A Study of Thrombosis

by

Raymond Floyd Gard, B.S., M.D.,
University of Kansas, 1925, 1927

Submitted to the Department of Surgery and the Faculty of the Graduate School of the University of Kansas in partial fulfillment of the requirements for the degree of Master of Science.

Approved by:

Instructor in charge

May 20, 1932

Table of Contents

A STUDY OF THROMBOSIS

Introduction

It has been said that our interest in a disease should be in proportion, not to the rarity, but to the commonness of its occurrence. In our search for knowledge we are apt to follow after the unusual and to overlook as commonplace the more frequent phenomena which may be of paramount importance.

Physiological thrombosis is the preserver of life; it is the "sine qua non" of surgery. On the other hand pathologic thrombosis initiates many diseases, is coexistent with or contributory to others, and frequently occasions an untimely death. This being true, our attention may well be turned for a short time toward a consideration of a physiological process without which there can be no surgical healing and upon a pathological process the effects of which no one has been able to forestall.

It is the purpose of this paper to present the subject of postoperative thrombosis. An attempt will be made to collect from a voluminous literature a few facts or at least logical conclusions

and from these to formulate a pathogenesis of thrombosis that can in part be confirmed by clinical and experimental data. Thousands of articles regarding this subject have been written; obviously only a few of these can or need be cited.

Definitions:

Welch's definition of a thrombus as "a solid mass or plug formed in the living heart or vessels from constituents of the blood" is simple and adequate. Thrombosis is the "act or process of formation of a thrombus or the condition characterized by its presence". Embolism is the "impaction in some part of the vascular system of undissolved material brought there by the blood current". The impacted material is referred to as an embolus. An embolus may be solid, liquid or gas, and may be infected or not infected. However, it is generally understood to be a detached portion of a thrombus. Thrombi are composed of platelets, leucocytes, fibrin and red blood cells. These constituents do not always occur in the same proportions and because of this there is great variability in the gross and microscopical appearance of different thrombi.

"White thrombi are composed largely of platelets, leucocytes and fibrin with a small number of red blood cells." The "red" thrombi have a framework composed of platelets, leucocytes and fibrin but in this framework there is deposited a large quantity of red blood cells which accounts for the red color. Between these two extremes are the "mixed" thrombi which are gradations between the "white" and the "red".

The relative proportion of these formed elements is determined by the mechanical factors present at the site of the thrombus formation. White thrombi begin as tiny collections of platelets which attract from the flowing blood stream other platelets, leucocytes and fibrin and as this framework grows only a few red cells are entangled. Red thrombi form in a slowly moving or stagnant circulation and do not differ greatly in appearance or structure from clots formed in a test tube. The proportion of formed elements is almost the same as in the circulating blood. The laminated appearance, i.e., the alternating red and white layers may be due to changes in the circulatory mechanics during the time the thrombus is forming. A "red" thrombus may fade to a yellowish-gray after some time because of the loss

of hemoglobin from the red cells leaving them as partially translucent debris.

Since a thrombus is composed of constituents of the blood it is essentially a blood coagulum differing only in the relative proportions of each constituent and in its characteristic physical structure which is produced by the action of the flowing blood. Being a blood coagulum, its formation is inseparable from the mechanism of blood clotting. Being the result of the precipitation of fibrin from the bloodby the action of tissue fibrinogen within the vessel wall it is inseparably associated with the mechanism of aseptic wound healing.

Gross and Microscopic Appearance

The gross appearance of a completely formed thrombus found at autopsy is characteristic and should not be confused with the postmortem clot. The "head" of the thrombus or that portion formed first and while the blood is in active motion, is dry, inelastic, granular and friable and is attached to the vessel wall. If forcibly removed the underlying endothelium may be dulled, roughened or even torn away. This portion of the thrombus is grayish-white or at least less red than the "tail" portion.

The "tail" is that portion of the thrombus extending in either direction from the head. It is formed after the vessel has been partially occluded by the head portion and consequently in blood less rapidly moving or even stagnant. It is red in color and more closely resembles the postmortem clot. A cross-section of the head will show irregularly anastomosing strands or islands of grayish-white, sometimes hyalinized material, forming a bizarre network, the meshes of which are filled with dark, reddish brown, granular material. Section through the tail portion appears similar to clotted shed blood.

Microscopically, the thrombus is seen to be made up of islands or irregular strands composed of agglutinated platelets flanked on either side by rows of leucocytes. These strands are connected by a lacework of fibrin fibrils in which are enmeshed varying numbers of red blood cells. The fibrin is particularly dense near the edges of the anastomosing strands of agglutinated platelets but seldom is recognizable in these masses. These strands with their borders of entangled leucocytes make up the "lines of Zahn". Occasionally in early thrombi one can

see fibrin fibrils radiating from individual platelets.

The characteristic structure of the thrombus makes it readily distinguishable from the "postmortem" clot which is formed in immotile blood and upon intact endothelium. Under such conditions the blood clots very slowly and there is sufficient time for gravity to actually sediment the formed elements, so that this clot has its deep red dependent portion and lying upon this the elastic, yellowish, translucent layer. Its gross appearance suggests the term "chicken fat" clot.

Purpose of Thrombosis

The primary purpose of thrombosis is to heal an injured vessel wall or to occlude a severed vessel and so arrest hemorrhage. When a vessel is cut across the inner and medial coats contract and retract so that the caliber of the lumen is materially reduced. When a vessel is securely ligated these coats are ruptured and retract. In each instance the ruptured endothelial lining permits the interaction of tissue juices and blood with a resultant thrombus formation. This thrombus is speedily or-

ganized and precludes the possibility of hemorrhage after the ligature is absorbed. An attempt to heal an injury in a vessel wall is seen in the thrombus that forms in an aneurysm sac. The vessel wall weakened by disease is reinforced by buttresses of organizing fibrin lamellae.

Nonpurposive Thromboses

Nonpurposive thrombi are those which form following operative trauma, infection, parturition, changes in the circulatory mechanics incident to disease, and in other conditions.

These thrombi often arise in areas inflamed prior to, or incident to, operation and being formed from gramular rather than fibrillar fibrin, organize late or imperfectly and are the source of emboli responsible for postoperative complications and death. They may form in infected fields and their emboli result in abscess formation.

Occurrence of Thrombosis

While this paper is concerned particularly with the pathogenesis of postoperative thrombosis it is well to recall that thrombosis presents frequent

problems for the internist as well as the surgeon. The mural and valvular thrombi found in endocarditis are characteristic: so too are the embolic accidents so frequently associated with them. Its occurrence is spectacular in coronary thrombosis. Femoral thrombophlebitis commonly accompanies typhoid fever. Cerebral thrombosis and embolism are not uncommon. It occurs in pneumonia, acute articular rheumatism, tuberculosis, and many other similar diseases.

Surgery is never free from the dangers of thrombosis. It has followed every kind of major or minor operation. It is no respector of age or sex. It may occur after local, spinal or inhalation anesthesia. Patients in the best of condition having clean laparotomies or those moribund from toxemia and operated for obstruction may develop thrombosis.

Incidence of Thrombosis

Fränkel states that 5 per cent of all patients undergoing abdominal section develop thrombosis and that half of these are accompanied by embolism. In 3500 gynecological operations Zurhelle reports 34 cases of thrombosis, 15 of which died of pul-

monary embolism. De Quervain in 20,779 operations had 143 emboli with death directly attributed to emboli in 0.28 per cent. Heard cites 104 cases of fatal pulmonary embolism following 125,164 operations or one in each 1203, an average of 0.08 per cent. Schilling in Germany collected 32 cases over a period of 12 years, with a percentage of 0.12 per cent.

If the statistics can be relied upon there seems to be a definite increase in the incidence of post-operative thrombosis. For instance Hegler reports 10 thromboses in 14,600 cases in 1913 and 166 thromboses in 19,000 cases in 1928. In the intervening years there was a gradual increase.

Clinical Forms of Thrombosis

The veins commonly affected by thrombosis are the femoral, pelvic plexuses, mesenteric, iliac, and vena cava. Thrombosis of the femoral is probably the most common, although many more occur in the pelvic and mesenteric vessels than are diagnosed. The affection of these veins may be scarcely noticeable or it may be extremely severe and accompanied

by chills and high fever.

Thrombosis of the femoral veins occurs most often in the left (presumably because of a more difficult return-flow due to its passage beneath the right common iliac artery) but does occur in the right or is even bilateral. It occurs rather frequently, may follow any operation, or may appear spontaneously. The general symptoms most often occur at the outset and may consist of an initial mild chill with moderate elevation in temperature accompanied by pain and edema of the foot and leg. The leg may be greatly swollen, the swelling extending from the toes to the groin or it may involve smaller areas. If the edema is great the leg may be covered with a smooth shiny skin that occasionally shows mottled red areas, though usually the skin is pale. The pain may be mild or sever, is generalized or may be localized in the popliteal space or on the medial surface of the thigh along the course of the saphenous vein. The thrombosed vein may occasionally be palpated as a firm tender cord. The mild cases last only a few days with no after-effects; the more severe cases last weeks and may result in per-

manent enlargement and partial disability of the leg.

Postoperative thrombophlebitis occurs most often about the eighth to the tenth day though it may occur by the second day or several weeks after operation. It is accompanied by a low grade fever that seldom goes above 101° F. Thrombosis of the femoral veins infrequently extends up the iliacs and into or up the inferior vena cava. The characteristic symptoms of such an extension are edema of both lower extremities and of the abdominal wall with the development of a collateral circulation. The collateral circulation most often develops in the deep veins but may be also in the superficial lower abdominal veins.

Thrombosis of the mesenteric veins occurs most commonly in the superior mesenteric because of the greater frequency of infections in the right half of the abdomen. Acute appendicitis is the lesion most likely to be followed by thrombosis although it is often associated with ulcers and other morbid conditions in the intestine. It may follow gut resections and anastomoses. The clinical

symptoms of mesenteric thrombosis are those of intestinal obstruction; acute abdominal pain, nausea, vomiting, and a distended tympanitic tender abdomen. There may be absolute constipation or a bloody diarrhoea. Shock with cold sweat and subnormal temperature may develop. Hertzler says that the bloody exudate seen when the abdomen is opened is pathognomonic of vascular occlusion. Emboli from these thrombi frequently occasion liver abscesses.

Clinical Types of Embolism

The great majority of postoperative emboli occur in the lungs and this pulmonary complication is subdivided naturally into multiple infarction and massive embolism.

Pulmonary infarction is usually multiple and is the result of emboli small enough to pass through the larger pulmonary vessels and lodge in the smaller vessels in one or more lobes. Being peripherally located, they cause a pleuritis with sharp pain in the chest, cough, friction rub, rales, impairment of the percussion note, dyspnea, hemoptysis and sometimes cyanosis. Infarcts occur most often in the right lower lobe, are pyramidal in shape

and their bases are directed toward the visceral pleura which is covered with hemorrhagic fibrinous exudate. Contact between the parietal and visceral pleura produces pain. During the course of ten days or two weeks the infarcts are absorbed and the circulation re-established with a consequent disappearance of symptoms and physical signs. This clearing up of symptoms has often been considered to be the resolution of a post-anesthetic pneumonia. Post-anesthetic pneumonia, however, usually occurs in patients older than 50; pulmonary infarction usually in patients under 45. Pneumonia most often occurs immediately after operation and infarction seldom before four days have elapsed and frequently not until after a week or ten days. The temperature course prior to infarction is always febrile, ranging from 99° to 100° F. and remains up for 3 or 4 days after it slowly returns to normal as the infarcts are absorbed.

If the infarct is infected a lung abscess or gangrene may develop with a consequent continued septic type of fever. Following the first shower of infarcts by about eight days there may be a second

pulmonary infarction or a massive embolism. This occurs in about 10 per cent of the cases (Hampton and Wharton) and is well illustrated by the following case history:

Mrs. I.E., 44 years of age, underwent a cholecystectomy for gall stones. The postoperative temperature rise had subsided on the fourth day. The following day she complained of sudden pain in the left chest and had a respiratory rate of 32 and a pulse rate of 128. The chest was normal to auscultation and percussion and a diagnosis of diaphragmatic pleurisy was made. The next day the temperature was elevated to 102.2° F. and there was impairment of breath sounds over the left lower chest. In two days the chest findings had cleared up but the fever continued its up and down course. On the sixteenth postoperative day the patient was permitted to be out of bed. On the twenty-first day she still ran a low grade fever, and while she was in the bath room just before going home, had a sudden massive pulmonary embolus and died within fifteen minutes. Autopsy examination showed a large embolus in the right pulmonary artery and a portion

of a thrombus protruding from one of the tirbuteries of the left iliac vein. The gall bladder bed was well healed.

This case demonstrates the necessity of keeping operative patients in bed as long as they continue to have an unexplained fever.

In contradistinction to pulmonary infarction, massive embolism is the result of an embolus sufficiently large (or long) to occlude entirely the main trunk or the principle branches of the pulmonary artery. This sudden massive occlusion produces terrific shock and almost instantaneous death, although some patients survive for several hours, and may even in a few instances recover. In addition to the shock produced the pulmonary area occluded may be sufficient to account for death. If the patient remains conscious for any length of time, he may complain of a sense of severe pressure under the sternum, an inability to breathe and of a feeling of impending dissolution.

The lungs of such a patient show at autopsy little more than congestion, but there is marked dilatation of the right heart and the vena cava.

Pulmonary embolism occurs at any time from a few

minutes after operation to three weeks or more, but usually about the eighth to the tenth day. Most often it follows some intra-abdominal operation but may happen after thyroidectomy, suprapubic cystostomy, open reduction of a fracture or other procedure. For some reason it seldom results from a femoral thrombophlebitis. Hampton and Wharton saw it only once in 205 cases of thrombophlebitis, although pulmonary infarction occurred 14 times in their series.

Cases Occurring in the Halstead Hospital

In order to review the clinical features of this process I have collected the case histories of those patients at the Halstead Hospital showing signs and symptoms sufficiently clear to make an unquestioned diagnosis. Without a doubt there are many more but with symptoms insufficient to force recognition. This is particularly true in cases of pulmonary infarction misdiagnosed as pleurisy, bronchitis or pneumonia. Over a period of 12 years there have been 46 cases of thrombosis and embolism that followed closely enough upon operation as to seem to be resultant complications. The outstanding points are stated in the following tables:

Postoperative Femoral Thrombophlebitis

	Operation	Age	Sex	P.O. Day	Vein Involved	Clean or Infected Case
1.	Hysteromyomectomy	35	F.	8	L.	Clean
2.	Myomectomy	42	F.	7	L.	"
3.	Ventral fixation and perineorrhaphy	47	F.	11	L.	"
4.	"	43	F.	18	L.	"
5.	"	29	F.	8 &23	L. & R.	"
6.	"	57	F.	11	L.	"
7.	Ovarian Cyst	41	F.	7	L.	"
8.	"	36	F.	8	L.	"
9.	Cholecystectomy	37	F.	8	L. & R.	Empyema
*10.	"	44	F.	8	L.	Infected
11.	Appendectomy	28	M.	14	L.	Acute Infection
12.	"	47	M.	15	L.	Abscess
13.	Thyroidectomy	52	M.	16	L.	Clean
14.	Carcinoma R.breast	61	F.	12	R.	"
15.	" L. "	40	F.	13	L.	"
16.	Subphrenic Abscess	72	F.	15	L.	Infected
17.	Prostatectomy	59	M.	17	L.	Clean
18.	Hemorrhoidectomy	61	F.	12	L.	Infected
19.	Resection of Bunions	40	M.	17	L.	Clean
20.	Lanced boil R.Calf	41	M.	20	R.	Infected
21.	Vaccination on L.Leg	39	F.	3	L.	Clean

Female 15, Male 6

Left 17, Right 2, Bilateral 2

Average postoperative day 12

*Died on 21st day of pulmonary embolism.

Pulmonary Infarction

	Operation	Sex	Age	P.O. Day	Clean or Infected Case
1.	Defundation and Fixation	F.	63	4	Clean
2.	"	F.	47	8	"
3.	Myomectomy	F.	42	8	"
4.	Uterine Suspension (Baldy-Webster)	F.	23	2	"
5.	Appendectomy	M.	28	2	Infected
6.	Cholecystectomy	F.	28	17	"
7.	Thyroidectomy	F.	70	8	Clean
8.	Herniotomy	M.	39	4	"
9.	Resection of Thrombosed varicose veins	M.	46	13	"

Female 6; Male 3

Average postoperative days 7

Mesenteric Thrombosis

	Operation	Sex	Age	P.O. Day	Clean or Infected Case
1.	Appendectomy	M.	17	8	Acute Appendicitis
2.	"	M.	42	2	" "
3.	"	M.	54	3	" "
4.	Herniotomy (Inguinal)	M.	63	10	Clean
5.	Herniotomy (Richter's	M.	50	2	"

Pulmonary Embolism

	Operation	Age	P.O. Day	Time of death	Site of Thrombus
1.	Cholecystectomy	30	14	Lived 35 min.	Hepatic veins
2.	"	44	21	" 20 "	L.iliac
3.	Hysteromyomectomy	35	18	Instantly	
4.	Thyroidectomy	55	2		
5.	"	54	3		
6.	Resection carcinoma Rectum	67	8	Lived 20 min.	
7.	Strangulated Hernia	23	8		
8.	Cystostomy	64	12		
9.	Fractured Humerus	33	14	Lived 35 Min.	
10.	Hydrocele	67	1	Instantly	Mural Endocardium
11.	Delivery	41	During labor	Instantly	

Summary of Theories of Pathogenesis of Thrombosis

No one has been able to explain satisfactorily the initiation and development of a thrombus upon one single factor. It is more than probable that there are primary and contributory factors.

Eberth and Schimmelbusch, and Welch believed that there is a primary injury of the vessel wall with a liberation or production of blood clotting material. Aschoff maintains that endothelial damage is a result of rather than a cause of thrombosis and ascribes the process to changes in the blood itself and particularly to the mechanical influence of changes in the rate of circulatory flow with consequent "eddy" currents. Ritter combines mechanical circulatory disturbances with colloidal chemical process in the blood and endothelium. Bancroft and Kugelmass, and Stanley-Brown feel that thrombosis is largely due to alterations in the blood itself, affecting the several clotting indices, and incident to operative trauma, infection and diet. Hertzler looks upon thrombosis as a type of wound healing; a combining of elements of the blood and of the vessel wall with the precipitation of fibrin and the formation from it of connective tissue. He recognizes two types of

thrombi, "first intention" thrombi produced from fibrillar fibrin under aseptic conditions and "second intention" thrombi from granular fibrin under septic conditions. From the latter arise the emboli.

The Inception of Thrombi

It is more or less generally accepted that the thrombus starts as an accumulation of blood platelets. Eberth and Schimmelbusch in 1886 working with the mesenteric vessels of a dog actually saw under the microscope the accumulation of blood platelets at the site of endothelial injury. As a result of various influences such as contact with injured or diseased vascular walls the platelets underwent a "viscid metamorphosis". Because of this viscidity the platelets become adherent to each other and to the vessel wall and about this nidus the leucocytes and red blood cells collect. In their earliest thrombi they did not see fibrin and so concluded that a thrombus is not a coagulation but a conglutination of bodies pre-existent in the blood. Welch in 1887 studied thrombi under the microscope at intervals of minutes from their beginnings and found them composed of fibrin, clumped

platelets and leucocytes. He securely ligated a femoral vein of a dog and immediately removed the ligature. Then he removed and split the vein and studied the thrombi which had formed at the site of endothelial injury. He describes them as grayish homogeneous, translucent bits of material projecting irregularly into the lumen. They were fragile enough to be disintegrated by the weight of a cover glass. They had a sticky gelatinous feel and could be teased into slender threads. If teased in a physiological salt solution the youngest thrombi were seen to be composed almost entirely of platelets although a few leucocytes were found in those thrombi only five minutes old. Leucocytes continue to accumulate in larger and larger number until they form a prominent part of the thrombus. Even in the five minute thrombi fibrin strands were found. Following the initial deposition of platelets the remainder of the thrombus is formed by the processes of coagulation modified by the mechanical influences of the flowing blood.

In 1927 Howntree using an extracorporal collodion tube attached to the carotid and jugular vessels of rabbits saw with the microscope the initial beginning of thrombi and confirmed experimentally the findings of Welch and of Eberth and Schimmelbusch.

The experimentally produced thrombi possess a "base-work of tiny white thrombi composed of disintegrated platelets and a few leucocytes. On this foundation lies a stratum more or less rich in leucocytes, then masses of fibrin and finally delicate strands of fibrin with entangled leucocytes". His conception then of the essential formation of a white thrombus is that "a few platelets become attached to a pathologic surface, they swell and discharge their thromboplastic substance which induces the formation of fibrin and repeat the process until a huge mass of disintegrated and fused platelets results". This mass continues to grow into the lumen of the vessel until it retards the rapid flow of blood and thus allows the second stage of thrombus formation (the red portion or Schwanzteil) to occur.

Rowntree demonstrated also that retarding the circulation would tend to hasten the process and that speeding the circulation by the injection of thyroxin or ephedrin slowed the process.

Effect of Circulatory Disturbances on Thrombus Formation

It has been maintained by Aschoff that the essential factor in the pathogenesis of thrombosis is a slowing of the blood current by disease or by mechanical factors such as obtain in the proximal part of the femoral vein where large valves are present, in the pelvic plexus, venous networks or in the auricles. The pressure of the column of blood in the femoral veins retards circulation; the pressure of Poupart's ligament and of the right iliac artery as it crosses the left iliac vein tends to slow the blood stream. Eddy currents formed at the site of venous valves or at the junction of two vessels of unequal size are factors contributing to the formation of thrombi. Upon these factors and changes in the blood itself Aschoff builds a pathogenesis of thrombosis and denies that endothelial damage plays any role. It must be remembered that all of these local factors in circulation are present during the individual's entire life and that the blood must contend with them during its normal flow. For this reason these factors cannot be in themselves of any great sig-

nificance in the induction of thrombosis.

Baumgarten separated a segment of vein by careful double ligation under aseptic conditions and found the blood still fluid after a lapse of weeks. I have repeated this experiment by isolating the external jugular veins of dogs under aseptic conditions and ligating each in two places about an inch and a half apart. If the ligating is carefully done so that the endothelium is not injured the blood will remain entirely fluid and the red cells discrete after a period of thirty days. The red cells often are crenated and the leucocytes may disintegrate but there is no evidence of coagulation or thrombosis (Fig. 1). However if the endothelium is injured clotting will immediately occur. It seems evident from this that if blood will remain at a standstill for weeks and show no evidence of clotting or thrombus formation it can hardly be maintained that mere slowing of the circulation is the causative factor in thrombosis. If stasis plays the essential role in this process, why should thrombi form upon the edges of heart valves in a current of blood sufficiently strong

to sweep them away? There must be some cause other than stasis for the occasional appearance of thrombi in the aorta.

It is probably true that such local factors as stasis and eddy currents tend to localize many thrombi in certain vessels. Characteristic examples of this are the thrombi that occur in the auricles and atria, in the left femoral vein, and in varicose veins. MacCallum says that "as a predisposing and later as a guiding factor controlling the architecture of the thrombus, modifications of the velocity and directions of the current are undoubtedly of great importance, but for the first step in the lodgment of platelets injury to the endothelium seems of prime importance."

Endothelial Injury as the Cause of Thrombosis

The difficulty in regard to the origin of thrombosis is confined largely to the explanation of the first deposit of platelets. Growth of the thrombus after its inception is understood on the basis of the principles of clotting.

There is always endothelial injury at the site of thrombosis. Some of the older authors looked

upon this as a result of and not as a cause of thrombus formation and explained it on the basis of local anemic necrosis. However, most of the more recent investigators believe that injury of the endothelium is necessary for the initiation of this process. Endothelial injury that permits an interaction between the blood and the tissue juices (tissue fibrinogen, "cement substance") is the prime factor in the initiation of thrombosis. Ritter makes the positive statement that thrombi absolutely do not form on healthy endothelium. In his cauterizing experiments no thrombi developed where the endothelium retained good staining power. Cohnheim recognized that retardation of the blood stream or cessation of the circulation favored the occurrence of thrombosis, yet in his opinion these meant nothing as long as the endothelium was intact. The fact that blood will remain liquid for weeks and without sign of coagulation while at a complete standstill in an endothelial-lined space such as a doubly ligated blood vessel demonstrates that the integrity of the endothelium is essential in inhibiting thrombosis.

What is the actual mechanism that takes place when the endothelium is injured and the blood comes in direct contact with the tissues of the vessel lying beneath the endothelium? Hertzler says that endothelial injury is attended by the exudation from beneath the endothelial cells of the "homogeneous material called cement substance (the "Kitt substance" of Waldeyer). The collection of platelets about the injured endothelium and the cement substance which exudes from beneath it forms fibrillar fibrin." This constitutes the inception of a thrombus and from this beginning the thrombus grows by further deposition of platelets and fibrin with the accumulation and entanglement of white and red blood cells.

That such a material as cement substance exists and that it is essential in the inception of a thrombus can be demonstrated from the fact that it can be coagulated or inactivated by the application of silver nitrate and that when so coagulated or destroyed a thrombus does not form but the blood remains fluid at the site of endothelial injury.

I have done this by aseptically isolating the

external jugular vein of a dog and tightly ligating it with silk. If the ligature is drawn tightly the endothelium and intima are destroyed and the vessel will become thrombosed. This occurs consistently. However if before ligating the isolated vessel a small portion of the adventitia of the wall is painted with 3 per cent silver nitrate or touched with the silver stick and then the ligature is placed the blood will thrombose except at the point of the silver application. This is well shown by Figure 2. The cement substance being coagulated or inactivated by the silver which has penetrated the vessel wall cannot unite with the blood to form fibrin and the clot does not form. Away from the place of silver application in areas of active cement substance the thrombus forms as usual.

Welch in some of his experiments on thrombosis formation "injured the vessel wall with caustics" and to his astonishment failed in this way to produce a thrombus. His failure may be explained in the above manner.

The chemical nature of this cement substance is not known. The fact, as presented by Mills, that

tissue fibrinogen found in high concentration in vessel walls has such a powerful action in inducing intravascular clotting leads me to believe that tissue fibrinogen and "cement substance" are identical, or at least that "cement substance" contains tissue fibrinogen. The chemical nature of tissue fibrinogen has been established by Mills. It is the entire globulin fraction of tissue extracts. When precipitated by saturation with $MgSO_4$ or NaCl it is a grayish-white substance which has the full coagulation activity of the crude tissue extract. When extracted by alcohol it yields 42 per cent phospholipin and 58 per cent protein.

Every cell of the body contains tissue fibrinogen in its cytoplasm, the vascular endothelium being very rich in it. Any escaping blood must come in contact with injured endothelium and consequently in contact with tissue fibrinogen. Mills has shown too that platelets contain tissue fibrinogen. This being true, it follows that when platelets clump and begin to disintegrate tissue fibrinogen is liberated.

From this it may be concluded that the essential mechanism of the inception of thrombosis is an injury of the vascular endothelium that permits

the blood fibrinogen to come into direct contact with tissue fibrinogen and that union takes place in the presence of the blood calcium with the production of fibrin. From this initial beginning the clot or thrombus grows by the further deposition of fibrin and accumulation of formed elements from the blood.

Factors Causing Endothelial Injury

In operative surgery traumatization of vessel endothelium is unavoidable. The ligating and cutting of vessels is necessary. It seems too, that the majority of postoperative thrombosis occurs following those operations in which there is extensive trauma. A large percentage of thrombosis occurs following pelvic operations and particularly hysteromyomectomy. In this particular operation large vessels are clamped and ligated. Sometimes clamps are improperly placed and must be reset or ligatures break and are replaced. Because of this it is difficult to make certain that vessels are not traumatized proximal to the point of ligation. When fibromyomata in the broad ligament are enucleated and the uterus dissected

from the bladder wall extensive areas of traumatized tissue are left and may be the source of thrombi.

In the removal of a gall bladder with its frequent extensive adhesions and its close proximity to huge venous sinuses, trauma is inevitable and the scene is laid for thrombosis. Thrombosis occurs notoriously often in the puerperium and is incident in large part to the trauma caused to the large pelvic sinuses by the descent of the child through the birth canal.

Not only trauma but infection causes injury to endothelium. In the histologic sections of acute appendices one becomes familiar with the initial and progressive reaction of the endothelium to inflammation. Cross-sections of the appendiceal artery and vein afford almost unlimited examples. Here one may follow the various stages of thrombus formation from its inception to final complete occlusion. The first things one sees is the swelling of the endothelial cells with a changing of their shape from the normal flat pavement to globoid or cuboidal and an associated swelling of the subendothelial tissues. As the reaction continues the cuboidal

cell becomes columnar and even spindleshape with its long axis in a radial position. The cells are pulled apart from each other with a consequent breaking up of the endothelial barrier between blood and the subendothelial tissues (Fig. 3). By this time strands are evident and thrombosis has begun. The next stage in the reaction shows the disintegration of the endothelial cells and a definite thrombus formation (Fig. 4). A study of a series of such slides shows the entire process of thrombosis and is without the unknown elements injected by artificial experimentation.

In operative surgery opportunity for such inflammatory reaction as above described is legion. In the first place many cases are infected before operation and the trauma incident to operation only supplements that due to infection. The majority of appendices removed are infected, fallopian tubes often harbour infection, the gall bladder wall is frequently the site of infection and of course all abscesses, pelvic, abdominal or pleural are infected. Operative procedures frequently open routes of infection; particularly is this

true in supravaginal hysterectomy and all gut resections, anastomoses, and in operations about the mouth and rectum. Furthermore I believe it is generally agreed that there is no such thing as an operation without the introduction of organisms.

It may now be concluded that postoperative thrombosis at the site of operation is due to endothelial injury incident to operative trauma and associated or preexisting inflammatory reaction.

Postoperative Thrombosis Not at Site of Operation

A large portion of postoperative thrombi form elsewhere than at the site of operation. Of these thrombophlebitis of the vessels of the leg is most common. While postoperative femoral thrombophlebitis is most frequently preceded by some pelvic operation or occurs in the puerperium this is not necessarily true. Two of our cases followed mastectomy, two followed thyroidectomy and two followed cholecystectomy. What are the factors involved in the production of thrombosis not at the site of operation?

Bayne-Jones has demonstrated conclusively by injection experiments that blood vessels are present in the atrio-ventricular valves. Rosenow has shown that with injections of streptococcus viridans he

can produce bacterial colonies in the substance of the valves beneath intact endothelium. White admits the possibility of the introduction of organisms to the endocardium through blood vessels in the valves. Following this embolic infection in the heart valve the endothelium breaks down and thrombi or vegetations form. Is a similar route of infection possible and a probable factor in the production of thrombosis not at the site of operation? I believe it is possible.

"The walls of all arteries and veins with a caliber greater than 1 mm. are provided with their own nourishing blood vessels, the vasa vasorum. They originate from the adjacent small arteries and form a dense capillary network in the adventitia. In even the larger arteries they do not penetrate further than the external layers of the media. In the veins, however, they are in general more abundant and may even penetrate up to the intima; the veins of the blood vessels often open into the lumen of the vessels which they drain. Networks of thin-walled, frequently very wide lymphatics have been proved to be present in all the larger arteries and veins"

(Maximow).

Often following operation, particularly if infected tissues have been opened into, there is a bacteremia. This is certainly true in those patients who appear septic and run high temperatures. At times there is an actual pyemia as evidenced by multiple abscess formation throughout the body. It is conceivable that bacteria may find their way into the vasa vasorum of the veins and lodging in proximity to the intima set up an inflammatory reaction sufficient to cause the inception of thrombosis, a process identical with that which is known to occur in the heart valves. Bacteria may also reach and perhaps incite injury of the endothelium by way of the vessel lumen. These changes may be very slight and require the aid of a retarded circulation found in the femoral vessels to initiate the process. In addition to the predisposing factor of local retardation or circulation and the possibility of vessel wall infection by way of the vasa vasorum or lumen there must be some factor in the blood of the patients which predisposes toward the formation of thrombosis not at the site of operative trauma.

It has been shown fairly definitely by Bancroft, Kugelmass and Stanley-Brown that "certain of the blood substances, i.e.,prothrombin, fibrinogen and platelets tend to favor clotting and others (antithrombin) tend to reverse this process, i.e.,favor bleeding. In this chemical mechanism the activity for clotting or bleeding is proportional to the concentration of each interactive substance". These materials, prothrombin, fibrinogen and antithrombin are definite chemical substances and their respective concentrations in blood can be accurately determined.

These investigators, by a careful pre- and postoperative study of the bloods of 205 surgical cases, observed a marked elevation of those elements favoring clotting and a corresponding decrease in those elements favoring bleeding in 65 cases or 33 per cent. In this series of 205 there occurred eleven cases of thrombosis or embolism and all of these were contained within the group of 65 which showed a high blood clotting index. Many others of this group had prolonged postoperative temperatures and it is fairly certain that some of these had deep thromboses that were not recognized clinically. A group composed of the appendices, gall bladders,

hernias and pelvic cases showed higher clotting indices than the general run of surgical cases. It will be remembered that the large majority of postoperative thromboses occur in such cases.

It was shown also by animal experimentation that postoperative infection and to a certain extent ether anesthesia definitely increase the tendency to clot formation.

Postoperative Embolism

The accident of embolism occurs because the thrombus has been insecurely attached to the vessel wall and becomes dislodged either by the force of the blood current or by motion transmitted from without the vessel.

It is common knowledge that infected or inflamed tissues heal or organize more slowly than do aseptic ones. The same is true of thromboses. The function of a white thrombus is to heal a wound of the endothelium and it does this by attaching itself by fibrin strands which later become fibrous tissue. If the thrombus is aseptic this occurs speedily and securely. In inflamed vessels the process is much slower and insecure and the possibility of

embolism becomes a probability.

Recognizing this fact Hertzler has laid down as a principle of surgery that "a vein in a state of reaction should not be ligated". If necessary to ligate under such conditions it should be made away from the site of reaction in normal tissue.

Prevention of Thrombosis

It is true that no one as yet has been able to prevent thrombosis, but there are certain prophylactic measures that seem to be of value in the avoidance of this dreaded complication. It has been shown experimentally that thrombosis occurs more readily in unhealthy than in healthy laboratory animals. This being true certainly all elective operations should be deferred until the patient's health is good.

The technique of operation should be simple, careful and accurate so that all unnecessary trauma may be avoided. The removal and reclamping of hemostats, the breaking and replacing of ligatures and the trauma of strong retraction should be avoided. Surgical asepsis should be scrupulous so

that the factor of infection may be minimized. Before elective operations are undertaken foci of infection should, if possible, be removed. Every effort should be made to avoid the ligation of inflamed vessels.

Mills has shown that a diet rich in protein definitely increases the platelet count and consequently the clotting index. The platelet count is also elevated by ether anesthesia and by chronic infections. He suggests that all postoperative patients be placed upon a low protein diet until the usual time for thrombosis to occur is past.

The use of materials in the blood stream to retard or inhibit thrombus formation is contraindicated because thrombosis is necessary for vessel healing.

Conclusions:

1. Endothelial injury is the essential factor in the initiation of thrombosis. Intact endothelial surfaces inhibit the formation of thrombi.

2. The subendothelial tissues contain a material ("cement substance", "tissue fibrinogen" which

when the endothelial barrier is broken, unites with the blood fibrinogen. This union results in the deposition of fibrin and the initiation of a thrombus.

3. The growth of a thrombus after its inception is governed by the laws of blood coagulation. Its physical appearance is influenced to a great extent by the mechanics of the circulation in the vessel in which it forms.

4. Infection and operative trauma produce endothelial injury. Infection may reach the endothelium by contiguity, by way of the vessel lumen or possibly by way of the vasa vasorum.

5. Thrombi in infected tissue do not become organized speedily and securely and are potential emboli.

6. Changes in the blood composition and changes in the mechanics of the blood circulation are factors predisposing thrombosis.

Bibliography

1. Aschoff, Ludwig..Arch.Int.Med.,12:503-525,1913
2. Bancroft,F.W.,Kugelmass, I.N.,
and Stanley-Brown, M., Annals Surg.,89:161-189,1929
3. DeQuervain,F.....Schweiz.med.Wchnschr.,45:497-505,1925
4. Eberth and Schimmelbusch
(Quoted by Welch)..Papers and Addresses,J.Hopkins Press,3 Vols.,1920.
5. Fraenkel,A.....Arch.f.klin.Chir.,86:531-545,1908
6. Hampton, H.H. and
Wharton,L.R.....Bull.J.Hopkins Hosp.,31:95-117, 1920.
7. Heard,J.E.,.....New Orleans M. and S.J.,76: 451-459, 1924
8. Hegler, C.....Zeitschr.f.Ärztl.Fortbild., 26:48-53,1929.
9. Hertzler,A.E.....Surg.Path. of Skin,Fascia, Muscles, Tendons and Blood Vessels, pp.270-291,Lippincott, 1931.
10. MacCallum,W.G.....Textbook of Pathology,Ed.3, p.13,Saunders,1924.
11. Maximow and Bloom..Textbook of Histology,p.352, Saunders,1930

12. Mills, C.A.....Am.J.Med.Sc.,172:501-510,1926 .

13. Mills, C.A.....Ann.Surg.,91:489-491,1930.

14. Mills, C.A.....Am.J.Physiol.,95:1-6,1930.

15. Ritter, Adolph.....On the Importance of Endo-Thelium in Etiology of Throm-bosis, Jena,Verlag v. G. Fischer,1926.

16. Rowntree,L.G.,Shinoya,T., and Johnson,W.R.....Collected Papers, Mayo Clinic, 19:681-685, 1927.

17. Schilling.....Quoted by J.A.Victor, Ann.Surg., 82:193-198,1925.

18. Welch,W.H.....Papers and Addresses,Johns Hopkins Press, 3 Vols.,1920.

19. White, P.D.....Heart Disease, p.348,Macmillan Co.,1931.

20. Zurhelle.....Verhand.d.Gesell.Deut.Natur. V.Aerzte, 1907.

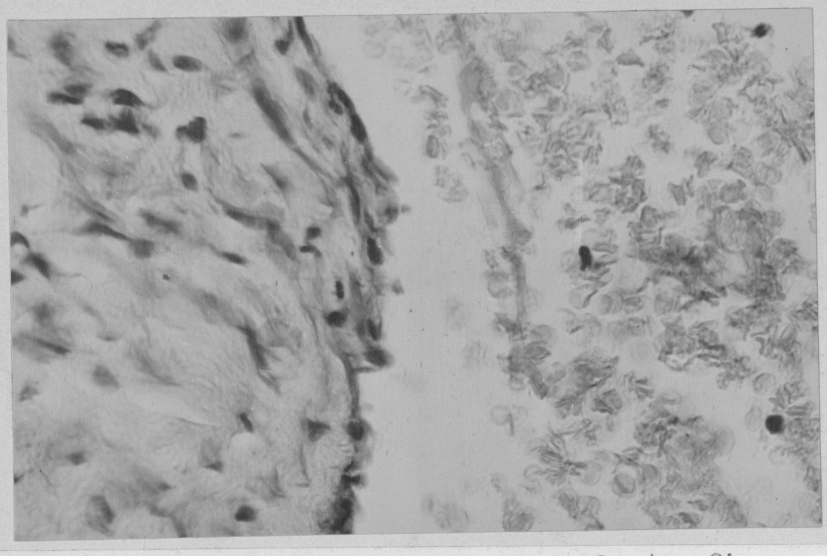

Fig. 1. Wall of blood vessel forty-five days after careful double ligation. Endothelium and blood cells are intact and there is no evidence of thrombus formation.

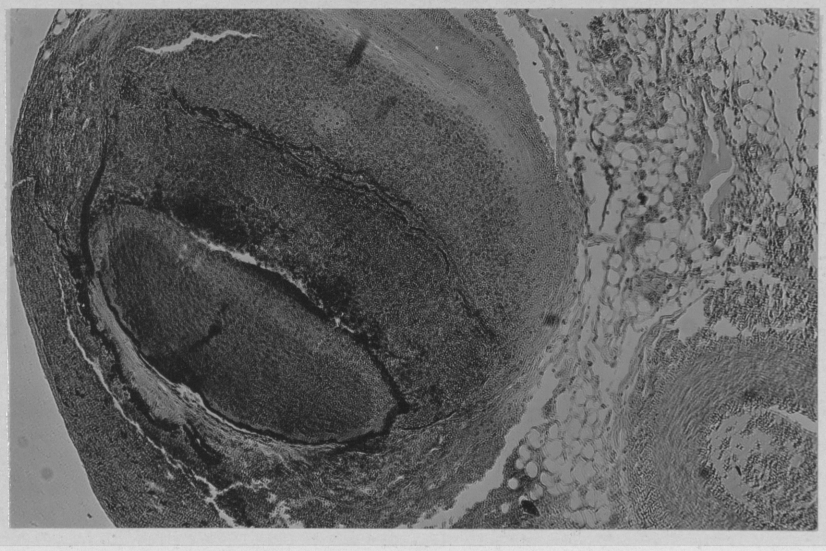

Fig. 2. Cross section of jugular vein; black precipitation of silver in subendothelial tissues. Blood immediately adjacent is not thrombosed. That at a distance is definitely thrombosed.

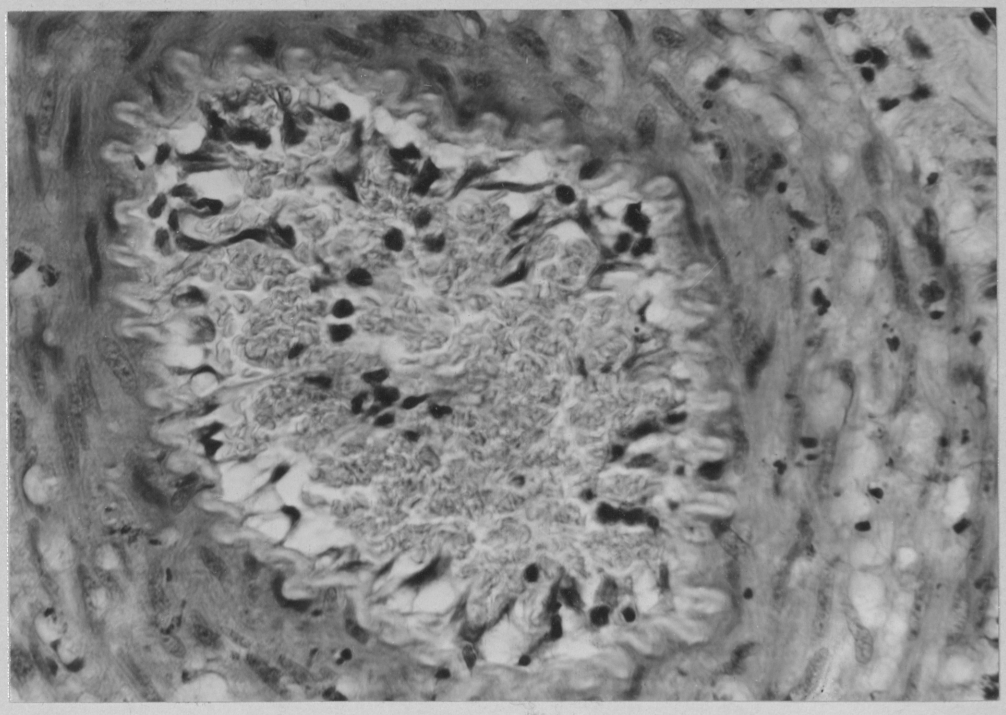

Fig. 3. Appendiceal artery in an acutely inflamed appendix. Endothelial cells are spindleform and lie with long axis in a radial position. Blood shows beginning thrombosis.

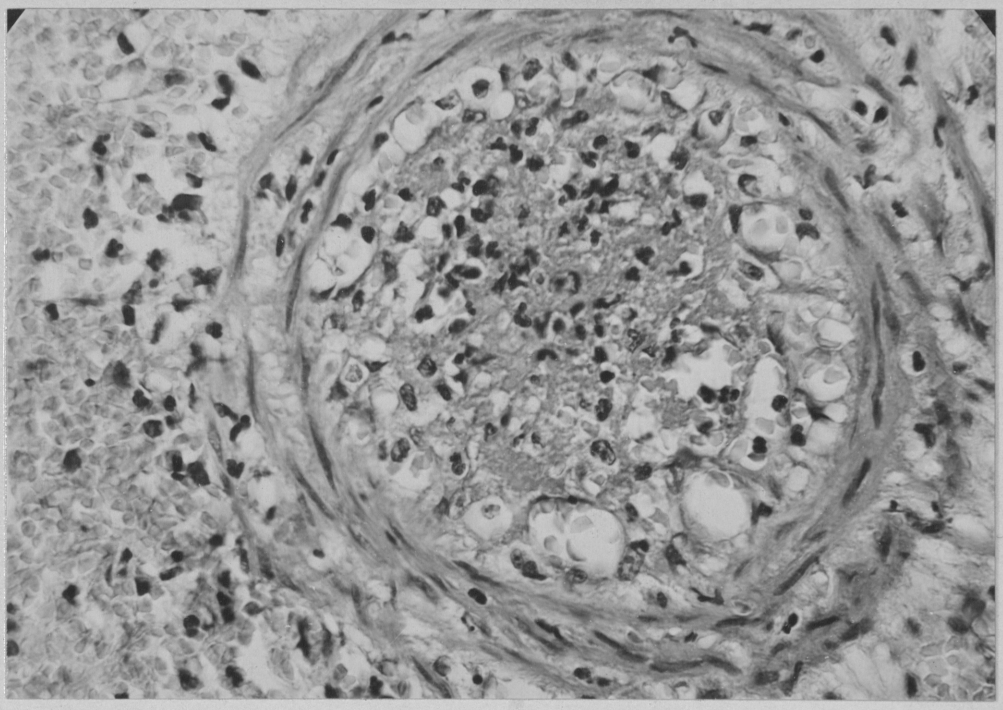

Fig. 4. Further advanced reaction of endothelial cells to inflammation. Definite thrombosis of blood.