Diseases of the Mediastinum.—The diseases of the mediastinum are acute and chronic mediastinitis, and mediastinal tumors.

Mediastinitis.—The etiology of inflammations in this region includes traumatism, extension from adjacent organs, and tuberculosis. The anterior mediastinum is by far the most frequently attacked. The symptoms of the acute and chronic forms are much the same except that in the former they are more intense. Pain is present in all cases and is located behind the sternum, from which it radiates to the shoulder blades. The sternum is often tender on pressure and may become red and œdematous. Fever is present particularly at the beginning, and in the acute cases may be accompanied by chills and sweating. As soon as pus has formed pressure symptoms may make their appearance, including dyspnœa and heart weakness. The abscess may finally work its way to the surface and point either in some intercostal space close to the sternum or at some more distant part. Rupture into the diaphragm, trachea, or pleural cavity may also occur. The treatment consists in evacuating the pus at the place where the abscess points, or in opening the anterior or posterior mediastinum. The anterior mediastinum is opened by resection of one or more ribs or costal cartilages, and the adjacent sternum. The posterior mediastinum has only seldom been attacked. On the cadaver it has been shown that removal of a transverse process of a vertebra and the underlying piece of rib gives a good opening for the discharge of pus.

Tumors of the mediastinum include the benign and malignant. Glandular enlargements form a goodly percentage of these new growths. Some of the tumors are primary, others are secondary. The benign tumors include fibroma, lipoma, and dermoid cysts. The malignant tumors, both carcinoma and sarcoma, may have their origin in the bronchial glands or in the bronchi themselves. In all varieties the symptoms are practically the same, and are chiefly those of pressure. The heart, lungs, large vessels, nerves, œsophagus, and trachea may be compressed and their function impaired. Furthermore, the chest wall may be pushed forward and ultimately the tumor may come to lie beneath or perforate the skin. Malignant tumors run a more rapid course than the benign, and may cause death before the tumor has appeared externally. Percussion is dull or flat over the tumor when it is situated close behind the sternum. Pressure upon the recurrent laryngeal nerve causes paralysis of the vocal cord on the same side. Pressure on the pneumogastric may result at first in slowing of the pulse, later in acceleration of the same.

The differential diagnosis from aortic aneurism can usually be made from its history and from the presence in the latter of arteriosclerosis, aortic insufficiency, friction sounds, etc.

As regards the prognosis the differentiation of the benign from the malignant tumors is of extreme importance. The malignant are the more common, and whether primary or secondary can usually be recognized by their more rapid growth, by the presence of glandular enlargements, by the greater severity of the pain, and by the rapid loss of flesh and strength.

The treatment may be begun by the internal administration of potassium iodide or arsenic, and in case of syphilitic lymphomata, malignant lymphomata, and some sarcomata a diminution in the size of the tumors will result. Other cases will call for active surgical treatment, and this should not be delayed too long either in the malignant or in the benign forms. The operation is the same as in suppurative mediastinitis, except that more room will be necessary for removing the growths than for opening the abscess. Excision of several ribs and part of the sternum or temporary osteoplastic resection of ribs by means of a flap of skin, muscle, and bone furnishes a good exposure of the anterior mediastinum. Through such an opening the tumor masses are enucleated, care being taken not to injure the pleura or the pericardium. If such an accident occurs, the opening is closed at once by suture or the wound packed, and the operation put off to a second sitting. Excessive hemorrhage may be another reason for postponing the completion of the operation. The benign as well as the malignant tumors may require extensive dissection, although adhesions with adjacent structures are more intimate in the malignant forms.

Diseases of the Pericardium.—As in the pleura exudations occasionally take place within the pericardium. Of these the suppurative form will demand surgical interference. Collections of serum or of blood may be removed by aspiration, but, should this not be sufficient, incision may be resorted to. Purulent collections, just as in empyema, require for a cure incision and drainage. Puncture and aspiration are frequently resorted to in making the diagnosis of the presence and character of the exudate. A safe place for puncturing the pericardium is at a point between the fifth and sixth ribs, close to the sternum. The third or fourth intercostal space can also be chosen. Care must be taken not to injure the internal mammary artery which lies at a distance of from 1 to 2.5 cm. to the outer side of the sternum. Puncture is performed with an aspirating needle or a trocar. As the heart may be pushed forward by the exudate behind and thus lie close to the anterior thoracic wall, care must be exercised in not injuring that organ. The instrument is thrust in cautiously in an upward direction, and it is often possible to feel the heart come in contact with the point of the needle. Délorme collected eighty-two cases of puncture of the pericardium with twenty-eight cures.

Incision of the pericardium may be performed through a variety of incisions. Ollier's incision seems the simplest and answers the purpose. The incision runs from the middle of the sternum along the centre of the fifth costal cartilage. The latter is dissected free, resected with a knife or bone-cutting forceps, and the internal mammary artery tied. In case sufficient room is not obtained, a piece of the sternum is resected. Another incision (Délorme) begins 1 cm. from the left border of the sternum and runs from the fourth to the seventh costal cartilage. Two short lateral incisions are made outward from each end of the longitudinal one, and the flap is turned back. The cartilages of the fifth and sixth ribs are resected, care being taken not to wound the internal mammary artery. Drainage is provided for by means of a rubber drainage tube inserted into the cavity. Among thirty-five cases of suppurative pericarditis operated upon by incision and drainage, Kobert found that forty-three per cent. recovered.

Benjamin T. Tilton.

THOROUGHWORT.—(*Eupatorium* U. S. P.; Boneset.) The dried leaves and flowering tops of *Eupatorium perfoliatum* L. (fam. *Compositæ*). This is a widely spread species, growing in the greatest abundance about the borders of ponds and brooks, and in wet places generally, from Canada to Florida, and from the eastern to the western side of this country. It is a handsome, large, perennial herb, with a hairy, rather simple stem, growing from two to four or more feet high, large, dark green and completely connate pairs of rough hairy leaves, and flattened, complex, cymose clusters of small heads of minute creamy-white flowers.

Description of Drug.—Leaves opposite, the two united by their broad bases, the uppermost often distinct, those of the inflorescence mostly alternate and greatly reduced; 8–15 cm. (3–6 in.) long and 1.5–5 cm. (⅝–2 in.) broad, tapering regularly from near the base to an acute apex, crenate-serrate, above bright green or somewhat yellowish-green, rugose and finely bullate; underneath yellowish-gray-green, densely short hairy and resinous dotted, the prominent, rounded, crooked, fine veins conspicuously reticulated; flower-heads very numerous, in broad corymbs, the branches rough hairy; mature involucre campanulate, the imbricated scales lance-oblong, obtusish, green, hairy, the inner longer and with whitish tips and margins; flowers of the head about ten to sixteen, tubular, yellowish-white, the pappus in a single

row, white, bristly; odor weak, aromatic; taste bitter, astringent, aromatic.

The constituents of thoroughwort are chiefly the bitter glucoside eupatorin, which is soluble both in alcohol and in boiling water, a very small amount of volatile oil, a glucosidal tannin, which constitutes the coloring matter, and another tannin. There are also gum, resin, and ordinary plant constituents. The presence of an alkaloid has been reported, but this subject requires further investigation.

Use.—Boneset has been long used in the United States as a tonic and antiperiodic, and even as an emetic, but always more of a family medicine than one prescribed by physicians. Since the beginning of the last century it has fallen very much into disuse. In small doses thoroughwort is a mild bitter tonic, like the chamomiles and others in the same family, but with less aromatic character than most of them. It is also a good deal like horehound in the *Labiatæ*. In larger doses, especially in hot infusion, it is diaphoretic, possibly diuretic, and is still occasionally used, followed by a sweat under blankets, to abort colds, and in the beginning of most acute diseases. In very large doses (an infusion of an ounce or so) it is a nauseating emetic. Doses as large as can be borne by the stomach, repeated for some days, have had a considerable reputation in the country, and have a little real value, in the treatment of intermittent fever and other malarial manifestations.

In domestic practice thoroughwort is usually given in the form of a decoction, especially when its diaphoretic, antirheumatic, or antiperiodic action is desired. Physicians also often prescribe it in that way, though more often at the present time in the form of the fluid extract. The dose of the latter, of which 1 c.c. is the equivalent of 1 gm. of the drug, is 10–15 minims as a tonic, 1–4 c.c. (fl. ʒ ¼–i.) as a diaphoretic and antiperiodic, and two or three times as much as an emetic.

Allied Species.—The genus *Eupatorium* comprises many hundreds of species, a large number of which, in various countries, are employed similarly to the above. Numerous plants belonging to related genera have similar properties. (See *Compositæ*.) *Henry H. Rusby.*

THREE SPRINGS.—Huntingdon County, Pennsylvania.

Post-Office.—Three Springs. Hotels and sanitarium.

Access.—Take the Pennsylvania Railroad (main line) to Mount Union, Pa.; thence take East Broad Top Railroad to springs.

The village of Three Springs is located in a valley formed by Jack's Mountain, 2,220 feet high, and Care Hill, 2,210 feet in altitude. The place takes its name from the presence of three mineral springs, situated about one hundred feet apart, and forming the corners of an equilateral triangle. The springs are known as "No. 1," "No. 2," and "No. 3." They have been known and used for many years, but it was not until 1891 that they came under control of the present proprietor, who has brought them to an advanced state of development as a resort. Spring No. 1, the most important of the group, flows about one thousand gallons of water per hour, having a temperature of 55° F. It is used commercially under the name of the Hygeia Natural Mineral Water, and is shipped in five-gallon demijohns. The following analysis was made in 1895 by Prof. G. G. Pond, of the Pennsylvania State College:

Spring No. 1 (Three Springs). One United States gallon contains (solids): Calcium bicarbonate, gr. 34; calcium sulphate, gr. 53.63; magnesium sulphate, gr. 33.54; sodium sulphate, gr. 5.91; sodium chloride, gr. 0.35; lithium sulphate, gr. 0.02; potassium sulphate, a trace; silica, gr. 1.15. Total, 128.6 grains.

Gases: Carbonic acid, cub. in. 5.47; oxygen, cub. in. 1.72; nitrogen, cub. in. 3.85. The water is bright, sparkling, and palatable, and entirely free from organic impurities. It is an efficient laxative and mild diuretic and has been found beneficial in cases in which activity of the emunctories is desirable. The water has been used with success in cases of obesity and in uræmia and general anasarca, as well as in local dropsies. In habitual constipation a systematic course of the water is often curative. It is also beneficial in other disorders requiring a sulphureted saline water. The sanitarium at Three Springs is kept open all the year. *James K. Crook.*

THROMBOSIS.—Definition.—Thrombosis is a pathological state or process in which there is a deposit within the heart or vessels, during life, of solid material originating in transformation of the blood.

The solid mass or plug thus produced is called a *thrombus*.

It used to be taught that thrombosis was caused by the coagulation of the blood, but fuller researches, more especially those of Eberth and Schimmelbusch, have proved that many thrombi, at least at first, are due to the agglutination of blood platelets or of corpuscles without fibrin formation, so that it is more correct to adopt a wider definition, such as that given above.

Varieties of Thrombi.—Any or all of the formed elements of the blood or their derivatives may enter into the composition of thrombi, viz., red corpuscles, leucocytes, blood platelets, and fibrin.

Red Thrombi.—These are produced in stagnating blood and are strictly comparable to clots formed outside the body, being composed of fibrillated fibrin, red and white cells, in much the same proportion as in ordinary clots.

White Thrombi.—Thrombi deposited from the circulating blood are generally of the white variety. The characteristic color, whence they derive their name, is due to the presence in excess of fibrin, leucocytes, and platelets. It is not, however, uncommon to find *mixed thrombi* in which there is an admixture of red cells, giving them a somewhat reddish tint. When recent, white thrombi under the microscope are composed of granular material having the form of clumps or strands of irregular size and shape which are embedded in fibrin, leucocytes, and a certain number of red cells. The granular matter in question is composed of altered blood platelets. The fibrin has frequently a distinct fibrillated structure, and is particularly abundant at the periphery of the masses of platelets, sending anastomosing branches into their substance or forming a loose meshwork in which red cells are entangled.

Fibrin Thrombi.—These are not infrequently found in inflamed areas, usually in the smaller vessels. They may be seen particularly well in the vessels of the lung in croupous pneumonia. According to K. Zenker, who has described them in detail, whorls or brush-like tufts of coarse fibrin may be seen springing from the wall of the vessel. These appear to radiate from a definite centre composed of degenerating material, such as endothelial cells, leucocytes, blood platelets, or débris. The amount of deposit is not usually sufficient completely to block the vessel. In old white thrombi also the cellular elements degenerate and are replaced by fibrin.

Leucocytic Thrombi.—As has been already hinted, leucocytes enter into the formation of a large proportion of white and mixed thrombi; but thrombi composed almost entirely of white cells are also to be met with, particularly in areas that are acutely inflamed. In this case the condition is really a capillaritis, arteritis, or phlebitis, and the plug is due to the accumulation of leucocytes attracted to the spot by chemotaxis. Somewhat similar masses are seen within the vessels in cases of leukæmia, but these are perhaps not strictly to be regarded as thrombi.

Hyaline Thrombi.—For the recognition of this form we are indebted to von Recklinghausen. Hyaline thrombi are found chiefly in the capillaries, but also in the smaller veins and arteries. The lumen of the affected vessel is filled with a homogeneous, translucent, and refractile substance, without color, or at most having a faint yellowish tinge, which gives the microchemical reactions for fibrin. This variety is found more especially in toxic and infective conditions and after exposure to heat

and cold. The most striking examples of it, according to Welch, are to be found in the renal capillaries of swine dying of hog cholera. It is also met with in pneumonia, hemorrhagic infarction, frost-bite, and eclampsia.

The Chemico-Physics of Thrombosis.—Until we are able to give a more complete explanation of the process of coagulation of the blood, we shall still be more or less in the dark as to the nature of thrombosis. As with all vital and semi-vital processes, the subject is beset with difficulties. According to the most painstaking investigators coagulation is a chemical process whereby the interaction of certain substances results in the precipitation of insoluble material. According to Schmidt ("Zur Blutlehre," Leipsic, 1893) the following are the determining factors: (1) Soluble proteids of the nature of globulin, with their derivative fibrinogen. (2) A fibrin ferment to act upon the substances just mentioned. (3) Various neutral salts, but especially those of calcium, which form insoluble compounds. Arthus and Pages (*Arch. de Phys.*, ii., 1890) have shown that without the intervention of calcium salts fibrinogen cannot give rise to fibrin, for if potassium oxalate be added to fresh blood in sufficient amount to precipitate the calcium salts, clotting will not occur; while if calcium salts be restored, clotting will rapidly take place. Pekelharing (*Festschrift f. Virchow*, Berlin, 1891, and *Deutsche med. Woch.*, 1892), basing his opinion on the fact that a nucleo-albumin can be isolated from the plasma, which when brought in contact with fibrinogen and salts of calcium produces a typical clot, believes that the fibrin ferment or "thrombin" of Schmidt is a combination of nucleo-albumin and calcium. When this is brought into contact with fibrinogen the calcium radical unites with a portion of the fibrinogen molecule to form an insoluble salt, fibrin. Fibrinogen and calcium salts are to be found in the blood plasma, while the nucleo-albumin is a product of the disintegration of the leucocytes and perhaps the hæmatoblasts. In terms of this theory, then, fibrin is an end-product of the chemical interaction of nucleo-albuminate of calcium and fibrinogen.

Besides this, however, the researches of Lister, Brücke, Baumgarten, and Freund have proved that certain mechanical principles enter into the question of coagulation. If, as was done by Lister, a section of a large vessel containing blood be isolated between double ligatures and removed, the blood will remain fluid for hours; and further, if the vessel be divided transversely into two so as to form, as it were, two test tubes, the blood may be poured from one portion to the other almost indefinitely without coagulating. The reason for this is not entirely clear. But Freund has shown (*Wiener med. Jahrb.*, 1888) that, provided decomposition be prevented, blood which has been received into glass vessels smeared with vaseline will remain fluid for a long time. A similar result follows if blood be dropped into some perfectly bland fluid such as oil. Freund thinks that when the vessel is not lubricated in this way the surface of the glass destroys some of the red corpuscles, and that this initiates coagulation. However this may be, the experiment at least shows that what are at first sight trivial changes in the condition of the vessel wall are sufficient to induce coagulation. However, something more than mere contact with a foreign surface appears to be necessary. Changes must be present of such a nature as to promote adhesion between the vessel wall and the corpuscles, especially the red cells. Small glass balls, presenting a smooth, unirritating surface may be introduced into the blood-vessels with impunity, as in Zahn's experiment (*Festschrift f. Virchow, Internat. Beitr.*, ii., p. 199); while if needles or other sharp objects be inserted, the blood-platelets are precipitated and thrombosis is rapidly induced. Anything, therefore, that impairs the integrity of the vessel wall, be it in the slightest degree, may on occasion determine thrombosis.

It may be asked why it is that coagulation of the blood does not take place under the conditions of normal existence. All the elements for the production of fibrin are in fact present, for there is constant disintegration of the red cells with liberation of nucleo-proteid; but so long as the vessel walls remain intact, the amount of nucleo-proteid is but small, and it is quickly neutralized or metamorphosed and thus rendered innocuous. The fact that it is difficult to produce thrombosis by the injection into the circulation of nucleo-albumins proves that up to a certain point the body is able to protect itself against coagulation. Lilienfeld has further shown that under certain circumstances during disintegration of leucocytes a proteid is formed, which he terms *histon*, that has the power to prevent clotting.

Numerous experiments, as well as clinical observations, have led us to realize that a variety of factors are concerned in the process of thrombosis. Most are, I think, agreed that the following points are of cardinal importance, although there is not always unanimity as to the relative value of each: (1) Alterations in the vessel wall, whereby the blood is brought into contact with an abnormal surface. (2) Slowing or other irregularities of the blood current. (3) Changes in the blood itself. As the sequel will show, it is beyond question that the action and reaction of the various factors mentioned are intimately bound up together.

It may be inferred, and rightly, from the experiments above referred to, that gross physical changes in the condition of the vessel wall are of powerful import in the causation of thrombosis, particularly if they be such as to impair the continuity of the intima or produce obstruction. Injuries or disease of the vessel walls, and foreign bodies of all kinds within the lumen, such as needles, bones, wire, lime salts, bits of tumor, and parasites, may act in this way. Advantage is taken of this fact in the well-known treatment of aneurisms by the insertion of fine wire. The thrombus itself often acts as a foreign body, a fact which explains its tendency to spread. Yet it is frequently observed at autopsies that the most extensive disease with roughness of the intima may exist, as in atheroma, without the formation of a thrombus. Again, Zenker has noted that degenerating endothelium often forms a nucleus for the deposition of fibrin, so that a star-like clot is formed. If, too, we inflict an aseptic injury on the valves of the heart in an experimental animal, relatively little thrombosis results. Should we, however, inject pyogenic micro-organisms at the same time, we get the most pronounced effects. Such observations suggest that in thrombosis, besides mechanical factors, chemical changes have to be taken into account, and it would appear necessary to assume certain specific properties on the part of the intimal cells and the injured tissue. This is further indicated by numerous experiments which have proved that certain substances introduced into the blood have the power of inducing coagulation. Such are thymus extract, laky blood, defibrinated blood, ether, tissue juices, snake venom, and biliary salts, among others. These substances probably act by affecting the vitality of the intimal cells, or possibly, as some think, by liberating the fibrin ferment. It is by no means proved, however, that the clots thus produced are identical with ordinary thrombi. In fact, there is every reason to think that they are not. It must, nevertheless, I think, be admitted that circulating toxins or perverted metabolism in the blood induce important alterations in the properties of the intimal cells, for, as we know, there is a decided tendency in many infective and cachectic states for thrombosis to occur. It is, perhaps, mainly in this way that the so-called "ferment thrombi" are produced.

Slowing of the blood stream has been referred to as one of the factors concerned in the production of thrombi. This in itself cannot be of prime importance since numerous experiments, notably those of Glénard and Baumgarten, have shown that the circulation may be completely obstructed within a vessel, by the application of aseptic ligatures, without thrombosis resulting. It is, nevertheless, a fact that thrombi are apt to form just where the circulation is feeblest, as in the veins and diverticula of the vascular apparatus. It would seem to be necessary, however, that some lesion of the vessel

wall should exist as well, and this as a matter of fact is generally present, owing to the impoverished nutrition resulting from the impaired blood flow. A slow circulation, therefore, determines the place rather than the fact of thrombosis. Baumgarten, indeed, attributes more importance to eddies in the blood than to mere slowing of the stream, and has laid stress upon the fact that thrombi are commonly formed in culs-de-sac, dilated chambers (dilatation thrombi of Virchow), and about the valves of the veins, in fact, where eddies are naturally produced. He has, moreover, shown that a carefully tied ligature, leading as it does to stagnation of the blood, need not necessarily result in the formation of a thrombus unless the inner lining of the vessel be ruptured.

Two main forms may be differentiated in this group of so-called "stagnation" thrombi, viz., those found in conditions of great prostration and cardiac weakness, called by Virchow, who regarded them as due to marasmus, "marantic" thrombi, and those due to local circulatory disturbances, as in aneurisms and varices, and in obstruction of the vessels. Not all the so-called "marantic" thrombi can be rightly attributed to marasmus, as it is impossible in such cases to exclude vitiated conditions of the blood and degenerative changes in the lining endothelium. Many of them are, no doubt, toxic in nature, due to accidental or terminal infection.

Little is known as yet with regard to the changes in the blood that favor thrombosis. Changes are, however, undoubtedly present in such cases as the infectious fevers, in snake-bite, arsenical poisoning, severe burns, and trauma. Weir Mitchell long ago pointed out that one of the characteristic features of snake-bite was the agglutination of the red corpuscles, and similar properties have been abundantly shown by more recent experiments to be possessed by a number of substances of which may be mentioned abrin, ricin, the blood serum of another race of animal, the toxins of certain bacteria as those of typhoid, hog cholera, pneumonia, and diphtheria. It is probable, therefore, that the so-called "ferment" thrombi and the agglutinative or hyaline thrombi are largely due to a toxin acting upon the red cells so as to destroy them and produce a uniform conglomerate.

In other ways, too, thrombosis may be promoted. In some diseases in which there are marked leucocytosis and an increase in the fibrin content of the blood, thrombosis is not infrequent. In others, like typhoid, in which there is leucopenia, thrombi are rare, at least during the height of the disease. When they are present in typhoid, it is only in the later stages, when the circulation is feeble, the vessels are relaxed, and there is an increase in the number of leucocytes, with possibly a secondary infection. It is here, again, impossible to exclude changes in the endothelium.

The Mode of Development of Thrombi.—It is a common event to find within the heart and great vessels at autopsy large soft clots of varying appearance. These are produced during the death agony or shortly after. When clotting has been rapid, a uniform, dark red, soft coagulum is formed, not differing specially from that produced in the process of extravascular coagulation. In cases in which clotting is slower, the red cells, being specifically heavier than the white, sink to the bottom, and the uppermost layers of the clot form a soft, yellowish, or buffy portion, while the deeper parts are of a reddish, raspberry-jelly-like appearance. In cases in which during life leucocytosis has been marked, as in inflammatory rheumatism and pneumonia, large yellowish, oily looking clots are produced. Such clots are readily distinguished from those produced during life by the fact that they lack the firm granular structure, and are only loosely adherent to the wall of the heart or vessel.

Very different are the real thrombi. When the blood is stagnating or the circulation prevented, red thrombi are formed, provided that the ordinary conditions favoring the deposition of fibrin are operative. Under the microscope these thrombi consist of masses of red cells, among which coarser or finer strands of fibrin can be seen together with an occasional leucocyte. At first the thrombus is soft and juicy, but later it becomes firm and dry, and presents a paler or a brownish or rusty appearance.

Zahn's researches (*Arch. f. path. Anat.*, Bd. xcvi., 1884) have shown that the essential factor for the production of a white thrombus is a continuous circulation. In the circulating blood-stream two regions are to be distinguished, an axial and a peripheral. The axial stream contains the red and white cells, while the more slowly moving peripheral current is chiefly plasma with an occasional leucocyte floating in it. Should the rapidity of the circulation be diminished, the number of the white cells in the peripheral zone is notably increased, and in the more extreme cases blood-platelets begin to make their appearance. The exact part played by the blood-platelets has given rise to much debate. Bizzozero (*Centralb. f. Deut. med. Wiss.*, 1882, 1883) believed that in the course of their destruction they liberated the fibrin, but his conclusion has been by no means generally accepted.

If, as Eberth and Schimmelbusch did (*Arch. f. path. Anat.*, Bd. ciii., cv., cviii.), we injure the mesenteric vessels in a warm-blooded animal, as, for instance, by silver nitrate, blood platelets are quickly deposited and become massed at the site of injury (conglutination), and eventually are fused into a more or less coarsely granular or homogeneous material (viscous metamorphosis). In some cases these deposits are cast off into the general circulation, but frequently they keep on enlarging until the lumen of the vessel becomes occluded. An occasional red or white cell can be made out in the mass, but these are clearly accidental, and have nothing to do with the initiation of the process. Very early in the experiment, namely, within fifteen or twenty minutes, as Welch has shown (Trans. Path. Soc. of Phila., xiii., 1887), leucocytes make their appearance in considerable numbers, and must now be regarded as taking an important part in the process. The leucocytes are chiefly of the polynuclear variety, and tend to accumulate at the edge of the clumps of platelets and to some extent between them. As soon as this takes place fibrils of fibrin are formed in close relationship to the white cells, while they are absent near the conglutinated platelets. Sooner or later, the period varying in different cases, a plug is formed consisting of platelets, leucocytes, and fibrin, in which a number of red cells are entangled, reproducing with great accuracy the appearance of the thrombi found in the human subject. No doubt all thrombi do not develop in this way, for there are some, notably the white mural thrombi, that are chiefly composed of white cells, as are those found in the small vessels of an acutely inflamed area. In the latter case the leucocytes are attracted by chemotaxis, and the whole process is obviously inflammatory.

As the white thrombus increases in size it gradually encroaches upon the axial stream, with the result that red cells become entangled in it and a mixed thrombus is produced. A somewhat similar result is brought about by alternating slow and rapid coagulation of the blood, such as occurs in aneurismal sacs, where the clots are commonly found to be laminated, or where the thrombi contract and leave crannies into which the red cells may penetrate. When occlusion of the vessel has taken place, a red thrombus may be superadded upon the white or mixed one (secondary or propagated thrombus).

A thrombus in its early stage, when simply attached to one side of a vessel wall, is called a *parietal* or *mural thrombus;* but when by continuous accretion it has filled up the entire lumen of the vessel, it is called an *occluding* or *obstructing thrombus.*

The Fate of Thrombi.—The thrombus in its original situation is called a *primary* or *autochthonous thrombus*, but it is quite a common event for the process to spread until a considerable section of the vascular district is involved—*secondary thrombosis.* As a rule, thrombi grow in length in the direction of the blood stream, but exceptions occur. The advancing end has usually the shape of a flattened blunt cone, and the process extends as far

as the next lateral branch. The appearances produced in an advancing thrombus are very striking. The primary thrombus is white or mixed, while the secondary thrombus is red. The secondary thrombus extends along the vessel to the nearest collateral branch, where it comes into contact with the circulating blood, with the result that a white thrombus is formed. This in turn grows until the mouth of the collateral vessel is occluded and a red clot is again formed, and so on almost indefinitely. In this way the circulation may be gravely interfered with over large areas.

Small thrombi may be absorbed and disappear, but the larger ones, provided the patient live, undergo various interesting transformations. Within a very few days of the formation of the thrombus notable changes set in, of which may be mentioned hyaline-granular transformation, organization, simple softening, and puriform liquefaction.

The *hyaline-granular transformation* is marked by the disintegration of the red and white cells. The hæmoglobin is dissolved out, diffuses itself among the fibrin, and is deposited or metamorphosed in various ways. The cells, fibrin, and platelets become finally a granular mass in which the granules become increasingly fine and are eventually fused into a homogeneous, translucent, hyaline-looking material. The chromatin of the leucocytes is liberated, and the thrombus shrinks, becomes more solid, and often assumes a reddish or reddish-brown color. Old thrombi not infrequently become fissured and fragmented, so that fresh reddish clot is deposited in the interstices. In the peripheral portions, too, inflammatory leucocytes and wandering cells from the vasa vasorum may be observed. By this method the thrombus may become so reduced in size that the lumen of the vessel may be reopened and, if these changes occur in an area upon which an operation has recently been performed, secondary hemorrhage may result. As a rule, the thrombus remains firmly attached to the vessel wall, but occasionally it breaks loose and forms an embolus with its ordinary results.

In cases in which the thrombus is bland and not infected it becomes organized into connective tissue. Starting at the place where the clot adheres to the vessel wall a thin layer of endothelium, derived from the lining of the intima of the unaffected parts near by, extends over the surface of the thrombus. Underneath this investment a zone of connective tissue is developed, apparently due to the proliferation of these endothelial cells. The endothelial cells divide and the newly formed cells invade the substance of the thrombus and secrete an intercellular substance. Synchronously with this process the thrombus becomes vascularized from the vasa vasorum and also from the endothelial investment. Fibrous tissue cells are carried in along with the capillaries and form an adventitia to them. The new-formed connective tissue, according to Thoma ("Text-book," vol. i., Eng. trans., p. 285, 1896), is thus a product of the vessel walls. In time the newly formed channels, derived from the endothelial lining on the one hand and the vasa vasorum on the other, meet and vascularization is complete. The portion of the original thrombus between the capillaries is gradually absorbed and the whole mass becomes transformed into a fibrous plug, which undergoes cicatricial contraction. In some cases, as a result of this process, only a few traces are left of the original thrombus in the form of small nodular thickenings of the vessel wall or a few delicate bands traversing the vessel. Not infrequently, however, absorption is not so complete, and new vascular channels are tunnelled through the thrombus. These become lined with endothelium and thus restore more or less completely the integrity of the circulation—the so-called "canalization" of the thrombus.

In *simple softening* the thrombus is converted into a pulpy, dirty-looking mass. This probably results from the action of unorganized ferments contained in the clot; but it is not always possible in these cases to exclude the action of micro-organisms. Simple liquefactive necrosis is particularly well seen in the case of the "ball thrombi" of the heart cavities, where central softening is occasionally found. Such softening may result in the formation of something like a cyst. The soft material is composed of the degenerated and granular components of the clot, and has a creamy-whitish or grayish-yellow appearance, not unlike pus, whence it has been called by some puriform softening.

Septic softening is usually found in cases of thrombophlebitis, and is a true suppuration of the clot due to the action of pyogenic micro-organisms, among which the streptococcus is a common offender.

Putrid liquefaction is due to the presence of putrefactive germs, and in this case the clot assumes a dirty brown or green color and emits a foul odor. The softening of septic thrombi and the subsequent dissemination of the infected products in the general blood stream is one of the common causes of systemic septicopyæmia.

Many thrombi undergo calcification. This is found commonly in the prostatic plexus, the broad ligaments, and in the spleen, in which localities there are formed small spherical concretions which lie loosely in the vessel. When present in the veins they are called *phleboliths;* when in the arteries, *arterioliths.*

Localization of Thrombi.—Thrombi may be formed in any part of the vascular or the lymphatic system. Consequently we may conveniently divide them into *cardiac, arterial, capillary, venous,* and *lymphatic thrombi.*

The site of election of thrombosis is in the medium-sized veins where the various anatomical and mechanical peculiarities before referred to, viz., a slow blood current, eddies, and counter-eddies in the stream, obstructions and dilatations, are found in the greatest perfection. Here such questions as the length and obliquity of the venous channels, the presence of valves, the fixation of the vessel walls to fascia, the flow of the blood from a smaller into a larger cavity, play an important rôle. Marantic thrombi are apt to be formed in the veins, particularly of the extremities, and in the large venous sinuses, while those due to infection and angiosclerosis are commonly in the arteries. Numerous exceptions to this generalization, however, might be cited.

Clinically speaking, the most frequent points for the development of thrombi are the vessels of the extremities, especially the lower, the cerebral arteries and sinuses, the portal vein, the inferior vena cava, and occasionally the renal and mesenteric vessels. Many conditions of extensive thrombosis, however, lead to no clinical symptoms, and the presence of thrombi may not even be suspected. Consequently a study of the subject from a post-mortem point of view reveals a somewhat different state of affairs. In this case intracardiac thrombi, and next to these the mesenteric, iliac, and cerebral, are more in evidence.

Leaving out of account post-mortem clots, which are not to be classed with the true thrombi, and cases of acute endocarditis, I have made an analysis of the fatal cases that have occurred at the Royal Victoria Hospital, Montreal, in 688 autopsies of which I have notes. Thrombosis occurred 66 times, or in nearly 10 per cent. of the cases. These were localized as follows: Intracardiac 16, mesenteric 9, aneurismal 8, common iliac veins 7, cerebral arteries 6, inferior vena cava 5, ovarian veins 4, portal 3, splenic vein 3, meningeal, left axillary vein, crural veins, coronary arteries, 2 examples of each; the aorta, pulmonary artery, popliteal vein, brachial vein, pelvic and omental veins, once each. In many cases, however, the thrombi were diffuse or multiple.

We may say in general terms that thrombosis in the arteries is due, in the vast majority of cases, to disease of their walls, usually sclerosis, while that in veins is brought about by inflammation, pressure, or marasmus.

Cardiac Thrombi.—Care should be taken not to confound the soft clots so commonly found at autopsies with true thrombi. These clots are merely coagula identical in origin and structure with the clots that form in blood withdrawn from the body. It is usually taught that they are produced during the death agony, but according to Welch they are more probably formed after death. In

diseases, such as lobar pneumonia and acute rheumatism, in which the fibrin content of the blood is high, they are often very abundant, and of a soft gelatinous and often oily appearance.

Intracardiac thrombi are apt to be found in chronic diseases of the heart or its valves, and of the lungs, arteries, and kidneys. The chief factors here are sclerosis of the valves or heart wall, myomalacia, and dilatation of the cavities. Changes in the composition of the blood and the influence of toxins do not play so important a rôle as in the case of the peripheral thromboses. Good examples of intracardiac thromboses, although not usually classed as such, are the vegetations in acute endocarditis. The verrucæ are nothing more nor less than small granulations capped with fibrin, leucocytes, and blood platelets. A very common site for intracardiac thrombi is in the auricular appendages and between the columnæ carneæ, where they may be rather firmly attached. They may also be found upon the surface of the valves. Mural thrombi are usually attached to some area of degeneration of the heart wall, such as is produced by atheroma, infarct, partial aneurisms, and gummata. The commonest form of intracardiac thrombi is the globular, which are usually multiple, and vary in size from that of a pea to an egg; they are sessile or pedunculated. The surface is smooth or again finely lined or ribbed. The interior is frequently converted into a grayish or grayish-brown detritus, or may present puriform softening. The curious rib-like markings found on intracardiac thrombi have attracted the attention of numerous writers, and were referred to by Bristowe as far back as 1855. The appearance has been attributed to wave-like or oscillatory movements in the blood.

A striking and interesting form, to which more than a passing glance should be directed, is the so-called "ball-thrombus." It is found invariably in the left auricle, and in association generally with mitral stenosis. According to Welch a true ball-thrombus presents the following characteristics: (1) Entire absence of attachment, and consequently free mobility. (2) Imprisonment within the cavity in which it is found. (3) Such consistence and shape that the thrombus must not of necessity lodge as an embolus in the ostium just ahead of it. Ball-thrombi vary in size from that of a walnut to a hen's egg and are usually spherical or ovoid in shape. They commonly show central softening, but organization has never been proved to occur. With regard to the clinical effects of such a condition, Wickham Legg has expressed the view (Trans. Path. Soc. Lond., 1878, xxix.) that "a loose thrombus in the left auricle would at any time be ready to act as a ball valve and stop the circulation in the mitral orifice." Contrary to what one would expect this is distinctly a rare event, although it has occurred, as in a case reported by Welch from Osler's clinic. Besides ball-thrombi pedunculated polyps of the heart wall have been described. Some of these are only organized or partially organized thrombi, while others resemble not a little fibromata and myxomata. Some, according to Bostroem, are thrombosed varices or local areas of hemorrhage. Ewart and Rolleston have recorded a case in which a pedunculated thrombus, arising from the fossa ovalis, passed through the mitral orifice and gave rise to the clinical signs of stenosis (Clinical Soc. Trans., vol. xxx.).

Arterial Thrombi.—Here the common causes are disease of the vessel wall or the lodgment of an embolus. Thus sclerosis of the vessel, particularly if associated with a solution of the continuity of the intima, frequently gives rise to the condition. Proliferating endarteritis, as von Manteuffel has shown, is often accompanied by an organizing thrombosis that in time leads to complete occlusion of the vessel.

The most frequent site for arterial thrombosis is, in my experience, in the arteries of the brain; but it is also often met with in the lower extremities, the coronary arteries, the mesenterics, and the aorta and its main branches. Arterial thrombi are to blame for a certain proportion of the cases of gangrene of the extremities. Apart from arteriosclerosis cases of arterial thrombosis are undoubtedly to be referred to inflammation of the vessel walls, a true arteritis. Probably of this nature are the cases sometimes met with in infective diseases like typhoid, typhus, scarlatina, pneumonia, endocarditis, septicæmia, smallpox, and tuberculosis. Nevertheless, it must be admitted that primary arterial thrombosis is to be met with in certain infective, cachectic, and anæmic states in the absence of gross disease of the vessel walls. It is, moreover, not always easy to exclude the possibility that some at least of the cases regarded as primary thrombosis are secondary to a previously occurring embolism.

Thrombosis of the pulmonary artery is believed by Welch not to be particularly uncommon, although cases of obstruction of this vessel have almost invariably been attributed to embolism. It is not unlikely that embolism of the smaller branches at least may be further complicated by thrombosis.

Of more importance is thrombosis of the coronaries of the heart, which is a condition that should be looked for in all cases of sudden death. It is usually due to sclerosis of the vessel or to atheroma of the aorta, aortitis, or to vegetations on the aortic valves; in fact, to any affection that causes obstruction in the vessel. The smaller branches of the coronary arteries are terminal or end arteries, and occlusion of these leads to marked changes in the heart wall, of the nature of infarction or coagulation necrosis. For this condition the term "myomalacia cordis" has been proposed by Ziegler. Provided the patient live long enough, reactive inflammation sets in, the patch softens, and there may be produced a local aneurism of the heart wall, an abscess or even rupture. It is common to find a thrombus on the endocardium of the affected region and sometimes also pericarditis. In some cases healing takes place with the formation of a fibrous scar.

The anastomoses between the main trunks of the coronaries are, however, more complete than has been usually taught, although in fact they are not always sufficient to restore the circulation where it has been suddenly interfered with. I have met with a case in which the orifice of the anterior coronary was completely occluded by sclerosis without the usual consequences of the condition, owing to a free communication with the posterior vessel at the apex of the heart.

Capillary Thrombi.—These are commonly of the fibrinous or hyaline variety, and are as a rule associated with necrosis or gangrene of the tissues. They are met with in the lungs in pneumonia and in hemorrhagic infarcts. In systemic toxæmia and infection they are to be found in the kidneys, the liver, and the lungs, and have also been described in the liver in cases of eclampsia, where they give rise to ischæmic infarcts and necrosis. They have also been described in connection with frost-bite and ergotism.

Venous Thrombi.—The most common site for thrombosis is in the veins. This is accounted for largely on the ground of certain anatomical and functional peculiarities. Chief among these may be mentioned the low blood pressure, the slow stream, the increased carbonic-acid content of the blood, and the presence of valves. While, as has been pointed out by Lancereaux, thrombosis is more liable to occur at regions where there is stasis of blood, this is not in all cases an entirely satisfactory explanation. It is more likely that von Recklinghausen's opinion, before referred to, is correct, viz., that a main factor is eddies in the blood (*Wirbelbewegungen*). These are specially liable to occur where the blood passes out from a small channel into a relatively larger one. In many cases local conditions play a part, as phlebitis, phlebosclerosis, varix, trauma, and compression.

In general, it may be said that venous thrombosis due to sepsis begins in the finer radicles, being produced in the first instance by a local inflammatory infiltration, while the so-called marantic thrombi are more common in the sinuses and medium-sized veins. An important feature in this connection is, that once they start, throm-