occured and also of the right internal jugular. This was followed by ocular palsy and left hemiplegia. The patient died and at necropsy thrombosis of all the veins mentioned was found and also of the prostatic plexus. Mural thrombi were found in both common iliacs and in the inferior vena cava extending to the renal veins. Canalized thrombi were found in the right saphenous and femoral. Organized thrombi were found in the right internal jugular and extending into the brain, with hemorrhagic infarcts. The fact that there was a negative

blood culture and that the leukocyte count was normal favors the idea that this progressive phlebitis and thrombosis might have been of the thrombovasculitic nature discribed on page 17. One is at a decided disadvantage when it comes to saying whether there was ever an infection present or not. It is quite evident that even if an infection had been present at the beginning it was quite possible for the thrombotic process to spread and for new thrombi to be set up without the infection remaining present.

That phlebitis and thrombosis can be caused under aseptic conditions is of course well known. The everyday treatment of varicose veins shows that the intima can be irritated sufficiently to set up those processes to the extent that the veins will be completely obliterated. The process is in some cases however set up when it is decidedly not desired. Two cases are reported by Smithies and Oleson (34) which demonstrate this fact. These followed the intravenous injection of sterile solutions of the sodium salt of tetrabromphenolphthalein according to the technique recommended by Graham and Cole. In one instance extensive , obliterating, traveling thrombosis followed. This spread so uninterruptedly, inspite of treatment, as to require surgical pro-

cedure to prevent the involvement of the major venous channels or the development of emboli. In the second case early and prompt treatment proved effective and the formation of a large clot was avoided. Both patients presented general physical impairment to a moderate degree. It is interesting to note that each was of Northern birth and residence, but had moved in later life to a tropical or a subtropical climate where each had become infested with intestinal protozoa and had developed lesions suggestive of early biliary tract malfunction.

Gants (14) reports a case which is very interesting from the standpoint of whether of not phlebitis can occur without infection or chemical irritation of some kind. This patient was a woman 53 years old, operated for gall-bladder disease. On the fourth day 1000 cc. normal saline was given into Scarpa's triangle rapidly followed by massage. On the 15th day the patient complained of soreness over the area of injection. On the 17th day she began to vomit, had severe cramps in the right calf, the entire right extremity was swollen and showed black splotches. The toes were cyanotic. There was a large bluish area over Scarpa's triangle. She complained of pain in each side of the chest and

smothering sensations and had the fear of impending death. She died that night. Necropsy showed edema of the lower extremity, cellulitis over Scarpa's triangle, thrombophlebitis of the saphenous, femoral, iliacs, inferior vena cava and also the pulmonary arteries. Pulmonary edema was present with infarction. Acute and chronic bronchitis with pleurisy was found, also a draining sinus from the gall-bladder, early interstitial nephritis, and fibroids. Microscopic study of the area of cellulitis showed loose edematous fibrous tissue with many infiltrated polymorphs. The vessels of the region were congested and also contained many polymorphs. The inflamatory reaction was most marked about the vessels and extending into the fatty subcutaneous tissue. No inflamatory reaction was found within the vessel wall. In discussing the case the author gave two factors to which he attributed the cause. The injections were given in the wrong place because of the presence of large vessels at that point. Also the solution was given too fast and there was too much massage given causing a destruction of the veins with a slough. In this case there was no in fection introduced and the solution was isotonic and should not have acted as a chemical irritant. In view of those facts it seems that surely this case of phlebitis was the result of trauma alone. How-

ever the old theory of,"Site of lowered resistance", must again be thought of. Here again I wish to refer to the experiment of Barrett's (3) regarding the etiology of phlebitis and thrombosis. His experiments led him to believe that infection was present but that necrosis of tissue or the presence of some form of toxin was also very essential. This experiment is more fully explained earlier in this paper.

The experiment of Armentrout (1) which is also referred to above lends itself to the arguement for the injury theory in the etiology of phlebitis and thrombosis. In this experiment he studied the formation of thrombi in a cat. Following embolism in the cat the first thing that was noticed was a separation of the foreign body by a white thrombus. This thrombus was very friable and broke off very easily. When the separation of the foreign body became complete the formation of the thrombus stopped. However if the endothelium had been injured in any way to any degree at all progressive thrombosis took place. The distinction in the amount of thrombus formation was due of course to the liberation of thromboplastic substances at the site of the injury. If progressive thrombosis didnot occur the white thrombus was simply bland and the blood continued to flow passed

it regardless of how small the opening was or how slow the stream flowed. All that was necessary was for one erythrocyte to be able to get through at a time.

The above discussion is another possible explanation for the case of progressive thrombosis and phlebitis that is given on page 18. This would explain the cases where one can see no infection present but where there is a history of injury at some time. The thromboplastic substance having once been set loose by an injury could be used as an explanation for any phlebitis or thrombosis. The difficulty here is that with all the injuries that one receives in the course of a life time it seems that everyone would ultimately have a case of progressive thrombosis. One must suppose that the reason for the condition in one individual and not in the other must be the presence of an unrecognized infection of a low grade in one, or the presence of a variation in the clotting properties of that individual's blood elements.

In any discussion of phlebitis in which one tries to correlate injury to the vessel wall one must consider a number of cases occuring in normal individuals. These conditions are of spontaneous thrombophlebitis and the

origin of the disease is attributed, wrongly or rightly, to a traumatism or an effort, this effort being an unusual or unaccustomed one. About 50 cases of this traumatic phlebitis or so-called "Effort Thrombosis" have been recorded in the literature. This kind of phlebitis involves the upper extremities; the right one being affected more frequently than the left. The disease occurs in other places only exceptionally. Two cases of thrombophlebitis of the iliac veins have been described.(20) One case of traumatic thrombophlebitis of the superior vena cava has been reported.

A typical case of this effort thrombosis would be interesting at this point, and as described by Lowenstein and quoted by Swindt (35) is as follows. "Following slight or marked exertion, but without direct injury to the vein, thereis a progressive swelling of the arm with pain usually referred to the axilla. With the increase in the edema there are evidences of collateral circulation, and cyanosis is a frequent occurance, although pallor may be present. Palpation of the axilla reveals a hard indurated cord sensative to pressure. The development of these phenomona usually occur without fever and are succeeded by a period of rapid or more often tardy retrogression". He argues against the etiology being infection due to the fact that there is no leukocytosis, there are no chills or fever, and the blood

culture is negative.

There are various explanations for the formation of the clot and the opinions have changed as time went on. Hunter and Cruveilhier (35) thought that the primary cause of the clot was the phlebitis. Virchow stressed the factor of the slowing of the blood stream. Widal and Vaquez again shifted the opinion to infection combined with inflamation of the vessel wall. Aschoff and Freiburg schools go back to the threefactors all in combination, that is slowing of the blood stream, changes in the vessel wall, and finally changes in the blood elements themselves. So it is easily seen that evan the authorities on the subject are decidedly not in accord.

The types of effort that are reported as being the cause of the effort thrombosis are greatly varied. Lowenstein (24) in reviewing the literature to study some of these variations reports many. Willian (39) reported three cases in which the patients were athletic, muscular men and regularly engaged in hard work. Schepelmann's patient (33) had been riding a wild horse, and Lanhaussois' patient (19) fell from a horse on his abducted arm, while Austin (2) writes of a patient who dev-

eloped swelling and passive congestion of his arm apparently due to axillary thrombosis following a fall on the shoulder. Rosenthal (30) cited two examples, one a woman who had been beating clothes, and one in a child playing ball. Another is reported who had become fatigued while writing on a table for a number of hours. The patients of Baum (4), and of Girard (15) and those of Schwartz, Murard, and Vossenaar (8) had been engaged in heavy labor, but Cadenat as well as Frievez (13) reports instances in which the effort was trivial, and indeed Pellot (27) and Routier and Potherat (8) had patients in whom no pre-vocative trauma could be advanced, while the patients of Ruge (31) and of Wilson (40) awoke to find their arms swollen. Lewis and Caen (23) give a report of a carpenter whose edema was not traceable to any unusual exertion.

In the discussion of this condition of effort thrombosis Lowenstein was of the opinion that the etiology of the thrombosis produced by the exertion was on a two fold basis. First to be considered was the slowing of the blood stream or in other words the venous stasis. This was brought about by the forced expiration that characterizes effort. This stasis is clearly manifested in the face and neck by the cyanosis of the face

and the swelling of the jugulars, and to a similar though less readily demonstrable extent in the upper extremities.

Second in the consideration was the marked abduction of the arm or the extension or drawing backward of the arm together with lateral rotation. All of these movements together produces a pronounced pressure by the costocoracoid ligament which is furthered by the subclavian muscle. This pressure is all exerted on the distended axillary vein. This results in changes in the vascular endothelium sufficient to cause an axillary thrombosis. It was brought out also that if an edema is to be justly laid to an injury or a violence of some kind the edema should show up within a few days.

The above discussion by Lowenstein is very interesting and also quite convincing. He did considerable dissecting on the human body to show and prove the existence of the pressure of the costocoracoid ligament as he has described. Therefore one is forced to consider seriously his writings. At the same time two other writers, Lenormant and Mondor, present two cases of apparently the same condition of effort thrombosis and yet they are explained from an etiological standpoint far differently from Lowenstein's viewpoint.

The first case was of a man 20 years of age admitted to the hospital because of an edema of the right upper extremity. The Wassermann reaction was negative. He was a painter but never had any signs of lead poisoning. For the lastfew days the patient had experienced pain under the right clavicle behind the pectoralis major muscle. The pain was continuous but not very stong. Simultaneously there was a sensation of heaviness in the upper right extremity. The patient attributed the signs to heavy work performed during the past week; his arm had been elevated practically all day long during work. The entire right extremity was enlarged and gradually became painful. The temperature was normal and the general condition excellent. The extremity was uniformly enlarged; the circumference of the right upper extremity was 31 cm., and on the left side it was 23 cm. The skin was distended, bluish, and cyanotic; the edema was hard, elastic, and resistant; no impressions were left after pressure with the fingers. The local temperature was not elevated. A slight collateral venous circulation was noticeable in the deltoid region. The pulsations of the brachial artery and of the radialis artery were normal. An indurated and painful tumifaction was present under the pectoralis major muscle corresponding to the course of the blood vessels. The edema was interfering

with the movements at the elbow, of the wrist, and of the fingers. A diagnosis of thrombosis of the axillary vein was made. A compressive dressing was applied and the extremity suspended. The following day the edema and the cyanosis diminished considerably. Within a few days both symptoms had subsided completely.

The second case was in a man 68 years old. The patient consulted the physician because of a tumifaction the size of a nut which developed on the lower portion of the neck on the left side. The patient stated that he made a wrong movement with the left arm while lifting a box on the morning of the day when the tumifaction appeared. The following day the tumifaction increased in size and became painful. The entire shoulder appeared to be larger. The next day the entire arm became swollen and the enlargement spread down to the hand. The patient complained of pronounced spontaneous pain on the internal side of the left upper extremity radiating towards the shoulder. A uniform swelling of the upper extremity was present. The skin was smooth, distended, and slightly reddish on the internal side of the arm. A marked "pitting" could be noticed after pressure with the finger. A tumifaction was present in the left supraclavicular region. An indurated band corresponding to

the external jugular vein could be palpated here. Dilated collateral veins were visable infront of the clavicle and in the left portion of the thorax above the nipple. Basilic and cephalic veins were enlarged but not indurated. The palpation of the edematous region was slightly painful. The radialis artery was pulsating in a normal manner. The diagnosis of phlebitis of the large venous trunks of the left upper extremity was made. According to the statement of the patient he had undergone prostatectomy four months previously to the present illness. The lungs and the digestive tract were normal; the blood picture gave normal figures; the coagulation time was normal; the Wassermann reaction was negative and the temperature was 36.8° C. in the morning and 37.8° C. in the evening. An elevation of the involved extremity was prescribed. The edema increased within the following few days. Edema was present in the axilla corresponding to the vasculonervous axillo-humeral bundle; this indurated cord could be traced down to the elbow. An incision was made in the upper portion of the arm. A large amount of serous fluid escaped from the incision. The brachial vein was as large as the little finger; it was either greenish or black in various places; the vein was hard. Two ligatures were placed in the vein and the vein resected between them. The

skin was sutured without drainage. Two days later the edema diminished, particularly on the hand and fingers. Seven days after operation the arm had a normal appearance. A culture of a blood clot aseptically removed during the operation revealed the presence of staphyloccoci and B. coli; these germs grew only slowly and weakly. Histological examination of the thrombosed vein revealed a large number of staphyloccoci in the periphery of the vessel and in the vasa vasorum, as it is usually found in the obliterating phlebitis. Usually an indurated cord which is painful, corresponding to the location of the vein is noticed; the edema of the involved extremity is uniform. The induration of the vein may be limited to a short segment so that the diagnosis may be difficult.

The authors do not believe that such cases deserve the name of traumatic phlebitis or "effort thrombosis". The statements of the traumatism are rare and disputable. Some persons perform certain work daily and yet they accuse a certain movement which they perform every day for being responsible for their phlebitis. It would be difficult to explain how even a violeht effort can produce a venous thrombophlebitis. A statement that the axillary vein may be compressed by the clavicle or by ligaments during forced abduction of the arms disregards anatomic findings. The hypothesis according to which

repeated movements may cause a chronic irritation of the endothelium of the veins is not supported by any evidence. (20) Some authors express the view that certain violent efforts may tear the venules away from some of the larger veins and that a thrombus may thus be formed, but a very strong effort is necessary to tear a vein and such a statement has never been verified. It must also be noted that nearly always the patient is able to continue his work after the traumatism or the accused effort; the patient becomes disabled a few hours or even a few days afterwards. The authors (20) conclude that a traumatism or an effort as such is not capable of producing thrombophlebitis. Probably the thrombophlebitis was in a stage of development but was latent when the effort occured; the clinical manifestations are noticed after the traumatism but is ignored before it. The main cause of such thrombophlebitis is the usual cause of any phlebitis, namely infection.(20) Probably the infection in such cases is only slight. The proof of the infectious nature of thrombophlebitis can be furnished only by detection of microbes in the blood clots or in the walls of the veins. To the author's knowledge (20), such an examination was made only in three cases. In two cases the results were positive. It is impossible that not only infections but intoxications such as lead poisoning may cause thrombophlebitis, but this theory has not been definitely proven.

As to the treatment the above authors found that merely compressed dressings and elevation of the arm was all that was necessary in the majority of their patients. It is interesting to note that none of their patients had any symptoms related to embolism.

So again with a great deal of experimentation and clinical inquiry one must be led to believe that probably the chief factor in the etiology of phlebitis and thrombophlebitis is infection, with injury to the endothelium playing an accessory role.

-Contributing Factors and Statistics-

With the three factors of slowing of the blood stream, changes in the vessel wall, and changes in the blood itself, as the basis of the etiology of postoperative thrombophlebitis Walters (36) gives his views as to the conditions which contribute to those factors. He says they are favored by:

1. Rest in bed without food which is the usual course in the postoperative treatment for a few days. This favors the stasis of the blood stream due to the lack of exercise.

2. Interference with the circulation by intra-abdominal manipulation.

3. Forty-eight hours quiet of the intestine after abdominal operation also favoring stasis.

4. Muscular splinting of the abdominal wall because of the painful incision. This again would favor stasis.

In a study of 267 cases of fatal pulmonary embolism following 63,347 major operations during the ten year period from 1917 to 1927 at the Mayo Clinic, Henderson found the average incidence of fatal postoperative embolism to be 0.34%

The use of a regimen directed towards increasing the rate of metabolism, of blood pressure, and the flow of blood in 4,500 major operations of comparable type during the last four and one half years has been followed by an incidence of fatal pulmonary embolism in less than 0.09% of the cases (36). Of the four patients in this series who had pulmonary embolism, three were aged 70 or more, and of those, two died from other causes. (Sepsis in one and uremia in the other). The age of the third patient was 54, and in each of the four cases there was myocarditis at necropsy; it was marked and associated with coronary sclerosis in three cases. These four cases illustrate the predisposition of patients with cardiovascular disease to the development of postoperative embolism, and emphasizes the part played by disturbances of the blood flow in their formation. Fatal pulmonary embolism did not accur among patients in general good condition when the described regimen of prevention was carried out.

It is interesting to note that at the University of Nebraska Hospital from the time it opened till the present (1917-1933) there were six deaths out of the total of 57 cases who showed any evidence of phlebitis. Three of these cases died of pulmonary embolism. One had had phlebitis for years, another developed it in the hospital in the course of a puerperal sepsis, and the third was complicated by a severe myocardial disease. Of the six fatalities, two of the patients showed cardiovascular disease, one being 38 years of age and the other being 66 years of age. Two of the six were of puerperal sepsis and septic abortion. One of the six entered the hospital with a fractured pelvis. She was put in a cast and developed a thrombophlebitis of the pelvic veins. She died as a result of the phlebitis and a complicating septicemia. The fact that she was in a cast would help to substantiate the argument that favors stasis as a factor in phlebitis and embolism.

There seems to be a definite relationship between chronic cardiovascular disease and thrombosis and embolism. Kuhn (18) believes that this relationship is developing due to the fact that intravenous injections are used along with the many other means of intensive life-prolonging treatment. This would bring the incidence into the older age group where the incidence of chronic cardiovascular disease is also greater. At the Institute of Pathology at Freiburg, the percentage of

thrombosis increased from 11.3 to 24.5 and the percentage of fatal embolism from 1.3 to 4.9%. In 1927 thrombosis was found in every fourth body examined and fatal embolism in every twentieth. In the clinic of Bakay (29) at Budapest during 1915 to 1927 there were 18,517 operations performed. During that time there were 13 deaths from pulmonary embolism. Eleven of those deaths occured during the last five years of that time. This, therefore, also shows the presence of an increase in the incidence of fatal pulmonary embolism. The clinic also had a like increase in the incidence of thrombosis which did not terminate fatally.

Vietor (41) studied 21 cases of fatal pulmonary embolism occuring in 12,615 operations. Necropsies in 9 cases showed thrombosis of the femoral vein in 4 cases. In one there was thrombosis of the common iliac and the inferior vena cava. In two cases a wound inspection was all that was allowed so the femorals were not seen. In the other two cases with complete necropsy no thrombosis could be found. The patients dying of pulmonary embolism gave no previous history or clinical signs of pre-existing phlebitis or thrombosis, except in one case of carcinoma of the pancreas. Here on the 13th day postoperative a swelling of the left leg was noted. On the 27th day hemiplegia developed. Death occured on

the 31st day apparantly from cachexia, but necropsy showed a large pulmonary embolus with thrombosis of the common iliac and the enferior vena cava. One patient with inguinal hernia complained of pain in the right leg on the third postoperative day but no phlebitis was shown clinically. The patient died on the eleventh day and necropsy showed a thrombosis of the right femoral vein.

Schenck (3) reported a collection of forty cases of thrombosis with embolism. 58% of these followed pelvic tumor operations. Barrett's records show 2.2% (thrombosis and embolism, inthe last 2½yrs, in1977operations) of 1610 laparotomies terminated with Schenck had eight cases of emboli, all terminated fatally, all being pulmonary. Of those eight cases, two were hysterectomy, one was prostatectomy, one was gastroenterostomy, two were gall bladders, one was a pus case of appendicitis, and the last was an infected knee joint. He found to be true that which a number of observers also found, namely that the fatal cases are usually not the cases of old thrombotic processes.

Borchard (6) in his study of the chief conditions which seemed to be predisposing to thrombosis and embolism found myoma, prostatic disease, and carcinoma of the gastro-intestinal tract to be prominent. Operations on the thyroid were seldom followed by this condition.

He also found that if infection was present the danger of thrombosis was increased about two thirds. Previous infections as the Influenza or Angina Pectoris were also factors to be considered. He laid much stress on the slowing of the blood stream as the result of the patient remaining in bed and being very quiet postoperatively. His cases of carcinoma of the stomach seemed predisposed to thrombosis and the condition was found more frequently on the right than on the left. It seemed in his cases also that cachexia and extreme amounts of fat were common to those cases.

In the cases studied here at the University Hospital it was not possible to get the exact percentage of cases in which the phlebitis was in the right or in the left leg. It was not always recorded. The particular veins involved were not always designated either in the case histories. Therefore these figures are not the exact but only the nearest percentage thatcould be reached. It is quite probable that the proportions are about the same however. These cases showed the percentage of involvement to be higher on the left than on the right. The right being 28% and the left 36.8%.

In Brown's report 66% of all cases were in women while 34% were in men. Contrasted with ours we found

68.4% in women with 31.5% in men. This certainly is a remarkable agreement as to the incidence among men and women. The age varies however. Brown's series varied from 18 to 72 years with an average of 47.1 years of age. Our series here varied from 15 to 66 years of age with an average of 38.2 years. Our figures included all cases af phlebitis which had been in the University Hospital. Brown's included just those that had occured postoperatively. Our figures for only those cases that had surgical intervention showed an average of 39.5 years. So there is still quite a discrepancy. Of all the cases that were in the hospital and had any kind of phlebitis, 29.8% had some form of surgical procedure. Brown also had the figures as to the average weight of all the postoperative cases. This average was 151.6 pounds. They were on the average 15% definitely obese. He could find no correlation between the cases with the phlebitis and their blood pressure.

As to the conditions which seemed to be predisposing as far as the surgical procedure was concerned 84.5% followed intra-abdominal operations, 15.5% followed extraperitoneal procedure. 40.0% of the abdominal operations were in the pelvis. 60.0% were on the stomach, gall bladder, and the appendix. One followed a

mastectomy.

Here at the University Hospital the procedure which was followed by the highest percentage of phlebitis was obstetrical. 38.6% of all phlebitis cases were obstetrical. It is also interesting to note that 14.0% of all phlebitis cases were septic abortions. These cases of septic abortions were included in the list of obstetrical cases. Of all the other operative procedures that were followed by phlebitis, herniotomy ranked highest. This operation resulted in 8.7% of all the phlebitis cases in the hospital. As stated before cardiovascular diseases were seen quite often in the cases of phlebitis, being present in 8.7% of all the phlebitis.

Brown found a spring and fall incidence in his cases of phlebitis. We found the greatest incidence in January of both the postoperative and the total phlebitis cases. However in the study of the total cases the incidence was raised in May, August, and October also. In the postoperative cases there was a very slight elevation in the incidence in March and October which would point to a confirmation of Brown's figures. Probably if there were more cases to study this percentage would come out more markedly. See Figure 1.

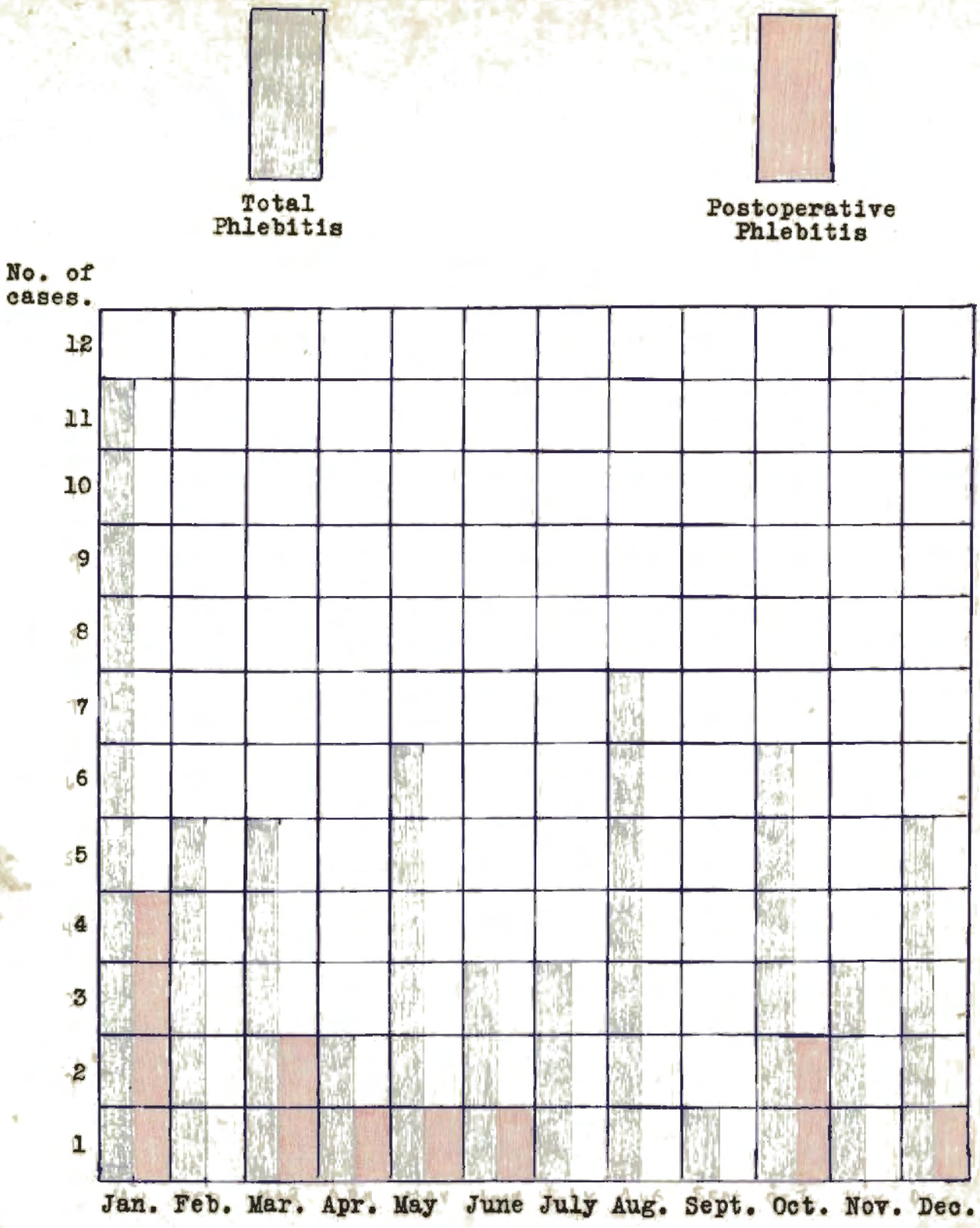

Figure 1.

Showing seasonal incidence of all phlebitis and also of the postoperative phlebitis at the University of Nebraska Hospital.

Henderson (7) showed that in postoperative fatal embolism phlebitis was present in 29 cases or in 11% of all the cases. This is probably higher than the actual incidence. In Brown's series of 87 cases of phlebitis no fatalities occured. However pulmonary infarction was present in 33% of the cases and this figure would probably have been higher had all the chests been carefully examined.

-Summary and Conclusions-

In this paper the etiological factors of phlebitis and thrombophlebitis have been considered, including also the contributing or predisposing factors and some statistics.

The material is the result of the writings of numerous authorities on the subject and also includes a resume of the case histories of all the phlebitis at the University Hospital.

The commonly accepted theory of blood clotting involving the formation of fibrin from fibrinogen by the interaction of thrombin and calcium is given in detail. Also some variations in this theory are considered.

Three factors are stressed as causing phlebitis or thrombophlebitis. First, changes in the blood elements; second, slowing of the blood stream; third, changes in the vessel walls.

The clotting time seems to be some indication as to the probability of a thrombophlebitis resulting in operative cases. Associated with this is the fact that the platelet count seems to vary inversely with the clotting time, and in cases developing postoperative thrombophlebitis the count is highest at the onset of the phlebitis.

Slowing of the blood stream is commonly given as a factor. However, apparently reliable experiments refute this. It seems to be only accessory to some of these other factors.

Many cases of "effort thrombosis" or "effort phlebitis" are recorded. Some authors think these are due to injury to the endothelium and are aseptic.

Infection probably is the most important factor and possible may be practically a constant factor in all phlebitis. It was shown to be present in even the cases of "effort thrombosis".

Contributing factors seem to be the quiet and

inactivity maintained in postoperative cases. Fatal pulmonary embolism is rather common in cases showing cardiovascular disease. Thrombosis with embolism is found often following pelvic tumor operations and also following severe infections or in cachectic states.

Fatal cases usually did not show clinical evidence of phlebitis but it was generally found at necropsy.

The age incidence seems to be around forty. However, this varies with the observer.

At the University Hospital 38.6% of all cases of phlebitis were obstetrical, 14% being septic abortions. 8.7% were following herniotomy operations.

A Spring and Fall incidence seems to exist in the occurance of postoperative phlebitis and thrombophlebitis.

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BIBLIOGRAPHY

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Bibliography

1. Armentrout, A.W., Embolism and Thrombosis, Arch. of Path. 11:519-545, April 1931.
2. Austin, M.A., Personal Communications to P.S. Lowenstein on the subject of Effort Thrombosis. See Ref. No. 24.
3. Barrett, W.D., Thrombosis and Embolism, Canad. Med. Assn. Journ. 14:129-132, Feb. 1924.
4. Baum, H.L., Effort Thrombosis, Duetsch. Med. Wchnschr. 39:997, 1913. Quoted by Lowenstein, Ref.24.
5. Black, J.M., Mesenteric Thrombosis, Brit. M. J. 15:245-246, Dec. 28, 1929.
6. Borchard, A., Ueber Thrombose und Embolie, Beitr z. klin. Chir., 144:163, 1928. Quoted by Nagel et Al, A Review of Abdominal Surgery, Arch. of Surg. 191:526-565, 1929.
7. Brown, G.E., Postoperative Phlebitis, Arch. of Surg. 15:245, 1927.
8. Cadenat, F.M., Effort Thrombosis, Paris med. 10: 253, March 1920. Quoted by Lowenstein Ref. 24.
9. Chlumsky, V., Phlebitis Chronica Migrans, Zentralblatt fur Chirurgie. 54:75-77, Jan. 1927. Ab. by W. F. Prior, Consulting Bureau Service, Hagerstown, Md.
10. Cittens, C.W., A Case of Staphyloccocus Phlebitis, Lancet 2:488, Oct. 1918.

11. Davies, J.C., Splenic Anemia and Portal Thrombosis, Lancet 2:498, 1928.

12. Dawbarn, R.Y.,Earlam, F., and Evans, W.H., The Relation of the Blood Platelets to Thrombosis after Operation and Parturition, J. Path. and Bact. 31: 833, 1928.

13. Fievez, J., Effort Thrombosis, Bull. et mem. Soc. de chir. de Paris 47:935, 1921. See Ref. No. 24.

14. Gants, R.T., Fatal Thrombosis following Hypodermoclysis, J. Kan. Med. Soc.33:13-15, Jan. 1932.

15. Girard, C., Traumatic Thrombosis, Rev. med. de la Suisse rom. 34:220, 1914. See Ref. No. 24.

16. Henschen, Folke, Concerning a Peculiar Reaction of the Vascular Endothelium Associated with Thrombosis, Acta Med. Scandinav. 65:539, 1927. Ab: The Author, Arch. of Path.5:887, 1928.

17. Jacques, L., Varico-phlebitis and the Injection Treatment, Ann. Surg.95:746-753, May 1932.

18. Kuhn, Causes of Increases Incidence of Thrombosis and Embolism in Germany from 1925 to 1927, Journ. Am. Med. Assn.93:499, 1929.

19. Lahaussois, M., Traumatic Thrombosis, Presse med. 18:410, 1910. See Ref. No. 24.

20. Lenormant and Mondor, Effort Thrombosis, La Presse med. 39:1669, Nov. 1931. Ab: W. F. Prior Co., Inc., Consulting Bureau Service, Hagerstown, Md.

21. Lequeux, Suppurative Puerperal Thrombophlebitis, La Vie Med. p. 425, April 1930. Ab: The British Medical Journal, No. 3633:33-34, Aug. 1930.

22. Lipschitz, M., Progressive Thrombophlebitis, Deutsche med. Wchnschr.55:744, 1929. Ab: Breslich, P. J., Arch. of Path. 9:107, 1930.

23. Louis, L., Caen, Thrombophlebitis of the Upper Extremity from Strain, Ann. de Med. leg. 8:188, 1929. Ab: E.R. LeCount, Arch. of Path. 8:1009, 1929.

24. Lowenstein, P.S., Thrombosis of the Axillary Vein, Am. Med. Assn. Journ. 82:854, 1924.

25. Mac Callum, W.G., Clotting and Thrombosis, Textbook of Pathology. p. 3-12, 1918.

26. Metcalfe, R., Mesenteric Thrombosis, Am. J. of Surg. 12:266, May 1931.

27. Pellot, Traumatic Thrombosis, Presse med. 24:523, 1916. See Ref. No. 24.

28. Picot, M.G., The Role of Coagulation of the Blood in the Pathogenesis of Postoperative Phlebitis and Embolism, Bulletins et memoires de la Societe nationale de chirurgie, 57:281-287, Feb. 1931. Ab:W.F. Prior Co., Inc., Consulting Bureau Service, Hagerstown, Md.

29. Prochnow, F., Increase of Postoperative Thromboembolism and its Causes, Arch. f. Klin. Chir. 151: 99, 1928. Ab: Le Count, E.R., Arch. of Path. 8:1011, 1929.

30. Rosenthal, W.J., Effort Thrombosis, Deutsch. f. Chir. 117:405, 1912. See Ref. No. 24.

31. Ruge, E., Effort Thrombosis, Med. Klin. 7:1615, 1911. See Ref. No. 24.

32. Sato, T., Role of Infection and Vessel Wall Injury in Thrombosis, Virchows Arch. f. path. Anat. 257: 561, 1925.

33. Scheplmann, E., Effort Thrombosis, Beihefte z. med. Klin. 7:23, 1911. Ab. Ref. No. 24.

34. Smithies and Oleson, Aseptic Phlebitis, Journ. Am. Med. Assn. 84:1495, 1925.

35. Swindt, J.K., Traumatic Thrombosis of the Upper Extremity, Calif. and Western Medicine 27:635-638, 1927.

36. Walters, Waltman, A Method of Reducing the Incidence of Fatal Postoperative Pulmonary Embolism, Surg. Gynec. and Obst. 50:154, 1930.

37. Wildegans, H., Origin of Thrombosis in Veins, Arch. f. Klin. Chir. 148:592, 1928. Ab: Le Count, E.R., Arch. of Path. 8:1010, 1929.

38. Wilensky, H.O., The Mechanism of Bacterial Infection, Arch. of Surg. 13:228, 1926.

39. Willan, R.J., Effort Thrombosis, Edinburg M. J. 20: 105, 1918. See Ref. No. 24.

40. Wilson, G., Effort Thrombosis, Am. J. M. Sc. 163: 899, June 1922.

41. Vietor, J.A., Thrombosis and Embolism, Ann. Surg. 82:193, 1925.