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THE TONER LECTURES

INSTITUTED TO ENCOURAGE THE DISCOVERY OF NEW TRUTHS FOR THE ADVANCEMENT OF MEDICINE.

LECTURE VII.

THE NATURE OF REPARATORY INFLAMMATION IN ARTERIES AFTER LIGATURE, ACUPRESSURE, AND TORSION.

BY

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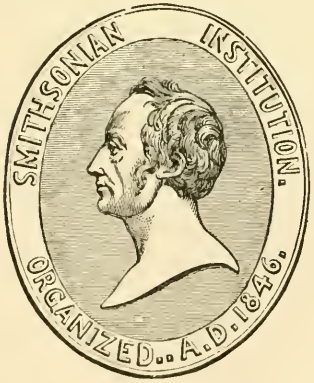

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LECTURE VII.

Delivered June 27, 1878.

THE NATURE OF REPARATORY INFLAMMATION IN ARTERIES AFTER LIGATURE, ACUPRESSURE, AND TORSION.

By Edward O. Shakespeare, A.M., M.D., of Philadelphia.

Gentlemen: Hemorrhage has formed a favorite theme for study from time immemorial. Its nature and the most efficient means for its arrest have commanded the earnest attention of the most distinguished physicians in all ages and in all lands. Yet in despite of the labors of centuries, in despite of the triumphant march of modern surgery, and the countless revelations of the microscope, it must even to-day be admitted with humility that the hand of man is again and again raised in vain to stay the puissance of this hydra-headed foe. The arrest of hemorrhage, therefore, still remains a subject of the most vital importance. But the time at our disposal does not admit of a discussion of the general question; it does not even permit of a very thorough treatment of a single one of its phases.

HISTORY.

Let us preface our own investigations with a few words concerning the work of our predecessors. Jean Louis Petit, so far as I can learn, was the first who made any systematic attempt to determine the cause of the frequent secondary hemorrhages after wounds and amputations, and to discover a more efficient method of applying the ligature (Mémoires de l'Académie Royale des Sciences, 1731–1732). Since no experiments are related, it may be inferred that his observations were such as

opportunity permitted him to make upon the human body at interrupted intervals.

M. Petit thought as follows:—

After ligation or compression of an artery a clot is generally formed above the place or on the cardiac side of the ligation, or the point of compression.

The constitution and density of the coagulum are varied in different portions by reason of the massing together in places of the several elements composing it—the position of the corpuscles and the fibrin being determined by their specific gravity relative to that of the liquor sanguinis.

It is more advantageous that the clot should be formed of the white part (lymph) only, than that it should consist of a mixture of the lymph and the red globules.

The clot in a short time becomes as firmly united to the sides of the artery as the granulation-tissue which forms cicatrices is to the lips of wounds. This intimate union once formed, not only is secondary hemorrhage prevented, but the clot in this state remains and disappears only as cicatrices diminish, in proportion to their condensation.

M. Morand (Sur les changements qui arrivent aux artères coupées; où l'on fait voir qu'ils contribuent essentiellement à la cessation de l'Hémorrhagie. Mémoires de l'Académie Royale des Sciences, tome liii. Année 1736) communicated some observations and conclusions upon the subject matter of the foregoing essays of M. Petit, le Chirurgien.

The paper concludes with the following sentence, which is in reality a formulation of his opinion concerning nature's mode of stopping blood, viz.:—

"The changes which take place in the arteries (retraction and contraction of the walls) contribute, then, to the cessation of hemorrhage conjointly with the clot, generally in every case; and if it is possible that the artery alone or the clot alone can

do so, the cases which may be cited in proof thereof will be extremely rare."

Mr. Sharp, a few years later (Operations of Surgery, 1739), entertained and taught principles governing the checking of hemorrhage very similar to those advanced by the last-named investigator.

M. Pouteau is the next person we find publishing the results of investigations relating to the healing of bloodvessels (Mélanges de Chirurgie, 1760).

He concluded, " That when an artery is divided, a coagulum does not always form; that the retraction of the artery has not yet been demonstrated; that the retraction of the walls is not more effectual for the arrest of hemorrhage than is the presence of a clot; that the presence of a clot is only a very weak and subsidiary means toward that end; that the infiltration and swelling of the cellular membrane at the circumference of the cut extremity of the artery offer the chief obstruction to the bleeding; that by exciting and aiding in a more rapid and general induration of that membrane, the use of the ligature is valuable for the arrest of hemorrhage."

The name of Kirkland appears next upon the list of those who have endeavored by a series of observations to penetrate the ways which nature adopts for the cure of a wounded vessel (Essay on the Methods of Suppressing Hemorrhages from Divided Arteries, 1763).

His opinions may be formulated as follows:—

The hemorrhage from a very considerable artery is easily and effectually suppressed by merely making a perpendicular pressure upon the end of the vessel for a few minutes.

The bleeding is not suppressed by congealed blood, but by the vessel being quite closely contracted for near an inch or more from its extremity.

Interruption of the passage of the blood for a while is all that is required from art.

Gooch (Chirurgical Works, 1766) turned his attention only a year or two later to the subject before us.

Mr. White (Cases in Surgery) agreed with Pouteau, Kirkland, and Gooch in rejecting Petit's theory of a coagulum as not at all probable. He concluded that the formation of a coagulum is only incidental, and is of no use whatever except under particular circumstances.

Hunter believed in the adhesive inflammation of all the tissues of the vessels. He considered that the clot adheres to the walls, and undergoes organization.

John Bell (Principles of Surgery, 1801) also ranged himself on the side of those who opposed the views of Petit and Morand. He thought that hemorrhage is always permanently prevented by the changes which take place in the surrounding cellular tissue, and by adhesive inflammation of the arterial walls themselves.

J. Thomson, of Edinburgh, made some observations upon the effect of ligation.

The next to be mentioned in chronological order is the classic work of J. F. D. Jones, M.D. (A treatise on the process employed by nature in suppressing the hemorrhage from divided and punctured arteries, and on the use of the ligature, etc., 1805). The completeness of this man's experiments, and the apparent soundness of his judgment upon the principles to be deduced from his results, succeeded in settling, at least for a lengthened period, the much-vexed question which he set himself to solve. Indeed, such have been the closeness and accuracy of his investigations that, even to-day, his excellent monograph remains admittedly the authority upon the means which nature adopts for the suppression of hemorrhage. The occasion is taken here to acknowledge our indebtedness to his paper for much of this history.

With respect to spontaneous arrest of hemorrhage from divided vessels, Jones states that for the reason that the for-

mation of the internal blood-clot is uncertain, or that when formed it rarely fills the canal of the artery, or if it fills the canal does not adhere to its internal coat, it is not to be ranked among the means which nature employs for the suppression of hemorrhage, for in ordinary accidents it contributes nothing to those means.

The permanent changes which take place in an artery and in the circulation through the limb, in consequence of the application of the ligature, are precisely similar to those after the division of an artery. Some of the effects of tying an artery appear to be the following: to excite inflammation in the middle and internal coats by having cut them through, and, consequently, to give rise to the effusion of lymph (colorless clot), by which the wounded surfaces are united and the canal is rendered impervious; to produce an inflammation on the corresponding external surface of the artery, and at the same time, by the exposure and inevitable wounding of the surrounding parts, to occasion inflammation in the latter and an effusion of lymph which covers the artery and forms the surface of the wound.

According to Jones, it is a fact that in most cases only a slender clot is formed at first, which gradually becomes larger by successive coagulations of the blood, and it is for this reason that the clot is always at first of a tapering form, with its base at the extremity of the artery. But the formation of this coagulum is of little consequence, for soon after the application of the ligature the extremity of the artery begins to inflame. The wounded internal surfaces of its canal being kept in close contact by the ligature adhere, when this portion of the artery is transformed into an impervious and, at first, slightly conical sac. It seems to be entirely owing to the effusion of lymph that this adhesion is effected.

Hodgson (Diseases of the Arteries and Veins, 1815) contended that the veins are liable to all those morbid changes

which are common to the soft parts in general, but the membranous lining of those vessels is peculiarly susceptible of inflammation.

Bouillaud (Archives Générales, 1824, série vi., tome 5) maintained the organization of the thrombus and its adhesion to the walls of the vessel, as also did Ribes (Revue Médicale Française et Étrangère, 1825, tome 3), as well as Roche and Sanson (Nouveaux Eléments de Pathologie. Medico-Chirurgicale, Paris, 1826).

Scarpa (Memoria sulla ligatura della principali arteori, edizione 1825) has occasionally observed, two or three days after the application of the ligature, the adhesion of the walls without the intervention of a clot.

Gendrin (Histoire Anatomique des Inflammations, 1826, tome ii.) perhaps deserves mention here, since a theory respecting the mode of formation of lymph in inflamed vessels had derived much of its support from an often-cited experiment which he reported. He claimed that the inner coat of veins affords a concrete layer of lymph which obliterates the vascular canal.

Ebel (De natura medicatrice sicubi arteriæ vulneratæ et ligatæ fuerunt, Guersa, 1826) denied that the internal coagulum takes any part in the organizing process, and affirmed his belief in its disorganization and disappearance.

Cruveilhier (Anatomie Pathologique, 1829) spoke of the disappearance of the thrombus by absorption

The next great communication on the subject of hemorrhage came from M. Amusat (On a new method of arresting hemorrhage from large vessels without the aid of the ligature. Académie Royale de Médecine, 1829). The conception of this new method was first suggested to his mind by the long-recognized fact that torn wounds do not bleed. The development of this suggestion was worked out by experiments upon animals. The perfected plan was applied upon

the human subject, and the practice of torsion was introduced and published to the world.

Blandin (Journal Hebdomadaire, mai 1830) accepted the organization of the thrombus, and its thorough adhesion to the vessel walls, and Mannec (Traité Théorique et Pratique de la Ligature des Artères, 1832) was in accord with this view; on the other hand, Walther (Système de Chirurgie, 1833) and M. Lobstein (Pathologische Anatomie, 1834) were of the opposite opinion.

W. B. Costello, a former pupil of M. Amusat, followed the communication of his master by a paper read before the Westminster Medical Society on "Torsion of Arteries for the purpose of Arresting Hemorrhage" (London Lancet, March 8, 1834), in which experiments upon dogs were detailed.

Stilling (Ueber Bildung und Metamorphose des Thrombus in verletzten Blutgefäsen, Eisenach, 1834) repeated and corroborated the researches of Petit. He saw the adhesion of the clot to the wall of the vessel, its pyramidal shape, considered eighteen hours as about the length of time requisite for its formation, and admitted, with Moran, the action of the ligature on the two inner tunics of the vessel.

Pirogoff (Ueber die Durchshneidung der Achillessehne. Dorpat, 1840) defended the general proposition that fibrin possesses a power of self-organization.

Zwicky (Metamorphose des Thrombus, 1845) recognized fibrin as a formative element in the process of organization. For him fibrin forms a plastic exudation upon the inner wall of the vessel, and effects the growth of the latter to the thrombus. The fibrin found in the thrombus as one of its elements likewise soon organizes itself there. He observed the formation of vessels in the thrombus.

Both Castelnau and Notta (De la cicatrisation des artères. Gazette des Hôpitaux, 1851, No. 13, 14) confessed to the same

opinion, and claimed further that the thrombus is subject to purulent degeneration.

Thierfelder (De regeneratione tendinum, 1852) is to be ranged with Pirogoff and the others who admit the formative power of fibrin.

Henry Lee (On the deposition of fibrin in the lining membrane of veins. Med.-Chir. Transactions, 1852) did not think that in Gendrin's experiments sufficient care had been taken to exclude the possible presence of a small blood-clot. He devised a method by which this dilemma could be avoided, and he aspired to put the question of the rôle of the vessel wall at rest forever by performing a solitary experiment. This author concluded that the blood coagulum is necessary to the presence of inflammation, and that it acts as a foreign body, the inflammation excited by it being a natural process for its elimination. This inflammation begins in the outer, and thence extends to the inner coat; extends *to* the lining membrane of the vein, and not *from* it.

Boner (Die Regeneration der Sehnen. Virchow's Arch., 1854) acquiesced in the independent formative power of the fibrin wherever found.

Rokitansky (Pathologische Anatomie, 1856) regarded the walls of the vessel as the origin of the material which finally fills the lumen and becomes organized.

Meckel (Microgeologie, Herausgegeben von Billroth, 1856) was among the first in this connection who began to perceive in the white blood-corpuscle an element which might possess capabilities that should not be entirely overlooked in the examination of these processes. However, he neither ascribed to the leucocyte any great rôle, nor yet denied to it a power of organization.

Virchow (Canstatt Jahresbericht, Bd. 1, I. 31) advanced the opinion that the white blood-corpuscle as a formative element carries the fibrin.

Simpson (Acupressure as a new hæmostatic process. Royal Society of Edinburgh, 1859) claimed that the acupressed vessel is closed by adhesive inflammation of its inner walls.

Bogdonowsky (Medicinische Zeitschrift (Russia), 1862) summarized the results of experiments upon varicose veins by the declaration that the thrombus formed by injecting into the veins liquor ferri sesquichloridi acts as a foreign body, and can only degenerate; that the vessel is obliterated at the expense of its walls.

Ardreef (Ueber das Blutkörperchen in histologischer Beziehung, St. Petersburg, 1862) affirmed that he had observed the transition of the red blood-corpuscles into the white, and subsequently the formation of connective tissue from these.

Koslowsky (Untersuchung ueber die Strabotomie. St. Petersburg, 1863) and Rindfleisch (Apoplexia cerebri. Arch. d. Heilkd. von Wagner, 1863) confirmed this observation.

Billroth (Allgem. chirurg. Pathologie und Therapie, 1863), studying the thrombus with the microscope, made observations which he considered to be a demonstration of the truth of Virchow's suspicion of the formative activity of the white blood-corpuscle.

Schmidt (Ueber den Faserstoff und die Ursache seiner Gerinnung. (Russische) Militär-Medicin Journal, 1863) contended that the length of time requisite for the formation of a coagulum after ligation depends upon the various conditions affecting the coagulability of the blood. He conceived that a fibrino-plastic substance exists in the vessel walls, and, that after its destruction, by any injury to the walls for instance, it is endued with the capability so to act upon the fibrinogenous substance of the blood as to condition, from the latter, coagulation.

Janowitsch Tschiansky (Dissertatio, St. Petersburg, 1864) repeated and confirmed the experiment and conclusions of Bogdonowsky.

O. Weber (Ueber die Vascularisation des Thrombus. Berliner

Klin. Wochenschrift, 1864) made a series of experiments upon dogs and rabbits, directed to the determination of the mode of vascularization of the thrombus. He concluded from his numerous observations:—

1st. That the red corpuscles and the fibrin degenerate and disappear.

2d. That the white cells by means of their peculiar movements during the first hours undergo a change into bodies of a peculiar shape, and very soon become transformed into spindle-form cells.

3d. That in the first four days the extremities of the prolongations are seen uniting and forming a network, taking position in lines having every semblance of vessels.

4th. That the younger vessels are generally formed in the periphery of the thrombus.

5th. That by the end of the third or fourth week, the vessels of the thrombus have formed a union with those of the adventitia. At the place of ligature where the intima and media are lacerated, the vessels of the adventitia pass directly into the thrombus; farther away from the ligature, they reach the thrombus by penetrating the intima.

6th. That by the fiftieth to the sixtieth day the whole thrombus, especially its periphery, is full of bloodvessels. A single large one is often seen in the centre.

7th. That these vessels subsequently close up.

Forster (Handbuch der Patholog. Anatomie, 1865) denied the organization of the thrombus, and believed that the healing and final obliteration of the veins are due to a growth of the walls.

Stricker (Ueber das Leben der farblosen Blutkörperchen. Sitzungs-berichte der Akademie der Wissenschaften, 1867) admitted the viability of the white corpuscle in the thrombus, but did not affirm its formative power.

Obolensky (Ueber die Organisation des Blutes. Protokoll

des Vereins russicher Aerzte, 1867) attempted to test the various theories concerning the organizing power of the white blood-cells. His observations were made on a clot of blood and a large number of white blood-corpuscles, which were taken from one frog and placed under the skin of another. He found by this experiment that the whole mass—the red and the white blood-corpuscles, as well as the fibrin—underwent degeneration by fatty metamorphosis. The red blood disks first decolorized, and then degenerated. On the fourth day, there remained of the clot only pigment and fatty particles.

Bubnoff (Ueber die Organisation des Thrombus. Central Blatt, No. 48, 1867), under the direction of Von Recklinghausen, performed three series of experiments, aiming at the tracing of the movements of the white blood-corpuscles in the organization of venous thrombi.

1st Series. Ligation of jugular vein. Rubbed vermilion on exterior wall of the vessel. Result—the colorless corpuscles penetrate the wall of the vessel, absorb the vermilion, reach the thrombus, and then organize themselves, the color not disappearing.

2d Series. Ligature of one jugular. Twelve hours afterward injection of vermilion into the other jugular. Result—vermilion did not reach the thrombus.

3d Series. Two ligatures on one vein. An injection of vermilion into the thrombus. Result—the white corpuscles did not absorb the vermilion.

Conclusions: 1st. The thrombus organizes only by means of the white blood-corpuscles, which penetrate the vessel-wall.

d. The white blood-corpuscles do not reach the thrombus directly by way of the blood-current.

3d. The cells of the vessel-wall are probably concerned in the organization.

Waldeyer (Zur pathologischen Anatomie der Hautkrank-

heiten, Virchow's Archiv, Band xl., 1867) has affirmed his belief that the tunica intima takes an active if not the sole part in the organization of the thrombus.

Thiersch (Chir. von Pitha und Billroth) would be named among those who, *a priori*, incline to the view that the epithelial cells and the nuclei of the different lamellæ of the intima should be considered as formative elements, active in the organization of thrombi.

Henry Lee and Lionel S. Beale (On the repair of arteries and veins after injury. Med. Chir. Trans., vol. i., 1867) studied the phenomena following a puncturing wound of an artery, and found that a colorless fibrin-like material fills the wound. It consists mainly of colorless blood-corpuscles derived from the blood in the lumen of the wounded vessel. This forms layer after layer, a temporary tissue. The subsequent changes which take place in this fibrin-like material, and effect the permanent closure of the wound, they did not investigate; but they were convinced, *a priori*, that the formation of a new permanent fibrous tissue results from the masses of germinal matter (colorless corpuscles) of the temporary adventitious tissue above mentioned, and not from the masses of "germinal matter" of the arterial tunics, or of the vasa vasorum.

Hewson (Pennsylvania Hospital Reports, vol. i., 1868) made a careful study of several specimens from human arteries after acupressure had been performed. Longitudinal section of the acupressed vessel showed the opposite surfaces of internal coat glued together by lymph. No clot beyond the point of pressure, and no laceration of the internal coat. What struck most forcibly was the extent of the exudation which had taken place upon the internal coat, and even outside of it. The thickening extended nearly a half inch above, gradually diminishing up to the first branch.

Tschausoff (Ueber den Thrombus bei der Ligatur, in dem "Verein russicher Naturforscher" vorgelesen, Protokoll des

Vereins russicher Aerzte, 1868, and Archiv für Klinische Chirurgie, Band II., 1869) published an exhaustive paper—which we have extensively used in this history—on thrombi after ligature. The author states that—the thrombus never organizes; the muscle-fibres of the media are never concerned in the organization, and the same may be said of the epithelium; changes are soon observed in the wall of the vessel, and in all its tissues; growths from the walls encroach upon the lumen of the vessel; this newly formed tissue, both of the wall and of the lumen, is rich in vessels; from the arterial wall the vessels go direct into the lumen, which either altogether or in part is closed up; the development of the vessels progresses at the same time with that of the newly formed tissue; the circulation of the blood comes from the wall of the vessel itself.

The author repeated the experiments of Bubnoff, and failed to obtain the same results. He states that in five experiments, colored form-elements were perceivable in the thrombus, but they were small, in large numbers, and without definite form. They somewhat resembled altered red blood-corpuscles.

Bryant (On the torsion of arteries as a means of arresting hemorrhage. Experiments. Med. Chir. Trans., vol. ii., 1868, and On torsion of arteries, a description of some models made to illustrate the effects of torsion, Guy's Hosp. Rep., Series III., vol. xv.) believed that in torsion the twist of the cellular coat of an artery, the division and subsequent retraction, incurvation, and adhesion of the middle coat, and the coagulation of the blood in the vessel as far as the first branch, are the three points upon which temporary as well as permanent safety depends. In his opinion the permanent safety of acupressure rests upon the last point alone, and the temporary effects upon the pressure produced by the needle.

Kocher (Ueber die feineren Vorgänge bei der Blutstillung durch Acupressur, Ligatur, und Torsion. Archiv für Kli-

nische Chirurgie, No. 11, 1869) made a number of experiments and microscopic studies upon the mode of permanent arrest of hemorrhage, by the use of the ligature, acupressure, and acutorsion. He found that by the employment of each of these means the presence of a clot in the vessel was usually secured; that these clots were sufficient to arrest hemorrhage temporarily from a small vessel; that in acupressure or in acutorsion they are gradually formed and increase slowly in size, not usually being sufficiently large by the end of forty-eight hours to check the bleeding from a large vessel.

Cornil and Ranvier (Manuel d'Histologie Pathologique, 1869) have carefully examined the method of healing in an artery after ligature.

With respect to the *double ligature* of *veins*, they think that what Bubnoff claims to have observed is incontestable. But never in a single ligature of arteries and veins, where the bottom of the wound had been smeared with vermilion, did they see the latter penetrate through the walls of the vessel. En résumé, they declare that the definitive obliteration of arteries after ligature is effected by a neoplasm, the point of departure of which is the arteritis consecutive to the traumatic lesion. As to the clot, it disappears by a series of retrogressive alterations similar to those which the blood goes through when it escapes from the vessels into the tissues.

Durante (Entzündung der Gefässwände. Med. Jahrbüch., Band III., 1871, and Recherches expérimentales sur l'organisation du caillot dans les vaisseaux, Arch. de Physiologie Normale et Pathologique, tome iv., 1872) has conducted a most careful and thorough examination of the still unsettled question as to what are the organizing elements active in the processes inaugurated by the ligature of an artery.

He admits the formation of a temporary and a permanent clot. The former is of blood, and is not homogeneous; it gradually disappears. The latter is a colorless clot formed

mainly of epithelioid cells; it effects the permanent closure of the vessel. He thinks that his preparations clearly demonstrate that in the case of the single ligature the organizing elements of the permanent clot are derived from the tunica intima. In the double ligature, on the contrary, the internal membrane in the portion limited by the two threads becomes modified. The substitution of the temporary by the permanent clot is accomplished more slowly, since the coagulated blood must produce mortification of the internal membrane, and later become the irritating agent of the middle and external membrane.

Following the experiments of Bubnoff, Durante declares that never in the single ligature, when the coloring matter has been simply placed upon the vessel, has he been able to find, in the clot or in the wall of the vessels, cells containing granules of vermilion. The same is true of the double ligature when the inflammation has not yet destroyed the limit between the walls of the vessel and the surrounding tissue. If the vermilion is gently applied to the walls of the vessel, the coloring matter remains for many days at the periphery of the artery, and in transverse sections it appears as a line distinct and continuous, at the surface of the adventitia. But when the walls of the vessel become confounded with the neighboring tissues by the progress of inflammation, the vermilion may be recognized here and there in the midst of the tunics. In the single ligature, if the greatest possible care is taken, it is easy at the end of the twelfth day still to perceive the vermilion limited to the perivascular connective tissue; but after prolonged and somewhat rough friction, he has been able, at the end of a few hours, to demonstrate on the jugular vein of rabbits, exposed and included between two ligatures, that there exist in the middle of the clot granules of vermilion *in a free state.* The walls of the vein were infiltrated with similar granules. The same manœuvre practised upon the arteries causes the vermilion to reach only as far as the

muscular tunic "It is then by mechanical penetration, and thanks to the thinness of the venous walls, that the particles of vermilion have travelled as far as the clot." Durante thinks the origin of the formative cells in the single ligature is to be found in the endothelium, or the ramified cells of the internal membrane.

Baumgarten (Centralblatt für die Medicinischen Wissenschaften, No. 34, 1876) publishes the very latest investigation upon the healing of arteries. He sums up the substance of his researches as follows:—

1st. The so-called organization of red thrombi is due to two distinct processes: first, a proliferation of the arterial endothelium; and, second, an invasion from without of connective tissue elements from which the new bloodvessels are solely formed.

2d. The part played by the clot in the organization is *nil;* an occasional fragment of encapsuled pigment is the only remnant it leaves.

A. Pitres (Recherches expérimentales sur le mode de formation et sur la structure des caillots qui déterminent l'hémostasie. Arch. de Phys. Nov. et Path., 1876) affirms that hæmostasis is usually spontaneously secured by a clot composed of three distinct portions: an external part, which is a simple blood coagulum, and which is only an accessory; a middle part, which is lodged in the wound, or lumen of the vessel, which is the most constant and active agent of spontaneous hæmostasis, and which consists almost exclusively of white blood-corpuscles; and an interior clot, which has merely an accidental office, and which has a complicated constitution.

SUMMARY OF PREVALENT OPINIONS.

We have seen that notwithstanding the apparent confidence and sometimes even dogmatism with which the leading pathologists have published opinions and advocated theories con-

cerning the organization of the blood, there has at no time been a unanimity of opinion among the investigators whose labors have furnished the most important observations bearing upon the process of healing after wounds of bloodvessels, and that no less than four of the latest publications which have been furnished by the pens of most distinguished pathologists directly contradict the assumption of Billroth and Rindfleisch concerning the activity of the wandering cells in the organization of thrombi.

In commencing the relation of our own personal observations, perhaps it may be proper to state at the outset that the conclusions which we believe to be legitimate deductions from the facts which shall be reported are, in many important points, at variance with some opinions generally admitted by the scientific world to be well established. If these deductions shall stand irrefuted it will become necessary to modify greatly the present prevalent opinions concerning the nature of inflammation. It is not our intention, however, upon this occasion, to discuss the nature of inflammation in general. The question of inflammation will be raised only by indirection, and will be limited to the inflammatory processes as they are seen in wounded arteries.

It is by the light of pathological histology alone that we propose to examine to-night "The Nature of Reparatory Inflammation in Arteries after Ligature, Acupressure, and Torsion."

Just here let it be premised that if our conclusions are not in accord with views considered as established, it cannot be charged by the defenders of the latter that our investigation has been undertaken or conducted with an unfavorable bias. Until the completion of our experimental study of ligation, no authorities upon the pathological histology of the subject had been examined by us other than Rindfleisch and Billroth. Their opinions upon this subject had, up to the time of the

inauguration of this investigation, been in our mind unquestioned.

Before entering into details of our own studies, it seems advisable to summarize the opinions concerning the intimate nature of the healing process in arteries after ligation which are at present supported by the weight of authority, and are consequently accepted by the medical world as beyond dispute.

Billroth, in his celebrated work on surgical pathology, says that after ligation the plugging of an artery by a blood-clot is only a provisional attempt on the part of nature to arrest hemorrhage. The thrombus does not remain in the same condition for all future time, but it becomes transformed into cicatricial tissue, shrinks and atrophies, when the artery at the point of division has become solid by the complete fusion of this cicatricial mass with the walls of the vessel. For the completion of this process months, and even years, are required. In what these changes of the blood-clot actually consist, the microscope gives valuable evidence. The clot is homogeneous throughout, that is to say, there is no stratification or grouping of the blood-disks, either of the white or red; but, on the contrary, they are scattered evenly through the entire coagulum.

It is the further development of the colorless cells of this clot which secures the definite termination of the whole process. Since the blood-clot, consisting of cells and coagulated fibrin, is at first a non-vascular cellular tissue, which can only at first maintain its existence in thin layers, it is apparent (and observation confirms this) that large blood-clots are not organized at all or only in their peripheral layers, while they disintegrate in the centre.

What are those cells which organize the thrombus? and whence do they come?

On a previous page of this distinguished author's most excellent work a sentence appears which places Billroth upon

even more radical ground with respect to the Cohnheim theory than the celebrated author thereof himself takes.

These are the exact words: "*All young cells* which in inflammation are found abnormally in the tissues *are wandering white corpuscles.*" Himself replying to the questions above propounded, the Vienna Professor makes use of the following unequivocal language: "After having abandoned the idea of proliferation of stable tissue cells in inflammation, we can no longer talk of the *proliferation of the intima* in the old sense." And again: "I have no doubt that they originate from the white blood-cells, which have been partly inclosed in the thrombus, and partly may have wandered into it, according to the observations of Von Recklinghausen and Bubnoff." As to the ultimate origin of the wandering cells Billroth conceives their factories to be the lymph glands, and remotely the stable cells of the connective tissue.

The great German pathologist Rindfleisch in the main accords with Billroth respecting the formation and organization of the thrombus in a ligated vessel.

They agree that it is formed suddenly, and that it is unstratified, there being no accumulation of numbers of white cells in places; it is homogeneous throughout.

They also agree that the blood-clot is organized; that the white corpuscles (wandering cells) are the organizing elements; that the red disks slowly degenerate and disappear.

Rindfleisch believes that the thrombus is largest immediately after coagulation, which takes place almost immediately after the blood is placed out of circulation by the constriction of the ligature; and in this also accords with Billroth.

Both authors think that the clot becomes gradually converted into ordinary cicatricial tissue, and that through the cavernous metamorphosis of this the clot and the vessel-wall surrounding it are at length converted into a mere cord or thin band of

dense fibrous tissue, the only remains of the previous blood channel.

To summarize briefly, the standard authorities publish in very positive terms the opinions which they believe have been indisputably demonstrated, viz.: that immediately after the ligature of an artery a blood-clot is formed which plugs the lumen of the vessel, generally up to the level of the first collateral branch; that this clot is homogeneous, unstratified, is formed at one time, and is larger during the first hours than at any other period; that it offers a temporary barrier to the flow of blood; that soon the blood-clot thus formed, itself becomes organized and supplied with its own vessels, which form a communication first with the lumen above the clot, next with the vasa vasorum mainly at the bottom of the clot; that it is by this organization and vascularization of the temporary blood-clot, and the intimate union of this newly formed tissue with the vessel-walls, that the lumen of the wounded artery becomes permanently closed against the blood current; and that the organizing elements are solely and exclusively the white blood-corpuscles and their descendants—either those which are caught in the clot at the time of its formation, or those which may have wandered into it afterward, or more probably those derived from both sources. It is thus that their ideas concerning the nature of the inflammatory process in wounded arteries are made to coincide entirely with and to give some further support to Cohnheim's theory of inflammation in general.

PERSONAL OBSERVATIONS.

More than three years ago, at the request of my friend Prof. Agnew, of the University of Pennsylvania, and for his benefit, I (with the surgical assistance of my friend Dr. Wm. Mastin, of Mobile, who was at that time an Interne of University Hospital) traversed experimentally some of the ground which O. Weber had gone over while making his researches relative to

the march of the vascularization of a thrombus in a ligated vessel. To my surprise, I was unable in any single instance to find under the microscope appearances in my sections of thrombi which could to my mind be fairly considered as confirmatory of the foregoing statements of Billroth and Rindfleisch, either as to the formation, the constitution, the organization, the vascularization, or the obliteration of the blood-clot.

After having given to Dr. Agnew the results of the examination which I had undertaken for him, I inaugurated for myself a more thorough and systematic experimental study of the whole question of the manner and the means by which a ligated artery is healed. This second investigation was conducted at odd times, and had extended in this way over a year and a half, when, at the commencement of January of 1877, I determined to embody the results I had attained in an essay, which secured for me the award of the Warren Triennial Prize for that year. Since then, as occasion has offered, I have from time to time added to the number of my experiments and observations, and have pushed them into the question of the healing of an artery after acupressure and torsion as well. The conclusions based upon the entire series of observations are more comprehensive than those derived from my first study, and, in a few points, are slightly different.

Upon the healing of arteries four regular series of preparations have been secured, the experiments principally being performed upon the femoral arteries of young, vigorous dogs.

In obtaining the *first series* the following order has been observed, viz.: the artery was exposed and tied in continuity with the ordinary silk ligature, the thread being allowed to remain on the vessel until the animal was killed, or until it came away without assistance. The subjects were then killed in rotation at such times as to afford preparations of their arteries, 24, 36, 48, and 94 hours, and 5, 8, 10, 15, and 21 days after ligation. Each number of this series was duplicated,

at least once, and several of them, such as 24, 48, 94 hours, and 10 and 15 days, were repeated two or three times and oftener.

A *second series* was begun, but owing to pressure of other engagements was not entirely completed. This series was intended to supply as full a number of preparations as the first. The procedure followed in the preparation of this series consisted in a slight modification of the ordinary manner of performing ligation: the ligature was applied in the continuity of the vessel in the usual manner; immediately afterward the vessel was compressed an eighth of an inch above the point of ligature, by means of an ordinary pair of dressing forceps, so as to moderately rub together opposite points of the inner surface of the internal membrane of the vessel, and thus produce at these points a sufficient irritation, at the same time avoiding if possible any rupture of the inner tunic. A number of preparations from this were obtained, varying from three to ten days.

The *third series* consisted of a limited number of preparations to show the method of healing after *limited torsion.*

A *fourth series* was obtained, the number of preparations also being much smaller than the first. They were intended to supply a full series for the satisfactory study of the process of healing after *acupressure.* In performing acupressure, the procedures known as the third and fourth methods were adopted — the third being done in the continuity, and the fourth after the division of the vessel. The needle was allowed to remain in the tissue until the specimens were hardened for examination. I may say here that a *fifth series* was also commenced, wherein specimens were to be obtained to show the results following a mere occlusion of an artery in continuity, by moderate pressure produced by the inclusion of the artery for a few hours between the arms of a small serre-fine. The ex-

periments for this last series were made upon the femoral and carotid arteries of good-sized rats.

The various operations upon dogs were performed during anæsthesia; those upon rats after they had been bridled and tied down to a board. The vessels containing thrombi five days old and upward were generally injected with Beale's Prussian blue fluid. In all cases the vessel operated upon was removed immediately after the death of the animal, extreme care being taken to avoid pressing upon or stretching that portion of the vessel which contained the thrombus. Immediately after removal from the animal the specimens were usually placed in dilute alcohol, which was subsequently gradually strengthened from day to day by the addition of small quantities of strongest alcohol. Occasionally a specimen was hardened in chromic acid or Müller's fluid.

The specimens were allowed to remain undisturbed in the hardening agent until they had become thoroughly firm and hard.

After that they were placed for a day in absolute alcohol. They were subsequently removed from this and saturated with oil of cloves, and were then imbedded in a mixture of about one part of benzine to twelve or sixteen parts of paraffine. Thin sections, both longitudinal and transverse, were then made from each specimen. Generally all such sections were subsequently stained with carmine, and temporarily prepared for microscopic examination by being mounted whole in oil of cloves, or by being torn apart by needles for examination of their isolated elements. A few gold and silver preparations were also made. It may be stated at this point, that the original drawings which illustrate my own part of the labors chronicled in these pages are not mere diagrams, but are actual copies of objects in the field of the microscope, traced by myself, as accurately as possible, by the aid of a good camera.

First Series. — Microscopic examination of sections from the *first series* demonstrated the fact that the apparent sequential order of the various phenomena exhibited throughout the series, presented a marked uniformity.

Nearly every preparation twenty-four hours old showed, under a low power and in longitudinal sections, a blood-clot, not unusually extending as far as the first collateral branch. This clot was usually egg-shape, and it did not fill the entire calibre of the vessel. Ordinarily it was adherent to the vessel-wall only at one side, while it was slightly separated from the opposite side. It did not extend quite down to the point of ligature, for the bottom of the little cup formed by the constricting action of the thread upon the arterial walls was generally covered over several layers deep with colorless cells, and it was upon this cushion of colorless cells that the butt-end of the blood-clot rested. The outer surface of this cup-shape cushion of colorless cells was everywhere closely adherent to the inner membrane of the vessel-walls. At the sides this cup-shape cushion extended along the inner surface of the vessel-wall for a considerable distance from the ligature—occasionally up as far or even farther than the apex of the blood-clot. The bottom of the blood-clot was adherent to the bottom of this cup-shape cushion of colorless cells, and it was also adherent to one of its sides. To avoid confusion, I shall hereafter refer to the blood coagulum as the *blood* or *fibrinous clot*, and in distinction shall speak of the cup-shape cushion of colorless cells as the *cellular* or *plastic clot*. The number of the colorless cells of the plastic cup or clot, or, in other words, the thickness of its walls, rapidly decreased in proportion to the remoteness from the point of ligation. Concerning the constitution of the fibrinous or blood clot, the declaration is emphatically made that, when viewed in longitudinal section, in not one solitary instance in any of these series was it observed to be homogeneous in structure; but that, on the contrary, when so viewed

every blood-clot presented the most *unmistakable* appearance of *lamination* or stratification. This feature was uniformly present throughout the whole of the first series, as well as throughout all of the others. It may be stated, however, that some of the transverse sections did not present this appearance of lamination. Fig. 2, although drawn under a low power from a preparation of forty-eight hours, fairly represents the stratified appearance of all these blood-clots when seen upon section in profile.

In order as much as possible to avoid repetition, the further discussion of the constitution of the blood or fibrinous clot will be deferred until we consider the structure of that of forty-eight hours.

Recurring once more to the plastic or cellular clot of twenty-four hours, running through the accumulation of colorless cells at the bottom of the vessel are to be found narrow, highly refractory bands, evidently portions of the elastic layer of the split and lacerated tunica intima. Dissociation of the plastic clot with needles shows the great majority of the cells constituting it to be flat, swollen, granular, and generally oval, with ordinarily one moderately large and round or slightly oval granular nucleus. Sometimes these cells contain a large nucleus with a constriction in the middle; sometimes two or more smaller nuclei; occasionally the body of the cell itself shows a tendency to the same constriction. They often possess a transverse diameter twice as large as that of the white blood-corpuscle, and a longitudinal diameter sometimes three and occasionally even four times as great as the latter. The general arrangement of these cells seems to have special relation to the plane of the elastic layer of the tunica intima, whether this layer occupy its accustomed position relative to the media, or whether it be found scattered through the cellular accumulation in the shape of the previously mentioned bands. While the disposition of these cells evidently is to

flatten themselves upon the elastic layers parallel with the surface of the latter, still through the whole of the accumulation cells can be seen occupying every conceivable position, and, consequently, presenting widely varying profiles. In consequence of being viewed in profile, many of the cells appear to be spindle-shape. Interspersed among these epithelioid cells are to be found also many round granular cells, precisely similar in size and general features to the white blood-corpuscles. In still greater number are to be seen round or polygonal granular cells twice and even three times the size of the latter. Besides these three general types of cell elements, a few red blood-corpuscles can be distinguished here and there. Examining this cellular accumulation throughout its whole extent, it was observed that, in proportion as the distance from the ligature increased, the endothelial cells along the sides of the vessel indicated a smaller degree of activity or irritation. The tunica media nowhere, except at and immediately above the situation of the thread, showed decided signs of increased activity. It might be judicious to remark, however, that in the portion of the media immediately beneath the elastic layer of the intima and in the neighborhood of the ligature, possibly the cells may have exhibited slight traces of irritation. At this date, then, the plastic or cellular clot mainly consisted of an accumulation of epithelioid or, more correctly speaking, endothelioid cells and their progeny. In the tunica adventitia, especially near the ligature, and in the surrounding connective tissue a considerable cellular increase had commenced.

Fig. 1 represents the femoral artery of a dog twenty-four hours after ligature. A transverse section just above the level of the bottom of the blood-clot, which has fallen out while handling, and which has not been drawn. *a.* Adventitia, not much cellular increase at this level. *c.* Surrounding cellular or connective tissue, showing greater increase of cell elements. *m.* Media not perceptibly altered. *e.* Elastic folds of the inti-

ma; highly refractive, very distinct, also apparently unaltered. *p*. Thick layer of colorless cells closely adhering to each other and to the elastic layer of the intima, entirely filling up the crypts made by the folds of the latter; dissociation demonstrated these cells to be of the same general character as those described above. The section has passed through the sides of the plastic cup or clot.

Preparations from this same series thirty-six hours old, in the main presented similar characteristics. It is only necessary to remark that the thickness of the plastic clot at the bottom and sides of the arterial stump had considerably increased, and that a comparatively greater number of the cells had assumed the oval or spindle outline. The cellular infiltration of the adventitia and surrounding connective tissue had become much more decided. Now, also, one could speak a little more positively concerning a slight irritation of the protoplasm immediately outside of the elastic layer of the intima. The elastic layer itself still showed no change; neither did the muscular elements of the media.

Of the same series, the preparations next in order of date are those containing thrombi forty-eight hours old. Careful study of these demonstrated the following. The cells of the plastic clot presented changes which were a progression of those already noted in the two younger clots. The size of the plastic clot was found to be considerably increased. Some of the cells constituting it were spindle-form, and numbers of them now possessed one, sometimes two or even more, slender and somewhat lengthened processes. Occasionally two or more cells were united together by a long process, and then a tendency to the formation of a cellular network could be made out. The nucleus of many was oval or oblong, and frequently there were two or more round nuclei in the cell. The elastic bands of the tunica intima were still to be seen near the bottom. These and the elastic layer of the intima in its proper

position now for the first time appeared to have undergone some change. Their index of refraction had slightly lessened, and their substances had begun to imbibe the carmine—previously they had remained entirely unstained. Through growth of the cellular covering of the intima, the walls of the plastic cup or clot now generally extended some distance above the position of the blood or fibrinous clot, sometimes as far as the first collateral branch. The cellular infiltration of some of the tissues in the neighborhood of the ligature was very decided. The adventitia and the adjacent connective tissue, as also to a slight extent the media, here presented points approaching to a purulent infiltration—an obvious preparation for the separation of the ligature. This infiltration extended some distance above and below the ligature; but in proportion as the distance from the latter increased, the infiltration became more and more limited to the internal portion of the adventitia and to the external layer of the media. No tendency of the capillaries or other vessels of the vaso vasorum, which were as yet entirely confined to the outer coat and the external layers of the media, to send projecting loops toward the lumen of the artery could be observed. A transverse section, extending through the vessel at such a level that its plane passed immediately below the bottom of the blood-clot, showed a considerable cellular increase in those inner layers of the media in apposition with the elastic layer of the intima. This cell increase could still be discovered even in cross-sections at the level of the apex of the blood-clot, but there it was not well marked.

Fig. 3. Preparation forty-eight hours old. Transverse section extending through plastic clot. High power. *c.* Cellular tissue, showing cell increase. *a.* Adventitia, also showing increase of cell elements, but not so markedly. *m.* Media, in its inner layer showing considerable cell proliferation. *e.* Folds of elastic layer of intima still very distinct and highly refractive, yet showing a tinge of carmine which cannot be so

distinctly seen in younger preparations. *e'*. Elastic bands from the lacerated intima, not so highly refractive or so free from carmine-staining as the preceding. *P*. The cellular elements of plastic clot, which when separated by needles correspond in outline and character with their description previously detailed.

Now we come to the consideration of the blood or fibrinous clots.

It has already been stated that Fig. 2, although drawn from a preparation forty-eight hours old, fairly represents the stratified appearance of all of these blood-clots. It can be seen by a glance at the thrombus represented in Fig. 2, in longitudinal section, that the clot is stratified, and that the strata are so placed that, if judged from their position alone, one would naturally conclude that the strata have been deposited at four or more different epochs. It is not to be expected that the blood caught by the ligature in the end of the stump of the artery should, against experience, form at one time four separate coagula, distinct and superimposed. The burden of proof must rest upon him who will attempt to support the assumption that the deposition of four distinct portions of the blood-clot has been simultaneous. Moreover, the different portions of this blood-clot, when studied closely and with a high magnifying power, bear internal evidence of a diversity of age. They present ocular proof that they are of different density and firmness; in other words, that the fibrin in the lower has contracted more than it has in the higher portions. The condition of the protoplasmic elements which the different portions contain also adds a confirmation to the inference that the contents of the lower have been longer placed aside from the circulation than have those of the higher. Considering all these indications then, it would appear that there is reason for the belief that the four portions of the blood coagulum under discussion have been set aside from the circulation at four

different periods, and that there has been a succession of depositions from below upward, so that the bottom portion has been first and the top last formed. While speaking of the differences shown by the several portions of this fibrinous or blood coagulum, it may be well to mention that there is still a further want of homogeneity besides that for which a mere difference in age will account.

The three lower portions of this blood-clot, aside from changes due to differences of age, have a similar structure; their elements are similarly arranged. But the fourth portion, constituting the apex of the clot, is, respecting the arrangement of its elements, of very different constitution; but more of the peculiarity of this portion anon.

What now follows has reference only to the three lower portions of the blood-clot. As has been already remarked, each of the lower portions appears to have been similarly constituted. Their similarity in constitution appears to indicate that they have been formed in a similar manner. A detailed description of one of them will suffice for all. Each of the three lower portions itself appeared, at first glance, to be formed of from two to four or more strata, successively and interruptedly superimposed. But a more careful examination under a higher power proved that the edge of a stratum could be traced in an uninterrupted serpentine course from the bottom to the top of the portion. Still closer inspection demonstrated the existence of another unexpected phenomenon, viz., the middle portion or line of such a serpentine stratum was composed almost entirely of red blood-corpuscles, a very few white ones being intermingled, while the borders of the stratum were mainly composed of a network of bands of fibrin whose prevalent direction was parallel with that of the middle line of the stratum. In the meshes of this fibrinous reticulum were numberless white blood-corpuscles and a few red ones. The serpentine course of the stratum was such that between the lateral bends the border

of the stratum was in contact with that of the coil next above or below—adjacent coils being bound together by intervening bands of fibrin. The meshes formed by these cross-bands also were filled with numbers of white blood-cells, scarcely any red ones.

What is the significance of this interesting serpentine lamellation of each of those three lower portions of the blood-clot?

Before proceeding to the solution of this question, let it be again distinctly understood that in the examination of this clot of 48 hours we are not directing our attention to an exceptional formation, but, so far as my observation goes, to a typical blood-coagulum, such as usually forms when conditions are favorable to healing in arteries after ligature. The only exceptions as yet found have been limited to cases where it was impossible to discover the slightest sign of an attempt at healing, or where the first collateral branch happened to be given off immediately above the ligature, in which case there generally was no blood-clot at all.

Let us recur now to the serpentine lamellation of these portions of the fibrinous clot.

Possibly the following observations made upon the large vessels of the mesentery and tongue of the living frog may contribute something toward an explanation.

The abdomen of a curarized frog was opened at a convenient point, and a loop of intestine was withdrawn. The latter was so placed as to bring to view in the field of the microscope one of the mesenteric arteries. By carefully stretching the exposed loop the velocity of the circulation was easily reduced to a convenient slowness. The most important fact obtained by this experiment may be best stated by detailing that portion of the observation which relates to it. By stretching the intestinal loop not only could the blood-current be slowed, but, by the employment of a little more force, it would be arrested entirely, and by continuing the strain a few moments it could be even

reversed. During such a reversal of the current, the fork of one of the large arteries was brought into the field. Instead of the backward-flowing blood columns intermingling with each other at the fork where the smaller branches joined the larger trunk, and then travelling toward the heart in one solid round and homogeneous cylinder, it was observed that as far as the field of view extended the blood on the proximal side of the fork continued to flow backward in two distinct streams. Sometimes indeed the two currents travelled with different velocities. These two separate currents appeared to preserve their individuality, and as nearly as possible the shape which characterized them while within the smaller branches. They were, in fact, two separate and distinct cylinders of flowing blood contained within the lumen of the larger arterial trunk, still preserving by their inherent tendencies, or by the viscosity of their elements, the relative positions in which these elements had previously travelled. So far as the corpuscles of a column of blood moving in a vessel are concerned, we know their relative position; the mass of red corpuscles generally occupies the centre, while the greatest number of white blood-cells are near the periphery of the column. Thus the capability of arterial blood, when flowing sluggishly, of receiving and for some time retaining forms impressed by a narrow mould, received ocular demonstration.

The tongue of a frog was next operated upon. It was drawn out and fixed conveniently for observation. One of the medium-size arteries of the organ, at a point where the vessel gave off a branch about half the size of the main trunk, was arranged for study by placing it in the field of the microscope. By means of a delicate *serre-fine* the main trunk of the selected vessel was compressed at a position a little below the branch in such a manner that the point of compression, the collateral branch, and the intervening portion of the main trunk were all in the field and well seen at the

same time. Almost immediately after compression of the main trunk the collateral branch commenced to dilate. Confining the attention to what was taking place in the main trunk between the branch and the point of compression, it was noticed that for a short time the calibre of that portion of the artery remained unaltered, and that during this time the blood within it, suddenly arrested and placed out of circulation by the compression, underwent no visible change in the position of its elements relative to themselves or to the walls of the vessel. The only movement which could be perceived at that time was that which was due to the regular impulse of the heart. Soon, however, this portion of the vessel began to dilate, reaching finally to nearly twice its original diameter. The concurrent change in the included blood-column was curious and highly instructive. As the calibre of the vessel increased, the blood-column did not correspondingly fill out the widening space by attempting to increase its diameter while shortening from above downward. No doubt this shortening and spreading out to some extent took place. But if it did so, it was to a greatly insufficient degree, for the column began to assume a curve. As the lateral resistance of the vessel-wall was removed and the heart continued to impel the column from above, this curve gradually shortened and bent more and more until the bands became finally flattened against each other, and the column was coiled in the widened lumen similarly to the successive coils of a rope or of a condensing pipe. Subsequently this clot was examined under a higher power, when the serpentine strata, of which it was composed, and the relation of their elements were found to present the same characteristics, except for age, as have already been stated for the lower portion of the blood-clot of 48 hours. Before dismissing these observations it may not be amiss to remark that no accumulations of white corpuscles sticking in masses to the walls either at the side or bottom of the vessel were seen.

The above observations were several times repeated, usually with the same result. They left in my mind but little doubt that the three lower portions of the clot of 48 hours, and the same appearance of the other blood coagula found in my preparations, were produced in a similar manner.

The different portions of the clot of 48 hours were bound together rather firmly by intercrossing bands of fibrin in the same manner, although not so tightly, as the previously mentioned juxtaposed bands of the serpentine lamella were united. The coagulum was found to be more adherent to one side of the vessel than to the other. This union also was effected by bands of fibrin, similar to the preceding.

We now come to another remarkable feature in the construction of this particular thrombus, which, so far as my observation has gone, is only to be seen occasionally. The fourth portion—that which formed the apex of the thrombus—had a constitution different from that of the preceding. It appeared to be composed of three distinct layers, separately superimposed. Furthermore, each layer corresponded in homogeneity of structure to the description which Billroth and Rindfleisch have given of the whole of the recently formed thrombus. They were, so to speak, homogeneous throughout—no massing of red or white corpuscles anywhere, not the slightest appearance of stratification. Moreover, there were to be remarked throughout the separate coagula constituting this portion of the thrombus a small number of flat ovoid cells with clear contents, the nucleus slightly oval, and the quantity of protoplasm large in proportion to the size of the nucleus. The long diameter of these cells was often three or four times that of the neighboring white blood-corpuscles. These flat cells were more numerous in the superior layer, and more scarce in the lower stratum. Besides this difference in the strata composing this upper portion, it was also to be noted that the lowest was the largest,

while the highest was the smallest stratum. Not the slightest sign of a tendency to organization was recognizable here.

Fig. 2 represents a longitudinal section of a 48-hour thrombus in the femoral artery of a dog, low power.

a. Adventitia. *m*. Media. *p*. Plastic clot. *e*. Intima. *d*. Blood-clot, three lower laminated portions. *f*. Apex of blood-clot—different in structure from the three lower portions. *g*. Bands of fibrin uniting the blood-clot to the vessel-walls rather tightly on one side, loosely on the other. *b*. Small collateral branch.

Fig. 4. Apex of the thrombus represented in Fig. 2, magnified 200 diameters. *a*. Top of third laminated portion of thrombus. *f*. Lower stratum of the homogeneous clot constituting the apex. *f'*. Middle stratum. *f''*. Upper stratum. The white corpuscles are seen at regular intervals, and a few epithelial cells are present.

The 94-hour thrombus supplied the preparations for the succeeding examination. It was found that the blood-clot now extended a little higher. Its constitution was similar to that of 48 hours, except that it was not capped with an apex of homogeneous formation. The plastic clot had much increased in thickness, both at the bottom and sides of the vessel. The thickening of the cellular layer of the intima extended high up the walls of the artery. The cells constituting the plastic clot were somewhat larger and more spindle-shape, with larger and longer processes than before. Some tendency to form a foundation for the development or vessels might be inferred from a rather uncertain arrangement of some of the spindle-form cells in rows. Sections were made from three thrombi of this age. In those from one of them the plastic clot was observed to send shoots a short distance into the divisions between the laminated portions of the blood-clot. The latter presented no other signs of organization. In those from the other two preparations this relation between the plastic and fibrinous

clot was not to be seen, and no trace of any tendency to organization of the blood-clot could be made out. In the plastic clot only slight traces of the previously mentioned elastic bands from the intima could be observed. Yet the elastic layer of the intima where its relation to the media had been undisturbed by violence was sharply defined and not much changed. Neither had the protoplasm in the media immediately beneath suffered much visible increase. The cellular infiltration of the adventitia and media near the ligature had materially advanced —a still further preparation for the separation of the thread.

Fig. 5. A faithful representation of a highly magnified view of a transverse section of a thrombosed femoral artery of a dog, ninety-four hours after ligature. The section passed through the middle of the plastic clot. An attempt to loosen the thrombus from its attachment to the arterial wall had been successfully made, thus performing without the aid of needles a dissociation of the cells which were next the intima. *a.* Adventitia. *m.* Media. *e.* Elastic folds of intima perfectly defined, and showing as yet not much if any tendency toward breaking down. *p.* Oval- and lozenge-shape cells of the plastic portion of the thrombus, their outlines, processes, and nuclei being well seen.

The next stage of the healing process was made out from the examination of four preparations, viz.: two arteries at eight days, and two at ten days after ligature. The general result may be stated thus: In some cases, granulations springing from the plastic clot have penetrated nearly every crack and crevice of the blood-clot. In these cases the blood coagulum has formed early and firm attachments to the vessel-wall. It consequently occupies a height above the point of ligation nearly identical with that which it occupied at its first formation, the increase of the plastic formation finding vent in the honeycombing of the blood-clot rather than by uplifting the latter. In other cases the growth of the plastic clot finds the

additional room it requires by slowly uplifting and pushing before it the blood-clot, which had formed only loose lateral attachments. Under the latter circumstance, I have never found in any part of the blood coagulum the slightest tendency to organization. In all the preparations of this date, the plastic clot was found to be nearly double the size of the average clot last described. The cells were nearly all spindle-form, many of them possessing long processes. A number of large stellate cells were also observed. A considerable number of blood capillaries and vascular channels could now be discerned. These were in connection above with the open lumen of the artery; but in no place could an anastomosis with the vaso vasorum be made out. In longitudinal sections, the elastic layer of the intima could be distinctly traced without the slightest breach or interruption from the top of the section down to within an extremely short distance of the point of ligation, and it appeared in its whole extent to be still tough and resistant. Neither was the media vascularized; the vessels from the adventitia could not be traced inward beyond the exterior lamellæ of the muscular coat.

The preparations which exhibited the above-described invasion of the cracks and crevices of the blood-clot by granulations springing from the plastic clot, demonstrated the fact that these granulations also were composed of tissue identical in structure with that of the formation from which they sprung. They were not, however, vascularized. In cross-section of the granulations it was impossible to distinguish any appearance which could indicate the occupation of their axis by a capillary.

Fig. 6. Transverse section of the femoral artery of a dog, eight days after ligature, highly magnified. *a.* Adventitia. *m.* Media. *e.* Elastic layer of the intima, still sharply defined. *p.* Granulations springing from the mass of cells developed from the cellular elements of the intima; they consist of spindle-cells, the direction of whose long axis in the main ob-

serves a parallelism to the axis of the granulation. The surface of the granulation is covered with one or two layers of epithelioid cells; not the slightest sign of a capillary loop occupying the axis of the granulation, nor the least trace of a vessel to be seen anywhere in the inner layers of the media, preparing to send a vascular loop through the elastic layer of the intima.

It could not be found that the clot possessed any vascular communication with the vasa vasorum at this stage. The blood which permeated the plastic clot travelled by way of the previously mentioned capillaries and blood-channels, and was supplied from the open artery above the thrombus.

Preparations from thrombi fifteen days old exhibited only a more complete development of the conditions shown to be present in the last-discussed stage of organization. I will merely add that the blood coagulum, when lifted up from its proper bed by the growth of the plastic clot, still remained, at this date, as at first formed. No changes other than those of the inevitable consequences of contraction of the fibrin were to be remarked. The clots were attached to the top of the organized or plastic clot only by their base. When, on the other hand, the blood-clot had remained in its primitive position, firmly attached to the walls of the artery, the previously mentioned granulations had so increased in number and size as to cause, probably by pressure, a progressive degeneration of the red blood disks, and their slow disappearance by granular disintegration and absorption. Preparations for the establishment of an anastomosis between the vessels of the clot and those of the walls were now for the first time definitely observed. The capillaries at the bottom of the plastic clot had by cavernous dilatation become enlarged almost into sinuses. Opposite to these enlarged capillaries, beyond them, and on the other side of the intima and media, similar varices had been formed from the vasa vasorum. A loop from one of these varices

would occasionally be seen extending toward the intima, but would not be observed to reach the latter.

At this time, however, there was no tendency of any vessel to pass into the now thoroughly vascularized clot from the media, by penetrating, at the sides of the clot, the well-defined elastic layer of the internal lining of the arterial walls.

The last study of this series was made upon preparations from the femoral arteries of dogs, twenty and twenty-five days after ligature.

All that need be said of the thrombi twenty days old is that the two previously mentioned modes of growth of the plastic clot had reached a still further development. A complete anastomosis between the vessels of the clot and those of the walls had now been established at the bottom of the clot, by the before-mentioned varices sending toward each other capillary loops, which passed through ruptures in the intima, and which united together forming a network. Even now there was no visible advance toward the establishment of a vascular anastomosis between the vessels of the walls and those of the clot directly through the sides of the artery. At the sides of the vessel the elastic layer of the intima still appeared to be intact, or but little softened. The end of the artery had already begun to shrink by reason of the transition of the spindle-cells of the organized clot into cicatricial tissue. As this contraction continues the stump of the artery assumes a conical shape, and the organized clot slowly disappears by cavernous transformation.

In those blood-clots twenty and twenty-five days old which are found attached to the top of the plastic clot, no decided metamorphoses are yet observable. The red disks often have not even become decolorized or shrunken. Those blood coagula which become occupied by trabeculæ of the plastic clot generally at this date have disappeared, the only remains of them being small masses of colored granules occupying

some of the intertrabecular spaces. Frequently, however, considerable masses of decolorized red disks can be seen filling out the spaces, while the trabeculæ are stained and infiltrated with numerous colored granules.

Fig. 7. Vascularized tissue obliterating the lumen of a femoral artery of a dog twenty-one days after ligature, injected with Beale's blue, low power. *a.* Adventitia. *m.* Media. *p.* Vascularized granulation-tissue, the dark lines in which represent bloodvessels which are seen to be in communication above with the open lumen (*L*) of the artery. *v.* Varix in the cellular new formation below the point of ligature, the same being developed from the vasa vasorum. *p*, *v.* Similar varix in the bottom of the plastic clot. The two varices communicate by means of small capillaries passing between breaks in the elastic layer (*e*) of the intima. *i.* Thickened intima. This thickening extends up to the first collateral branch.

In other and a little older preparations, the communication between the varices was accomplished by one or two tolerably large trunks.

Fig. 8. Longitudinal section of the femoral artery of a dog twenty-five days after ligature, injected. Low power. *a.* Adventitia. *m.* Media. *m'.* Media at end of artery where ligature was applied. *c.* Cellular tissue. *e.* Elastic layer of intima at side of artery, where it appears unbroken and unchanged. *I.* Thickened cellular portion of intima, on a level with blood-clot. *V.* Varices in the cellular tissue at end of the artery. *T.* Large trunk which establishes the anastomosis of external vessels with those of the clot. A few smaller vessels pass directly from the varices to the capillaries at the sides of the plastic formation obstructing the lumen. *p.* Thoroughly vascularized plastic clot, now showing commencing cavernous transformation. Up the centre of this is seen to pass a large vascular stem.

It is observable, both in this figure and in the one imme-

diately preceding, that there is a rich capillary plexus extending from the bottom to the top of the plastic clot. *d*, *d'*, is a blood-clot showing the serpentine lamellation and exhibiting no sign of approaching organization or degeneration. It has been uplifted from its original position by the growth of the plastic clot. *g*. Fibrous filaments which probably served the function of bands of union between the clot and the arterial walls when the former was first deposited. At present the blood-clot has no attachment except at its base, where, with considerable firmness, it is united to a cellular mass (*h*) which itself is an outgrowth from the intima and from the top of the vascularized clot. This cellular mass (*h*) is permeated by large channels through which blood can freely pass. *L*. Open lumen of the artery.

Second Series. — The *second series* of experiments was instituted with the object of learning, if possible, what proportional part those wandering cells which may have reached the interior of the ligated artery, through the ruptures in the intima caused by the ligature, may have borne in the healing process as above described.

The sections from all of these preparations presented very uniform pictures. Each one showed the presence of two distinct blood-clots; the one above the point of compression by the forceps, the other between that point and the position of the ligature. At the same time they demonstrated the fact that these double blood-coagula were similar in constitution to those stratified clots found after the usual application of the ligature. They further showed that up to ten days there was no disposition in them to organize. The preparation five days old exhibited below the bottom of the lower blood-clot a very slight accumulation of plastic material. The cells of which the latter consisted were in the main similar to leucocytes, which had probably wandered in through the laceration in the coats produced by the ligature. Besides these, and confined mostly

to the neighborhood of the elastic layer of the intima, were a number of cells similar to those previously described as generally present after the ordinary application of the ligature, but neither the leucocytes nor the epithelioid cells seemed to be possessed of any great degree of activity. The media and adventitia in this neighborhood were the seat of a very lively cellular infiltration. The lower blood-clot appeared very completely to fill out that portion of the calibre of the artery in which it was located. The most striking phenomena were observed at the level of the point of compression by the forceps. At this point there were very decided indications of a lively state of activity in the intima and innermost layers of the media. At the point of compression, and in a decreasing degree a little above and below it, an accumulation upon the intima of the same kind of cells which constituted the previously described plastic clot of 24 hours, was very noticeable. In longitudinal section, this accumulation, having its greatest depth at the point of compression, formed a considerable promontory which projected from each side into the lumen. The elastic layer of the intima at this point was more deeply stained with carmine than were the portions more remote. It was also to be noticed that the elastic layer in this situation was slightly bulged inward by a tumefaction and a cellular infiltration of the inner layers of the media. This cellular infiltration of the inner layers of the media was limited to the inner lamellæ, and was not even here decided. There was no decided increase of protoplasmic elements, either in the external layers of the media, or in the adventitia. Nor was there any other appearance leading to an inference that there had been any wandering of white blood-corpuscles from the vasa vasorum.

Sections from the preparations eight and ten days old showed only a further advance of the same process. The two opposite promontories projecting into the lumen where

pressure had been applied, had met and formed an extensive union. They consisted almost entirely of spindle and stellate cells with long and anastomosing processes. They were observed to be permeated by a capillary and canalicular vascular network. At this early date the vessels from this plastic formation had extended as far as the inner layers of the media to a depth corresponding to the extent of the cellular infiltration above alluded to, but had not gone further outward. There was not the least trace of an anastomosis having yet been established with the vasa vasorum. The vasa vasorum of the adjacent adventitia did not yet exhibit any tendency to send vascular loops into the media. The blood coagula above and below this point of activity showed the usual serpentine lamellation, and presented no appearance of progressive organization. At the point of ligature the vessel-walls and the connective tissue were in a state of purulent infiltration, the ligature having nearly ulcerated through.

Fig. 9. Thrombus ten days old. A typical view, in longitudinal section, of the condition invariably found to be present after ligation in this manner. Low power.

A. Position of ligature. *B.* Level of application of forceps. *a.* Adventitia. *m.* Media. *c.* Cellular tissue. *p.* Cellular formation at the bottom of clot, non-organized and apparently not larger than such an accumulation usually is at five days; it consists mainly of cells similar to white blood-corpuscles; only a few epithelioid cells are scattered through it, and applied along the elastic layer of the tunica intima; no granulations springing from it penetrate the crevices of the laminated clot (*d*) immediately above.

The blood-clot (*d*) is seen to be formed of two separate portions of coagulum, exhibiting the previously named serpentine lamellation. This blood-clot is firmly adherent at the bottom, but possesses only slight bands of union with the lateral walls of the vessel. *L.* Lumen of the vessel. While manipulating this

section, a blood-clot similar to *d* fell out from the position, *L*. This clot was adherent, though not very strongly, to the top of p'', and it had no lateral attachment whatever.

On a level with *B* the enormously thickened intima, p', and the growing inner layers of the media are more or less blended. Large granulations arise from this tissue and project inward, entirely obliterating the lumen. They often meet and unite, forming a trabecular network with very small narrow interstices through which flows the blood; p'' consists of such a trabeculated mass. The structure of the granulations themselves is cellular, in fact identical with those granulations which form the plastic clot after the ordinary ligature. *v*. Capillary vessels and small blood canals in the inner layer of the media and the thickened intima: they are in communication with the intertrabecular spaces; the latter open into the lumen of the artery, and receive and return their blood thence. *e*. Position of elastic limiting layer between the intima and media. Only traces of this elastic layer, however, can be discovered here; immediately above and below the point of compression it is well defined. The cellular portion of the tunica intima is very much thickened.

Third Series.—The *third series*, consisting of a few preparations where *limited torsion* had been performed upon the femoral arteries of dogs, showed a process of healing similar in very many respects to that described for the *second series*.

At the point where the artery was seized and compressed by the limiting forceps, was to be seen the same growth of the plastic clot springing mainly from the irritated intima, as was described and represented in Fig. 9. The principal difference between the preparations from the two series in question was located in the lower end of the arterial stump, and was due to the mechanical difference between the operation for ligature as performed in the modified way, and that usually followed while performing *limited torsion*. In the latter, if the operation is

properly done, by means of the twisting forceps, the external tunic of the vessel is formed into a kind of knot, so to speak, while the middle and inner coats are separated from the adventitia for a slight distance, and are curved inward, thus forming a more or less perfect valve a small distance below the point of seizure by the limiting forceps. By pressure of the limiting forceps the internal tunic of the artery is rubbed together a little distance above the end of the arterial stump, as in the operation for the second series. This is the point where the healing process is again most active, where the granulations spring from the proliferating intima, and where, by the union of the latter and the subsequent changes which have already been mentioned, the lumen of the vessel is first permanently closed.

In the space below the point of compression by the limiting forceps (that part of the lumen of the artery included between the point of compression above and the incurved walls below) there was the same fibrinous clot having a serpentine lamellation and showing no signs of organization, and immediately below it the same accumulation of colorless cells represented at *p* just above the ligature in Fig. 9.

The incurved media was early infiltrated with a great number of cells, and the twisted adventitia still more abundantly showed this infiltration.

The healing in these cases seemed to progress with about the same rapidity as in cases forming the second series.

Fourth Series.—The *fourth series* of experiments was directed toward the determination of the sequence of phenomena after the flow of blood in an artery has been arrested by the temporary use of the needle. As was previously stated, the third and fourth methods of applying acupressure were followed. The number of preparations constituting this series was also somewhat limited. An examination of the few made has led to the conviction that the process of healing after acu-

pressure is very similar to that which secures the obliteration of the ligated artery. The sections examined show that the blood coagula in all have been fashioned in accordance with the same general law previously enunciated for ligature, and that there has been a similar although very much less marked increase in the cells of the intima at the point of greatest irritation, which in the third method is at the locus of the needle.

Fig. 10 represents a thrombus after *acupressure* (third method), 36 hours old. Low power.

a. Adventitia. *m.* Media. *n.* Position of needle. *p.* Plastic clot at the bottom. *d.* Stratified clot above. *l.* Portion of lumen now free; when the section was made this was occupied by a recent unstratified or homogeneous blood-clot which fell out during handling.

In the preparations obtained by acutorsion (or the fourth method), the chief difference from the preceding was that the processes were more active. In all the preparations of this series the plastic clot seemed to be the sole organizing agent, the blood coagula to be inert or passive.

Fifth Series.—The *fifth and last series* consisted of a few preparations obtained by compressing, between the arms of serre-fines, the femoral and common carotid arteries of good strong rats—the pressure being continued from two to four hours. In some of these preparations there was evidence that the channel of the artery had been restored soon after removal of the pressure. In some, however, the lumen of the vessel remained permanently occluded. In the latter the surfaces of the intima brought into contact by the serre-fines remained adherent, and a blood and plastic coagulum similar to those seen after acupressure by the third method were observed. The plastic clot here also played the same rôle as in the former series, but the inflammatory process, as might have been expected, was even less advanced than in the case of acupressure.

In concluding the discussion of the five series of experiments above related, let us again call attention to the almost unvarying uniformity throughout all of them, of apparently *one method of healing; i. e.*, by means of the *organization and vascularization of the plastic clot alone.*

Concerning the collateral circulation there is, as far as I know, no dispute. Since the time of Porter it has been well established that there are two species of collateral circulation, a direct and an indirect, which, however, may both be present in the same instance.

Respecting the length of time required for the perfect establishment of the collateral circulation, the following observation may have some significance.

A loop of intestine of a curarized frog was withdrawn from the abdominal cavity and placed under the microscope, so that the artery running along the inner curve of the gut was in the field. Numerous small capillaries were observed to come off from it and run around the intestine immediately beneath the serous covering. These capillaries gave off numerous branches which united with each other. The blood was now interrupted in its wonted course through the artery by pressing the point of a needle upon the latter, about half way between the places of departure of two adjacent capillaries. Immediately the portion of the artery on the distal side of the compressing needle became empty and contracted for a little distance; at the same time the proximal end commenced to dilate. Isochronous with this, the nearest capillary on the proximal side began rapidly to dilate; in the space of a few seconds the blood in it went by jerks, showing the arterial impulse. A few seconds later the lateral anastomosing branches also began to dilate rapidly. Later still, the first capillary branching from the artery on the distal side of the point of compression began to return its blood into the artery, at first slowly, then more rapidly, and finally with an arterial impulse.

By this time (certainly not more than twenty seconds after the first interruption of the arterial current), the anastomosing capillaries which had established the collateral circuit were nearly as wide as the artery itself, and were beating quite as violently. The arterial flow beyond this point did not now seem to be at all affected. The establishment of the collateral circulation in the frog's tongue, after the experiment related some distance above, did not take place so rapidly, since at least fifty seconds were necessary for its free establishment.

What is the origin of the cells which constitute the organizable plastic clot?

After the study of our preparations we have no doubt that the great masses of them are derived immediately from the endothelial and other cell elements of the tunica intima, by a process of proliferation excited partly by the irritation caused by the ligature, the needle, or forceps, and stimulated by the unwonted supply of nutrient material constantly retained within their reach, in consequence of the sluggish movements of the fluids of the blood.

Whence come those colorless elements which have been brought from some distance by the blood current—those both of the plastic and of the fibrinous clots of a thrombus such as we have been considering?

Let us consider first the migrated leucocytes, whose presence in the plastic clot in considerable numbers I have previously mentioned, and to whose agency Billroth and Rindfleisch ascribe, in a great degree, that organization of the fibrinous clot which they believe in.

Do they come directly through the walls of the vessel, or do they come principally, by way of the arterial current, from above the thrombus? Bubnoff declares that many of the white blood-corpuscles found in a blood coagulum after ligature of a vein, have travelled directly through the vessel-wall. Billroth repeated the experiments of Bubnoff, and extended

them to thrombosed arteries. He admits, in a general way, the conclusions of the latter, but while stating that he has found the vermilion granules in the midst of the blood-clot in the carotid artery of a rabbit, he says that *they are free*, i. e., not contained within the body of leucocytes. Rindfleisch also accepts Bubnoff's conclusions. Tschausoff has repeated the experiments of Bubnoff, and has declared that he has been unable to confirm the observations of the latter. Durante, after an elaborate series of experiments, contests the conclusions of Bubnoff (*vide* pp. 15, 16), as also do Cornil and Ranvier.

Thus we have seen that not only have the observations of Bubnoff concerning the source of the organizing elements of the thrombus failed to receive exact confirmation by the experiments and observations of any one of the previously named investigators, but that, on the contrary, no less than five most excellent observers, after carefully repeating and somewhat extending his experiments, have flatly contradicted him in many important particulars.

It therefore seems to me that, in the face of these negative results and positive assaults, neither the observations and conclusions of Bubnoff, respecting the migration and functions of the white blood-corpuscles found in the lumen of the ligated vessels, nor the theories of others based thereon, should stand for one moment.

We are, then, forced to the conclusion that if any leucocytes at all have wandered into the clot, they could only have come from the blood in the lumen of the artery above the thrombus.

As to the function of the leucocytes found in the blood or fibrinous clot, it is so nearly nil, as we have already seen, that whatever it may be it cannot save that clot from inevitable destruction. As to whether or not those leucocytes found in the plastic clot have any mission to perform, I have no facts to offer, and therefore refrain from advancing assumptions.

We next inquire into the genesis of those colorless cells

which may, by way of the blood current, have travelled to the thrombus from some distance.

The question of the genesis of the colorless cells of the blood has for years called forth the most indefatigable efforts of the most eminent microscopists, and has taxed the genius of the greatest physiologists of the age. Yet we are far from possessing an entirely satisfactory solution of the problem

It is, however, generally admitted that in the spleen, in the liver, in the lymphatic glands, and, according to some, in the red marrow of bones, the rate of increase of these cells is more rapid than elsewhere. It has, consequently, been claimed that each of those organs has something special to do with their generation. It has also been demonstrated by Striker and by others that the stable cells of the connective tissue may physiologically give origin to cells which enter the lymphatic circulation, and which cannot, by any means at present known, be distinguished from lymph corpuscles.

The lymph corpuscles themselves have been observed to increase during their own proper circulation, and it is generally admitted that whenever the circulation is sufficiently slowed and oxygen is present in sufficient quantity, their self-propagation is by no means infrequent.

The following observation constrains me to recognize an additional source of supply, especially very considerable during the existence of inflammation.

Fig. 11 represents a capillary of the mesentery of a frog, nine hours inflamed and magnified three hundred diameters, afterward amplified. *e*. Capillary walls. *l*. Leucocytes or wandering cells, external to the walls. *g*. Cells of adventitia swollen and granular. *f*. Capillary endothelia granular and swollen, their prominent bellies encroaching considerably upon the lumen of the vessel. The arrow indicates the direction of the blood current. *a*, *d*, *i*. Colorless corpuscles adherent to the walls. *d*. Is rather firmly bound to the wall by means of

a bud penetrating the latter. *i*. A corpuscle adherent at the point of union of two adjacent endothelial cells. *k*. An unattached white corpuscle. *a*. A white corpuscle, adhering tightly to the upper end of an endothelial cell (*b*). At the commencement of the observation, this cell (*b*) was flatly applied to the capillary wall as the other endothelial cells now are, but its upper extremity showed the slightest possible separation from the lower point of the next endothelial cell above. The upper point of this cell (*b*) appeared a little thicker than that of its higher neighbor. The blood current was sluggish, and at intervals interrupted. Occasionally for a few moments the current would move on with considerable energy. At the point of observation, besides the obstruction to the circulation by the swollen endothelia, the current was impeded by the adherent white corpuscles. The relative position of the corpuscles was such that, at the time when the current was forced forward with some impetus, the points of the red blood disks went with considerable momentum against the chink, and were violently jammed into the angle formed by the upper surface of the adherent white corpuscle (*a*) and the surface of the endothelial cell above it. In the attempt to pass on, these red blood disks must perforce bend around the white corpuscle (*a*). The tendency of these forces was evidently to loosen and to pry out from its bed the upper end of the endothelial cell (*b*).

During an energetic increase in the velocity of the current this was actually observed to take place. After that, the next violent movement of the blood current sufficed to detach the whole cell and to carry it off in advance of the other elements. When the movement slowed again, it was observed that the place of former attachment of this cell (*b*) was void of its endothelial covering. I have observed the above-described phenomena on one other occasion.

Now any one who carefully examines the course of capilla-

ries in the inflamed mesentery of a frog will meet, at not very infrequent points, with just such appearances of the interior of the vessel as the detachment of an epithelial cell will go far to explain the significance of. I confess that I am inclined to believe that this appearance would occur much more frequently but that soon a white corpuscle possessing unusual viscosity, fastening itself there, spreads out and fills the void. It will be remembered that, *à propos* of the apex of the forty-eight hour blood-clot of a ligated artery, a number of epithelioid cells present in the clot were both described and figured.

As a possible explanation of their presence, we may suppose that they may have been detached from the irritated intima at or above the level of their location in the clot.

Once admitting, in inflammations affecting the inner lining of bloodvessels, this detachment of swollen and irritated epithelium, it may be claimed as a necessary consequence that those cells must appear in appreciably increased numbers in the blood. Now precisely this is found to be true respecting the blood in the inflamed stump of a ligated artery; on the other hand, it has not yet been observed of the blood in more general inflammations. It may be affirmed respecting the latter cases that because the expected increase is not apparent the theory has at once been placed *hors de combat.*

But does it necessarily follow that herein is an insuperable objection? These swollen granular epithelial cells which are displaced from their position on the internal lining membrane of a vessel are in a state of irritation. What should happen to their shape after being set free in the blood current? Under this condition undoubtedly their tendency would be to assume a spherical outline, and, if they should remain suspended sufficiently long in the flowing blood, it is probable that every trace of their original form would be obliterated.

Concerning the changes which an endothelial cell may pass through under somewhat similar conditions, is an observation

of Cornil and Ranvier (Manuel d'Histologie Pathologique) on the behavior of the endothelial covering of the trabeculæ of the omentum of adult animals.

They found that after inflammation has been artificially excited, the peritoneal fluid becomes cloudy and contains many cellular elements somewhat similar to pus-corpuscles; others more voluminous, having one or more oval nuclei; and intermediate cells between these two. In cells which are applied to the trabeculæ are observed all the phenomena of multiplication. The multiplication is such that the hypertrophied cells form projections on the trabeculæ; or they are adherent to it, at one time by a large surface, at another by a single point; they become detached, and may continue to live and vegetate isolated in the peritoneal fluid. Their protoplasm, which is soft and granular, is susceptible of taking the most varied forms and of giving birth to amœboid prolongations and to new cells. After five or six days the majority of the detached voluminous and turgid cells reapply themselves to the trabeculæ, while presenting projecting bellies. They shrink, flatten themselves against the trabeculæ, present a protoplasm more or less similar to that of their primitive type, and may assume later the appearance of endothelium.

I conceive it possible for the endothelium of the vascular tract to undergo similar metamorphoses.

Applying the foregoing to the subject before us, it seems probable that in addition to the ordinary white corpuscles of the blood and their immediate descendants, there may be present, both in the plastic clot and in the blood of a ligated artery, other somewhat similar, often larger, corpuscles, which are the metamorphosed endothelial cells of the lining membrane or their descendants.

Furthermore, it is highly probable that among the epithelioid cells which constitute the mass of an organizing clot, and which spring, in the main, from the endothelial cells of the ad-

joining tunica intima, there may be no very inconsiderable number of endothelial cells detached from the arterial wall above, and but little changed.

CONCLUSIONS.

The foregoing study has led me to the following conclusions:—

1st. After the ligation of an artery, if the first collateral branch above is sufficiently distant, a blood coagulum generally forms at the bottom of the arterial stump, but not always.

2d. The formation of this blood coagulum, when conditions are favorable to healing, is not sudden. Frequently the structure of this fibrinous clot proves it to have been deposited at interrupted intervals. The blood-clot is, therefore, often larger some hours or days after its first formation, than when it is first deposited. See Fig. 2.

3d. The portions of the fibrinous clot which have been deposited at interrupted intervals have usually a stratified aspect. The blood-clot is not homogeneous in structure.

4th. The blood or fibrinous clot does not undergo a genuine organization or vascularization. It acts only as a temporary barrier to the course of the blood, and as a foreign body, whose tendency is first to produce a certain amount of irritation in the adjacent internal coat of the vessel, and to finally disappear after slow disintegration.

5th. The healing of an artery ligated after the ordinary method is effected by the organization, vascularization, and subsequent cicatricial metamorphosis of a plastic formation which grows between the blood-clot and the ligature, and which is mainly composed of colorless endothelioid cells.

6th. The origin of the cells of the plastic clot is to be referred chiefly to a proliferation of the endothelium and subjacent cellular elements of the tunica intima, between the point

of ligation and the first collateral branch above. See Figs. 1, 5, and 6.

7th. The rapidity of the healing process is usually proportionate to the growth of the plastic clot.

8th. The growth of the plastic clot is at first somewhat stimulated by the presence of a fibrinous or blood clot. The presence of the latter is not essential, for the formation and organization of the plastic clot occasionally take place without it.

9th. The plastic clot begins to present signs of commencing vascularization as early as the sixth day.

10th. The organizable or plastic clot is vascularized at first independently of the vasa vasorum. Some days before any trace of a vascular communication between the plastic clot and the vasa vasorum can be discovered, the former is thoroughly permeated by a rich capillary network which is in communication with the open lumen above the thrombus, by means of blood channels or sinuses of considerable size located mostly in the superior portion of the plastic clot. The first vascular formation generally appears in the peripheral portions of this clot

11th. Usually between the fifteenth and the thirtieth day after ligation an anastomosis is established between the vessels of the clot and those of the walls of the artery. The communication is established at the bottom of the arterial stump where the intima and media have been cut through by the ligature. At this date the elastic layer of the intima, from the top nearly to the bottom of the clot, is sharply defined, presents little evidence of softening, and offers no perforation for the establishment of a lateral anastomosis between the vasa vasorum and the vessels of the clot directly through the sides of the artery. See Fig. 7.

12th. The plastic clot, by a gradual metamorphosis into cicatricial tissue, and by a subsequent cavernous transformation of the latter, finally disappears—the only remains of the vessel and of the clot being a tough fibrous cord.

13th. If the blood-clot, during the first days of its formation, become firmly adherent to the vessel-wall, the increase in the size of the plastic clot causes granulations springing from it to grow into the crevices and channels of the blood coagulum. Through the continued invasion of the blood-clot by these granulations, and their increase in thickness, the blood-clot disintegrates in consequence of the gradually increasing pressure, and is finally absorbed. See Fig. 6.

14th. But if the blood coagulum form only slight connections with the walls, the plastic clot, while increasing in size during the process of organization, gradually uplifts the blood-clot and pushes the latter before it. In these cases, as late as the twentieth day, when organization and vascularization have been nearly completed in the plastic clot, not the slightest indication of change, except that naturally due to the contraction of fibrin, is to be seen in the uplifted blood-clot. See Fig. 8.

15th. If, in addition to the usual method of applying a ligature, compression be produced upon the walls of the artery a short distance above the point of ligation, in such a manner as to slightly rub together opposite points of the surface of the internal limiting membrane without rupturing the latter, and to excite at that place an irritation, the plastic clot mainly forms at that point instead of at the level of the ligature, and the obliteration of the lumen of the vessel and the permanent arrest of hemorrhage are more rapidly and more certainly secured. A practical application of the same procedure to the usual methods of performing acupressure may, *à priori*, be expected to secure similarly good results. See Fig. 9.

16th. The process of healing in an artery after limited torsion has been performed is, in its essentials, identical with that mentioned in the preceding paragraph.

17th. The process of healing in an artery after acupressure does not essentially differ (except in its slowness) from that which is usually seen after simple ligation has been done. In

consequence of the slowness of the healing process present in acupressure, either limited torsion, simple ligation, or the modified ligation above described, would seem in general more reliable. See Fig. 10.

18th. By the compression of an artery for a few hours between the arms of a pair of forceps or of a serre-fine applied directly to the vessel-walls, an inflammation may be excited through the agency of which the lumen of an artery may be permanently obliterated. This inflammatory process does not differ materially from that which is present after simple acupressure. This procedure should, *à priori*, be peculiarly useful when the vessel-walls are diseased, as in atheroma or in aneurism.

19th. The organizing elements which are active in the healing of arteries are neither the white blood-corpuscles which are a part of the fibrinous clot at the time of its formation, nor those which may wander into it afterward; nor are they principally the so-called white corpuscles of the blood and their progeny, which may have wandered into the plastic clot.

20th. The so-called wandering cells, which may be found in any part either of the plastic or of the blood clot, seldom, if ever, reach their destination by escaping from the vasa vasorum and passing directly through the vessel-walls.

21st. The endothelium which lines the inner surface of the arteries and capillaries may be considered the source of origin of some of the increased number of colorless elements of the blood in local inflammation. From this conclusion naturally issues the corollary, that the endothelia in general may be considered as some of the possible physiological progenitors of the colorless elements of the blood. See Fig. 11.

22d. In the inflammatory processes through the agency of which an artery is healed after ligature, acupressure, or torsion, the stable cells of the tunica intima play a very important—probably the most important rôle.

EXPLANATION OF PLATE I.

FIG. 1.

A transverse section of the femoral artery of a dog, 24 hours after ligature. High power. See pp. 26–27. (FIRST SERIES.)

FIG. 2.

A longitudinal section of a 48-hour thrombus in the femoral artery of a dog. Low power. See pp. 25, 35. (FIRST SERIES.)

Fig. 1

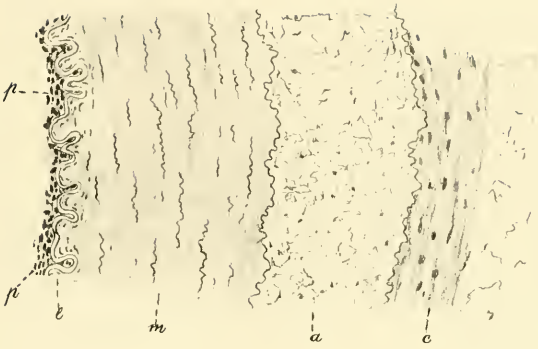
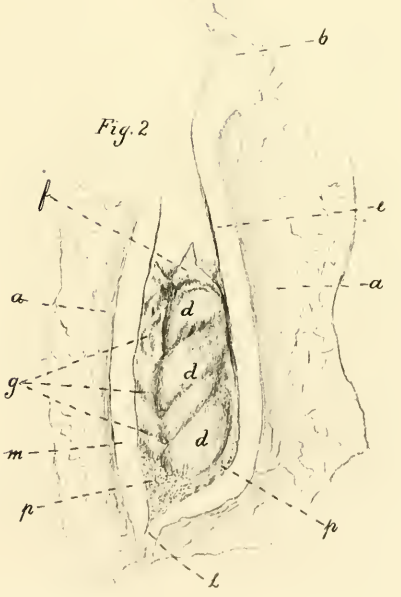


Fig. 2



EXPLANATION OF PLATE II.

FIG. 3.

Transverse section passing through the plastic portion of a clot in the femoral artery of a dog. Preparation 48 hours old. High power. See pp. 28–29. (FIRST SERIES.)

FIG. 4.

Apex of the thrombus represented in Fig. 2, magnified 200 diameters. See p. 35. (FIRST SERIES.)

Fig. 3.

Fig. 4

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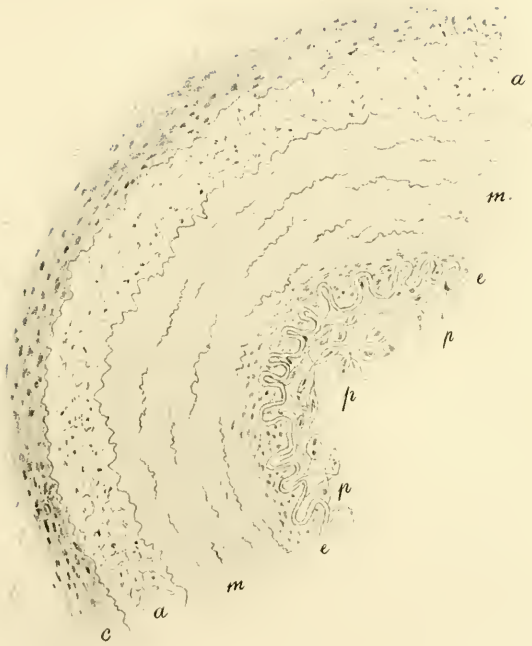
EXPLANATION OF PLATE III.

FIG. 5.

A faithful representation of a highly magnified view of a transverse section of a thrombosed femoral artery of a dog, 94 hours after ligature. See p. 36. (FIRST SERIES.)

Fig. 5.



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EXPLANATION OF PLATE IV.

FIG. 6.

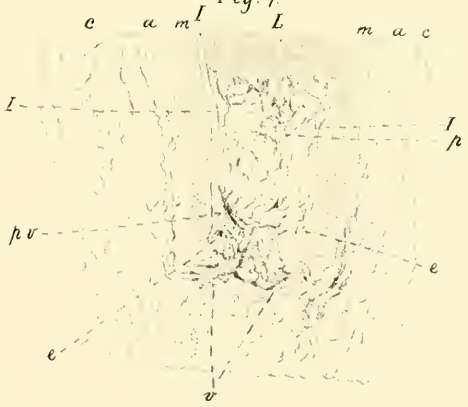
A transverse section of the femoral artery of a dog, 8 days after ligature. High power. See pp. 37–38. (FIRST SERIES.)

FIG. 7.

Vascularized tissue obliterating the lumen of a femoral artery of a dog, 21 days after ligature. Injected. Low power. See p. 40. (FIRST SERIES.)

Fig. 6.

Fig. 7.

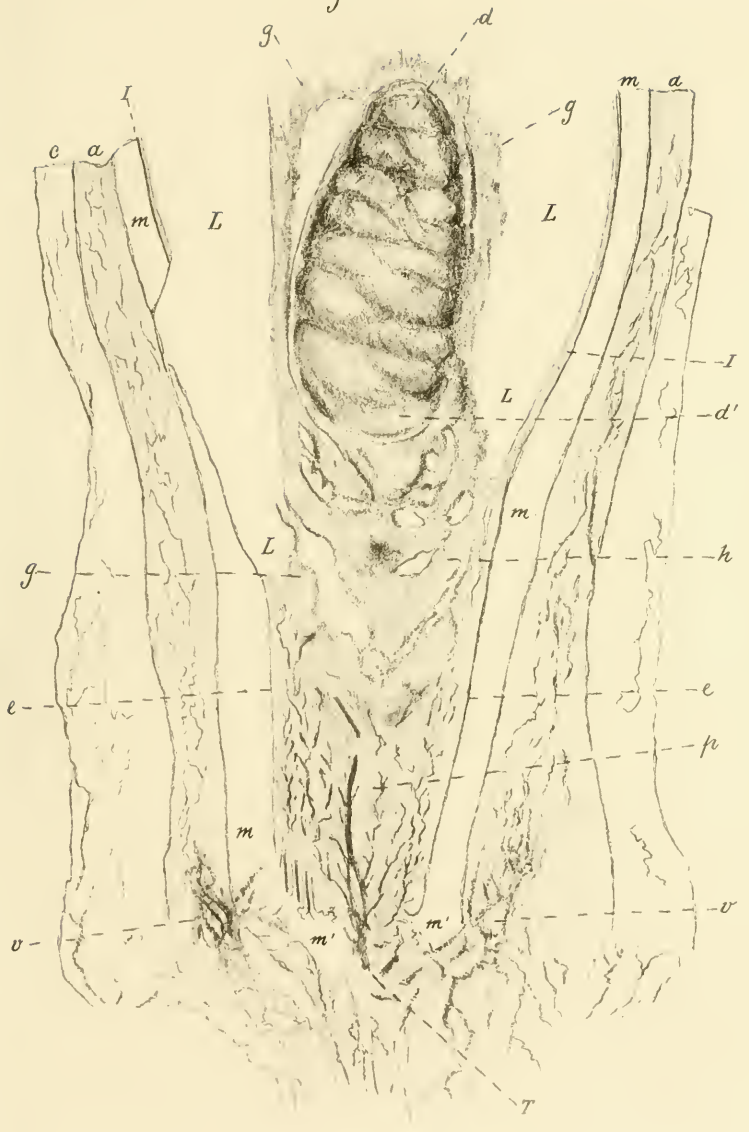


EXPLANATION OF PLATE V.

FIG. 8.

A longitudinal section of a femoral artery of a dog, 25 days after ligature. The blood or fibrinous clot has been uplifted from its primitive position. Injected. Low power. See pp. 40–41. (FIRST SERIES.)

Fig. 8.



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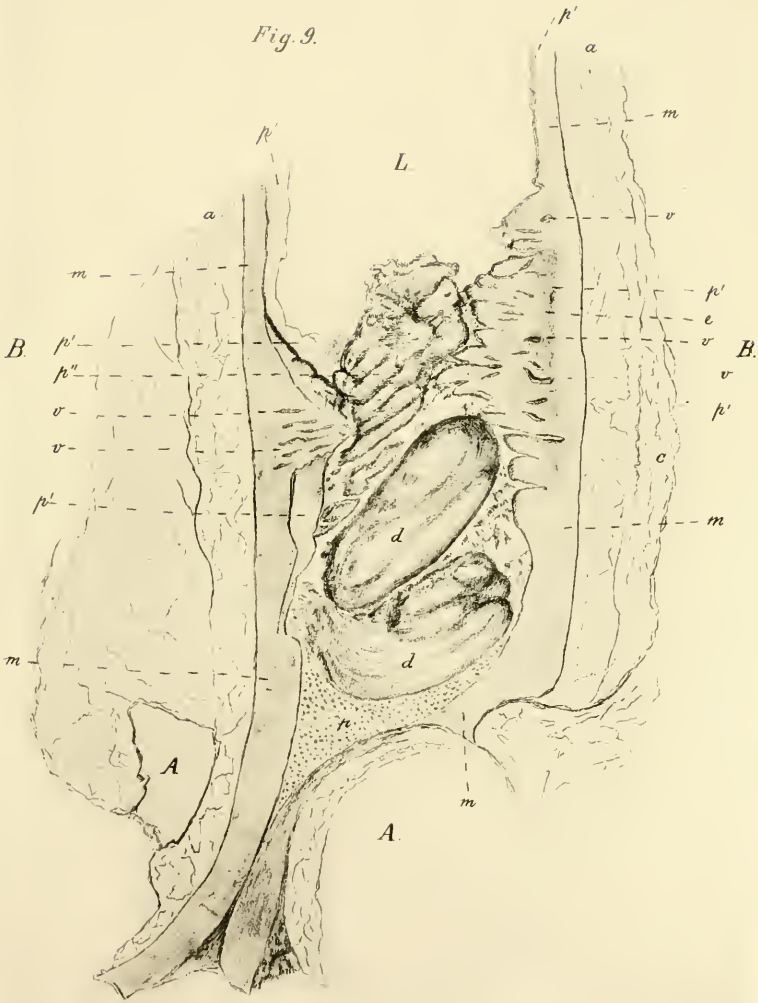
EXPLANATION OF PLATE VI.

FIG. 9.

A thrombus 10 days old. Longitudinal section. Modified ligature. Low power. See pp. 43-44. (SECOND SERIES.)



ARTOTYPE.

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EXPLANATION OF PLATE VII.

FIG. 10.

A thrombus after acupressure (third method), 36 hours old. Low power. See p. 46. (FOURTH SERIES.)

FIG. 11.

A capillary of the mesentery of a frog, 9 hours inflamed. High power. See pp. 50–51.

Fig. 10.

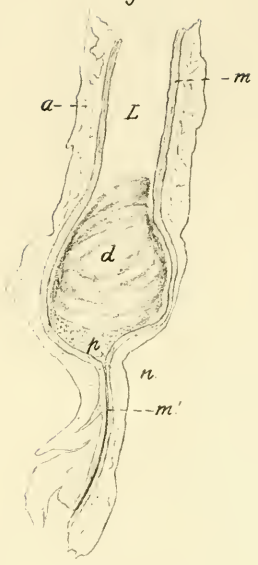

Fig. 11