Gangrene as a complication and sequel of the continued fevers, especially in typhoid / by William W. Keen.

THE SHATTUCK LECTURE.

GANGRENE AS A COMPLICATION AND SEQUEL OF THE CONTINUED FEVERS, ESPECIALLY OF TYPHOID.

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Mr. President and Members of the Massachusetts Medical Society: — It is first of all my pleasant duty most cordially to thank you for honoring a stranger by electing him to deliver the Shattuck Lecture for 1896. Yet I am not a stranger in the old Bay State, for I see around me many esteemed former pupils and many men who honor me with their friendship. Even were this not so, do we not all belong to one common guild united by one common impulse, the relief of human suffering and the prolongation of human life — a guild which, God be thanked, knows no dividing lines of State or nation, creed or color, but all around this goodly earth is marching on, hand clasped in hand, in its heavenly mission of healing?

When I received the invitation, in casting about for a subject, it occurred to me that it would be just twenty years since I delivered the fifth Toner Lecture on "The Complications and Sequels of the Continued Fevers," which required a sequel, a sort of "*Vingt ans après.*" That lecture for the first time gathered together the many isolated cases reported in the previous thirty years and systematized our knowledge of the surgical relations of typhoid fever. The twenty years that have elapsed since its delivery have rendered some of its pathology quite obsolete, especially by the discovery in 1880 by Eberth of the bacillus of typhoid; but

the clinical facts and deductions there set forth are as true to-day as they were then; and that typhoid and other continued fevers have important surgical relations is now well recognized by the profession.

It was my intention at first to consider in this, as in that, lecture all the surgical relations of typhoid; but when my intelligent and industrious friend, Dr. Thompson S. Westcott, of Philadelphia, who kindly consented to tabulate all the recorded cases of such complications and sequels since 1876, brought to me a harvest of between seven and eight hundred cases, I found that it would be quite impossible to review them all within the limits of a single lecture.

These, with the 433 included in the former lecture, make a total of nearly 1,200 cases (besides 352 cases of parotitis not included in the general summary in the first lecture, for they chiefly followed typhus), by far the largest and most complete table ever published. They practically cover the reported cases of the last fifty years.

I would neglect another pleasant privilege, as well as duty, were I not to acknowledge the repeated courtesy and broad-minded liberality of the officers of the Library of the Surgeon-General's Office of the United States Army, for the important aid they have rendered me in placing the treasures of their unrivalled collection at my disposal for frequent consultation, without which, this extensive tabulation would have been absolutely impossible.

The bone lesions following typhoid have been more or less prominently considered of late, especially by Parsons of Johns Hopkins in this country.* Gangrene as a complication or sequel, however, is less frequent, and also less well known; and I purpose, therefore, in the present lecture to consider it alone. The many other complications of typhoid I hope to take up in a monograph, which I shall

* Johns Hopkins Hospital Reports, Vol. v., 1895, 417; and Annals of Surgery, November, 1895, 623.

publish hereafter, which will include both my Toner and the present Shattuck lectures, with the tables of all the cases gathered together by Dr. Westcott, with observations and deductions as to their symptoms, pathology and treatment.

English and American authors in the past have not given the attention to gangrene after typhoid which its importance deserves. Thus Reynolds and Bartholow make no allusion to it; Wilson only alludes to gangrene of the lung and the mouth, two of its rarer sequels; Flint mentions it, but had never seen a case; while Murchison in his classical work and Hutchinson in an excellent chapter on typhoid in "Pepper's System of Medicine" give it only a brief notice. Nor have the surgeons done it any better justice. Neither Gross, Agnew, Ashhurst nor Holmes ("System of Surgery") mention it. Barwell, in the "International Encyclopædia of Surgery," refers to it briefly.

We owe our chief knowledge of the subject to French authors, and to a few recent German and American publications. Larrey,* Hildebrand,† Alibert,‡ and Fabre§ mention sporadic cases of gangrene; but attention was first seriously called to its occurrence in typhoid fever in 1857 by Bourgeois‖ and Bourguet.¶ The next papers of any importance were by Gigon in 1861 and 1863.** The former established the fact of gangrene from arterial obstruction by autopsy, though he regarded the gangrene as a coincidence rather than a consequence of the fever. In 1863, Patry†† confirmed these earlier observations. The cases reported by these authors were included in the summary published in the Toner Lecture already alluded to.

* Mém. et Campagnes, iii., 72.
† Typhus Contagieux, 1806.
‡ Thèse de Paris, 1838.
§ Gaz. Méd. de Paris, 1851, 539.
‖ Bull. Soc. Méd. des Hôp., Paris, iii, 311.
¶ Gaz. Hebd., 1867, 646.
** L'Union Médicale.
†† Arch. Gén., 1863, i., 129.

Since my own contribution, some of the more important papers are those of Spillman,* Gaston David,† Barié,‡ Deschamps,§ Haushalter,‖ Flexner,¶ and Quervain,** beside a very large number of individual cases, which have been reported by various authors.

One would suppose *a priori* that gangrene would only follow severe attacks, but so large a number of cases of gangrene have been reported after relatively mild attacks that we must concede the possibility of gangrene in mild cases as well as severe ones. Hence, the watchfulness of the physician should never relax by reason of the fact that the case is running a mild course and that gangrene is an infrequent result of typhoid.

Following the example of my Toner Lecture, Dr Westcott has included in his table a few cases of typhus and other continued fevers, as well as of typhoid. The vast majority, however, are cases of typhoid, much more so than appears in the statistical numbers, for by "typhus" is often meant "typhus abdominalis," especially in the cases of my first series. The other cases, therefore, do not materially affect the conclusions reached, and any one who desires to do so can separate those of typhoid from the remainder by referring to the table when published. Owing to the great preponderance of typhoid, I have often in the text used the word "typhoid" as a single descriptive word rather than the cumbersome, though more accurate phrase "the continued fevers, especially typhoid."

While gangrene is an important complication or sequel

* Arch. Gén. 1881, 7th, s., vi., 150.

† La Gangrene Typhoide, Thèse de Paris, 1883.

‡ Rev. de Méd., 1884, No. 1.

§ Thèse de Paris, 1886.

‖ Merc. Méd., September 20, 1893, 453.

¶ Johns Hopkins Hospital Reports, November, 1894, 120; and Journal of Pathology and Bacteriology, November, 1894, iii., 202.

** Centralbl. f. inner. Med., August 17, 1895.

of typhoid, it is fortunately rare, so that most practitioners, even men of vast experience in large hospitals, have never seen a case; for example, Flint and Murchison. Hölscher,* in 2,000 fatal cases of typhoid, does not report a single case, though he records 59 cases of thrombosis of the femoral vein and Bettke,† in 1,420 cases found only four cases of gangrene, all limited to the toes. In my former lecture I tabulated 43 cases from typhoid and 56 from typhus.‡ Since 1876, Dr. Westcott has found 90 cases of actual gangrene, in addition to which he has tabulated 21 cases of arterial and 48 of venous thrombosis not followed by gangrene. In its infrequency, therefore, it is in marked contrast to the bone lesions, of which he has found 168 cases, all after typhoid, to which from my former lecture are to be added 37 after typhoid and four after typhus, or a total in typhoid alone of 205 cases of bone lesions to 133 of gangrene.

Date of Onset.—While gangrene is generally a late complication during the course of the fever, or an early sequel during convalescence, it is never a very late sequel, as is the case in the bone lesions. The latter often do not occur till several weeks, sometimes months and occasionally even years after the attack of fever. This is doubtless due to the fact that the bacilli of typhoid find a favorable nidus in the bones, especially in the marrow, and have been repeatedly demonstrated by stain and culture after six, twelve or eighteen months, and even after so extraordinary long a period as six or seven years.[3] In addition to this, the slowness of all pathological processes in

* Münch. med. Woch., 1891, xxxviii., 43.

† Inaug. Diss., Basel, 1870.

‡ Thirty-four of these after typhus were reported by Estlander (Langenlick's Archiv, 1870, p. 453) in a frightful epidemic following a financial crisis and a series of bad harvests in 1862–7, in Finland.

§ Sultan: Deutsch. med. Woch., 1894, 675. Buschke: Fortschritte d. Med., 1894, 573.

the hard osseous tissues, as contrasted with their rapidity in the soft parts, would naturally lead us to expect that gangrene would occur far earlier than lesions in the osseous tissues.

The earliest time at which gangrene occurred, I find, is on the fourteenth day, and the latest in the seventh week. By far the commonest time for this dangerous complication to appear is the second and third weeks, during which 39.2 per cent. of all the cases occurred.

The causes for the appearance of gangrene in the second or third weeks, or later rather than early in the disease, are probably twofold. First, during the earlier stages of the disease, the general vitality of the patient and the resistance of the tissues are such that they can combat successfully the evil tendencies of the fever; but, secondly and chiefly, just as for the production of the intestinal lesions, so for the gangrene, a certain length of time is required for the diffusion of the bacilli and their toxic products, and for their resulting evil effects. Both causes unite in working together and to the same end. By the second or the third week, the bacilli and their toxic products have become diffused through the system; excessive feebleness has followed the small amount of food taken and the exhaustion from the continued high temperature;* the heart has become weakened and favors the formation of thrombi, not only in the heart but also in the vessels, either as a result of arteritis or of autochthonous thrombosis; emboli frequently result; and with the sluggish circulation, the general enfeeblement both of mind and body, and the frequently obstructed vessels, the advent of gangrene at this period of the fever should occasion no surprise. Indeed, the surprise is rather that it is so rare.

* We do not appreciate how much a continued high temperature alone exhausts a patient. Were the body composed of water alone, to raise the temperature of a person weighing 150 pounds from 98.5° to 103.5°, *i. e.* five degrees (to say nothing of the expenditure of force needful to keep it there), requires an expenditure of force equal to raising 285 tons one foot ($150 \times 5 \times 772$ foot pounds). A girl of 100 pounds weight, simply lying still in bed, suffering from such a fever, does daily the work of two or three men.

Let us now consider the pathology, symptomatology and treatment.

I. PATHOLOGY.

Various writers have been the partisans of one or another single cause for the occurrence of gangrene during and after typhoid fever. This seems to me an error, for, as I hope to show, there are a number of causes, of which one will exist in one case and another in another case; sometimes singly, sometimes in combination.

In my former lecture, I was disposed to regard the causes of gangrene as chiefly three: first, the altered blood; secondly, the weakened heart; and, thirdly, the mechanical difficulties in carrying on the circulation, especially in distant parts; and that all of these caused the gangrene by the production of thrombi either macro- or micro-scopic. Since that lecture was delivered, however, the bacillus of typhoid has been discovered, and has been proved by a very few careful examinations to play an important, and in some cases at least a direct rôle in the production of gangrene. It is greatly to be regretted that but very few cases have been studied with the scientific precision which they deserve. By calling renewed attention to the subject, however, I hope to stimulate others, especially in this country, to make thorough bacteriological examinations in the future. All the more are such careful examinations necessary, since the opportunities to make them are so rare, and when they do occur it is only too seldom that they fall into the hands of men with the opportunities and the capabilities for making such examinations.

The parts which should especially be examined bacteriologically are, first, the endocardium; secondly, the endocardial clots; thirdly, the walls of the arteries and of the veins at the point where they are obstructed by thrombi or emboli; fourthly, the thrombi or emboli themselves;

fifthly, the perivascular tissues in the same neighborhood; and, finally, if there are no visible coagula, then the gangrenous tissues themselves should be examined.

In two cases in my table, ergot had been freely given in consequence of hemorrhage. Were these the only cases of gangrene, one might suppose that this had had a determining influence, but as gangrene followed in 88 other cases, in none of which was this drug administered, its exhibition must be considered as merely incidental.

As a foundation for our study of the pathology of typhoid gangrene, let me recall a few of the facts which have been demonstrated bacteriologically.

First, not a few cases of typhoid fever suffer from a mixed infection. This is much more apt to lead, however, to other disorders than gangrene. For example, as I shall show hereafter, there have been a number of cases of tetanus, of erysipelas and of malignant pustule, due, of course, to a mixed infection of the typhoid and these specific bacteria. In addition to that, the large number of cases of suppurative disorders in various organs, bones, spleen, muscles, etc., presume the presence of the ordinary pyogenic bacteria, and their presence has been proved by stain and culture. In two cases in my table, pyemia or septicemia, a rare condition is noted. One by Wagner* commenced with a crural phlebitis relatively early in the disease (the ninth day), death occurring from pyemia on the eighteenth day. In another reported by Spillman,† gangrene of the lips occurred, probably from carious teeth, and the patient died from staphylococcus septicemia, the aureus being found in the spleen, kidneys and liver. They had probably obtained entrance from the mouth. That mixed infection should occur in typhoid fever is not at all remarkable, since the intestinal ulcers and, in a large minority of the cases

* Briefly mentioned in the British Medical Journal, 1891, i., 18.

† Merc. Méd. 1895, No. 13, 145.

also, the ulceration of the mucous membrane of the mouth, and the bed-sores which are so frequent in typhoid afford favorable ports of entry.

The researches of Vincent* are very noteworthy in this respect, especially as to mixed infection by the streptococcus. In mixed cultures of the bacillus of Eberth and the staphylococcus or the streptococcus, the greatest difference is observed in the influence of these two pyogenic organisms on the bacillus of typhoid. The staphylococcus is remarkably inimical to the growth of the bacillus of typhoid, so that the latter soon disappears, while, on the contrary, when mixed with the streptococcus the typhoid bacillus grows vigorously. In his experimental researches he found that doses of the streptococcus or of the bacillus of typhoid, neither of which was fatal if injected singly, if injected together would produce the most violent reaction and death.

In 41 cases of typhoid in which various suppurative processes occurred, in 32 the complication was due to the aureus or albus. All of these recovered in spite of extensive suppuration and multiple periostitis. On the other hand, of eight cases in which the streptococcus either alone or associated with the bacillus of Eberth was found, five died, showing a striking difference in the fatality of the mixed infection by these two pyogenic organisms. Sänger† also found the streptococcus in the vegetations of typhoid endocarditis.

Turning now to the cases in which bacteriological examinations have shown pure cultures of the bacillus of Eberth, we must note that they may be found (*a*) in the blood, (*b*) in the endocardium, (*c*) in the walls of the arteries, (*d*) in the walls of the veins, (*e*) in the thrombi, and (*f*) in the perivascular tissues.

* Annales de l'Institut Pasteur, 1893, vol. vii., 141.

† Deutsch. med. Woch., 1886, iv.

(*a*) Typhoid Bacillus in the Blood. The bacilli of typhoid are most numerous in the blood in the first twelve days of the disease. From then till the end of the third week they diminish rapidly, and during the fifth and sixth weeks are only found exceptionally (Park). It is probable that they reach the blood by the lymphatics, since they are found in abundance in the thoracic duct.* That they must be distributed by the blood (though so rarely actually found there) is made probable also by the fact that occasionally they are found in multiple organs of the body which could only be reached through the circulation. This is strikingly shown in the remarkably well studied cases of Flexner† in which he found them in the mesenteric glands, the spleen, the liver, the bile, the kidneys, the lungs, the marrow of the bone and in the blood of the heart. In the kidneys were a large number of abscesses resembling miliary tubercle, which, however, were proved to be real abcesses containing the bacillus of typhoid in pure culture.

Vincent also, in the paper alluded to, gives details of six cases in which they were found in the blood, the spleen, the liver, the mesenteric glands, the brain, the spinal cord, the cerebro-spinal fluid, the kidneys and the lungs. Moreover, the fact that in several cases they have been found in the fetus proves without possibility of question their transmission by the blood.‡

(*b*) In the Endocardium. Viti§ not only found the bacillus of Eberth in the granulations of endocarditis, but by the injections of the bacillus only into rabbits he was able to produce endocarditis with vegetations.

* Dêhu: Le rôle du bacille d'Eberth dans les complications de la fièvre typhoide, Thèse de Paris, 1893, p. 59.

† Loc. cit.

‡ Freund and Lovy: Berl. klin. Woch., 1895, No. 25. Chantemesse and Widal: Gaz. Hebdom. March 4, 1887, 146. For other references see Flexner's paper.

§ Atti della R. Accademia del Fisiocritici di Siena, 4 s., vol. ii., fasc. 5, 6, 1890.

Vincent* records another case of a soldier who was undoubtedly free from the preceding endocarditis, but died from typhoid and in the vegetations on the mitral valve pure cultures of the bacillus of Eberth were found. Girode† made a similar observation. Gilbert and Lion‡ were also able to produce such endocardial vegetations experimentally.

Besides the actual discovery of the bacillus of Eberth in the endocardial vegetations, it is not uncommon to find ante-mortem clots in the cavities of the heart. Forgues,§ Beaumanoir,‖ Fritz,¶ and Vallette (quoted by Ferrand), have all recorded such post-mortem findings. These clots are formed probably during the period of cardiac weakness, especially in the second and third weeks,** and, as the heart begins to regain its force and lose its frequency, are washed into the circulation as emboli. In the viscera their presence is shown by multiple infarcts; in the legs by the occurrence of gangrene.

(*c*) In the Walls of the Arteries. Rattoné†† reports four cases in which, in section of the arterial tunics, he was able to obtain pure cultures of the bacillus of typhoid.

(*d*) In the Walls of the Veins. Haushalter‡‡ found the bacillus in the sections through the veins; and both he and Vaques found the pyogenic microbes in the vein walls in cases of typhoid phlegmasia.

Arteritis, endarteritis and peri-arteritis, phlebitis and periphlebitis have been described by a number of authors, especially Ferrand, Deschamps, Mettler, Barié, Quervain and Haushalter. With the exception of the last two, the

* Merc. Méd., February 17, 1892, 73.
† Comptes Rendus Soc. Biol., 1889, 622.
‡ Comptes Rendus, 1889.
§ Réc. de Mém. de Méd. Militaires, 1880, 3d s., xxxvi., 386.
‖ Prog. Méd., 1881, ix., 364.
¶ Charité Annalen, vi., 169.
** Drewitt: Lancet, 1890, ii., 1023.
†† Della Arterite Tifosa in Déhu, loc. cit.
‡‡ Merc. Méd., September 20, 1893, 453.

descriptions are pathological, but without bacteriological confirmation. Ferrand quotes numerous cases of endarteritis of the iliac, femoral and popliteal arteries followed by thrombosis and gangrene. Barié describes two forms of arteritis; first, an obliterating form, and, secondly, a parietal. In the first there is profound alteration of the middle coat, the muscular fibre cells being infiltrated with embryonic cells, with sclerosis of the external coat and vegetations in the lumen. Sometimes, indeed, the three coats are indistinguishable. In others the lining membrance is covered with small elevations consisting of masses of round and fusiform cells. There is a loss of elasticity in the vascular walls, which become friable and easily distended. The loss of smoothness of the intima, the irregularities of its surface and the diminished calibre from the swelling are readily conceived causes for the formation of thrombi resulting frequently in gangrene. The thormbi at first red, but later decolorized, become adherent to the wall, and finally the artery becomes a solid cord. The secondary thrombosis is slow. The calibre is gradually oliterated, and the gangrene, therefore, is correspondingly slow and not sudden as in embolism; but from the original thrombi secondary emboli may form, and so hasten the gangrene by obliteration of the anastomotic circulation. As a rule, therefore, in arterial thrombosis the gangrene is *dry*, but occasionally during the course of the dry gangrene from arterial obstruction, the vein becomes obstructed and part or all of the limb may fall into sudden ruin from moist gangrene.

The parietal arteritis, according to Barié, is not attended with thrombosis, and is usually followed by recovery.

That arteritis should occur in typhoid is rendered also probable by its appearance in other allied specific diseases, such as small-pox, diphtheria, tuberculosis, syphilis, rheumatism, etc.

How the bacilli reach the walls of an artery or vein is a

question. Ordinarily they are not found in the blood; and yet the fact that they may be so widely distributed throughout the body, and that the only reasonable mode of such an extensive diffusion is by the blood, the cases of Flexner, Vincent and others amply prove. Haushalter believes that during their maximum they may reach the vessels by the vasa vasorum,* which, it must be remembered, especially in the veins, reach the middle and often the internal coat. He is inclined, however, to believe that the process is as follows: that an infection of the pelvic or crural ganglia occurs, followed by an infection of the perivenous cellular tissue by retrograde lymphatic circulation. In these cases, he supposes that a periphlebitis exists, followed by a secondary endophlebitis precipating a thrombus by the ferment furnished by the bacilli. This, I confess, seems to me much less likely than the former view.

(*e*) In the Thrombi. Both Rattone and Haushalter found the bacillus of typhoid in thrombi. The latter calls attention to the fact that he was not able to stain them in the thrombus, due, he thinks, to the fibrin, which being decolorized with great difficulty, probably obscured the bacilli; but he was able to demonstrate their presence by cultures. He found the endothelium of the veins destroyed. On the surface of the clot next the vein wall a layer of leucocytes was intimately united both to the clot and the wall of the vein. The typhoid bacillus existed only in the thrombosed portion of the vessels; and he is of the opinion that either the bacilli or their products caused the destruction of the endothelium and the resulting clot, and that in all probability in the products of the bacilli was found the ferment necessary to produce the coagulation.

(*f*) In the Perivascular Tissue. Quervain found the bacillus in pure culture in the pus surrounding the popliteal

* For a number of cases in which bacteria were found in the vasa vasorum, see Lockwood "Traumatic Infection," London, 1896.

artery and vein. That the bacillus should exist in the pus and in pure culture ought not now to astonish us.

The pyogenic power of the typhoid bacilli has been very generally doubted in the past; but, as I shall show hereafter, in connection especially with the bone lesions of typhoid, the bacilli have been so frequently found in pure culture, in abscesses, periostitis, osteomyelitis and other purulent conditions, that we can no longer doubt their occasional pyogenic function. If any additional proof were needed, the experimental researches of Orloff,* Colzi,† and later especially by Dmochowski and Janowski,‡ and by Flexner in the paper already alluded to, would dispel any lingering doubt. In Flexner's case, having in mind the objections of E. Fraenkel and Baumgarten, and especially the alleged difficulty of distinguishing between the typhoid bacillus and the colon bacillus, and the belief that all of the abscesses asserted to be from the typhoid bacillus were really the results of mixed infection of the typhoid bacillus and the ordinary pyogenic bacteria, special attention was paid to their differentiation. Inasmuch as the commonest pyogenic organism, the staphylococcus, has a greater vitality and is more persistent than the typhoid bacillus (cf. p. 67), so that the latter would die out before the former, it is reasonable to conclude that when the typhoid bacilli are found in pure culture in an abscess, they must have been its pathological cause.

Why in some conditions the typhoid bacillus should be pyogenic, and in others not, we can only at present speculate. No reason can be alleged. But we are precisely in the same position as to the pyogenic function of other bacilli, for example the colon bacillus, which we certainly know to be a possible, and one might almost say a frequent cause

* Wratsch, No. 49, 1889, and Nos. 4, 5 and 6, 1890.

† Lo Sperimentale, 1890, lxv., 623.

‡ Ziegler's Beiträge Path. Anat. ü Allgemein Pathol., 1895, xvii., 221.

of suppuration in certain conditions (for example, appendicitis), whereas ordinarily it is an entirely harmless intestinal organism. The care taken by Flexner and Dmochowski and Janowski, Haushalter and Quervain to distinguish the two bacilli by their various stains and different reactions are so manifold that the differentiation of the two may be regarded in these cases as complete.

Having now determined the bacteriological facts, let us see how they may be applied pathologically in explaining the causation of gangrene.

The cause of gangrene may be stated in practically a single phrase, *obstruction to the circulation*. The three factors I have already quoted from my first lecture, the altered blood, the weakened heart, and the mechanical difficulties of the circulation in distant parts, especially the last two, still hold good, but there must be added to them the important rôle of the typhoid bacillus in assisting, and often it may be in directly precipitating the coagulation of the blood, which is the cause of the obstruction. Four different varieties of obstruction, therefore, may exist and sometimes co-exist: first, arterial emboli of cardiac origin; secondly, autochthonous thrombi in the arteries; thirdly, autochthonous thrombi in the veins; and, fourthly—probably, though I believe there has been no cases absolutely demonstrated pathologically—thrombi in the peripheral vessels.

(1) Arterial Embolism of Cardiac Origin. This has been observed not only at post-mortems, but clinically. Thus Hayem* observed the alterations of the heart two days before gangrene of both legs commenced; the first symptoms being acute pain in the legs with a sensation of cold. The pulsation first in the dorsalis pedis, then in the popliteal, then in the femoral disappeared. Amputation showed that though the arterial walls appeared to be healthy, the femoral artery was partly obstructed by a clot. The obstruction

* Prog. Méd., 1875.

being only partial allowed a feeble circulation to go on. The popliteal and all its branches below the inferior articular were entirely free from any clot. The patient died, and the autopsy showed endocarditis and clots in the heart, the aorta obstructed by a clot extending from its bifurcation to a point above the origin of the inferior mesenteric, but the iliac arteries were entirely free. The spleen and the kidneys presented multiple infarcts. Mercier* reports also a case of dry gangrene of both legs with fibrinous clots in both the primitive iliacs, deep femoral and popliteal, the walls of which were healthy, and in the left auricle where there were old fibrinous clots with endocarditis. This form of arterial obstruction is quite common in my table, as will be observed in the *résumé* on page 79. It leads, as would naturally be supposed, almost always to dry gangrene, because it cuts off the supply of blood, as a rule, absolutely, though in a few cases, as in the one quoted from Hayem, a small amount of blood may still reach the distal parts and so restrict the extent of the gangrene. The very fact also that the walls of the arteries were healthy and that there were multiple infarcts in the viscera, all testify to the cardiac origin of such emboli.

(2) Arterial Thrombosis. In a great number of cases in the table, there were no evidences of preceding cardiac disease, and yet obstructive clots were found in the arteries, and were followed by dry gangrene. These are undoubtedly autochthonous thrombi probably produced largely from the ferment furnished by the bacilli themselves or possibly more frequently from an endarteritis, such as has been already described. The consequences of the thrombosis, as of the embolism of the arteries, will be a greater or less degree of dry gangrene, the extent of which will depend upon the completeness or incompleteness of the obstruction.

* Arch. Gén., 7th s., 1878, vol. ii., 402.

(3) Venous Thrombosis. This is much more frequent than the arterial form, probably from the more sluggish circulation, in addition to the infectious processes which undoubtedly sometimes cause a phlebitis or a peri-phlebitis. It results in gangrene in a moderate number of cases, but in the majority, as in venous thrombosis from puerperal fever, pneumonia, etc., gangrene is much less apt to follow venous than arterial thrombosis. The circulation is not nearly so completely cut off by venous obstruction as by arterial, since the collateral venous channels are less frequently blocked. Moreover, in arterial obstruction, the limb below the obstruction is entirely deprived of blood, whereas in venous obstruction the blood is dammed up in the part beyond the obstruction. The circulation may be hindered, but if it be not practically entirely arrested, a feeble nourishment goes on, sufficient at least to prevent gangrene.

It is to be observed that both in venous and arterial thrombosis, especially the latter, the clots are often discontinuous. (See cases of Hayem, Mercier and Beaumanoir.) This possibly may be due to isolated spots of local infection from the bacilli.

The venous clots are often very extensive, much more so than the arterial, as shown by a number of cases in my table. Thus, in a case of De Santi,* the clot extended downward to the deep femoral vein and upward through the common iliac to the vena cava. Beaumanoir† reports not only clots in the arteries of both legs, but also fibrinous clots in the right ventricle and pulmonary artery and its branches, in the left auricle and in the femoral arteries and veins and in the aorta to the level of the first intercostal artery. Naturally such extensive obstruction was followed by gangrene of both lower extremities. Clots ex-

* Rec. de Mém. de Méd. Militaires, 3d s. vol. xxxv., 1879, 502.

† Prog. Méd., 1891, ix., 364.

tending into the vena cava are also reported by Dumontpallier,* Sorel† and Bouley.‡

Occasionally, as would be supposed, venous thrombosis is followed by sudden death, as in a case reported by Nauwerck§ of thrombosis of the left iliac vein, which was followed by sudden embolism of the pulmonary artery while the patient was at stool, and death in ten minutes, and in another reported by Bourlet‖ also of thrombosis of the external iliac vein, which extended to the inferior vena cava and the right auricle of the heart, and the patient died from syncope. As would naturally be supposed also, the thrombosis, both arterial and venous, but especially the former, is apt to lead not only frequently to double gangrene, for example, of both lower extremities, but sometimes to a gangrene which is so symmetrical as to remind one of cases of Raynaud's disease.

When the gangrene results from venous obstruction rather than arterial, the gangrene is, as a rule, *moist*. Not uncommonly thrombosis of the arteries and veins is either successive or simultaneous. In either case, the gangrene is apt to be a combination of dry and moist gangrene. Occasionally when the venous thrombosis follows the arterial, the gangrene will be at first of the dry variety in the distal parts and when the venous obstruction occurs, moist gangrene will follow in the proximal.

(4) Thrombosis in the Peripheral Vessels. In addition to the three forms above recited, there are a number of cases reported in which the disease began as dry gangrene in the toes and gradually crept up the leg. The persistence of pulsation in the dorsalis pedis and other higher arteries showed that there was no arterial thrombosis or embolism

* Comptes Rendus Soc. Biol., 1879, 6th s., vol. iv., pt. 2, 3.

† L'Union Méd., 1882, 3d s., vol. xxxiv., 521.

‡ Prog. Méd., 1880, viii., 998.

§ Corresp.-blatt Schweizeraerzte, 1879, 485.

‖ Prog. Méd., 1880, viii., 988.

in the arteries higher up, but after a time the coagulation, which had begun in the periphery, extended centrally, and first the dorsalis pedis, then the tibials at the ankle, and later the popliteal and even the femoral were successively obstructed, resulting, of course, in a more widespread gangrene. The symptoms show that none of the three preceding conditions existed, but they enable us by analogy to reach the conclusion that spontaneous thrombi formed in the distal vessels. Whether the cause of this thrombosis is a bacillary infection or not has not been studied with that care which it deserves, and no absolute pathological or bacteriological confirmation of this view, I believe, has been reported.

II. SYMPTOMS OF GANGRENE.

The symptoms of gangrene are marked and characteristic.* Let us suppose the case to be one of arterial embolism or thrombus. Towards the end of the fever, especially in the third week or early in convalesence, as weakness is giving place to strength and the brightest hopes of speedy recovery are cherished, sudden, severe and persistent pain is felt. This may be at the seat of the impending gangrene, though perhaps more commonly it is in the obstructed artery, especially in the femoral, popliteal or tibial, and radiates thence to the periphery. It is followed by numbness, coldness, loss of sensation, and sometimes of motion, and in a short time discoloration and all the other usual evidences of gangrene appear. Sometimes, but not usually, these local symptoms precede the pain. If the vessels of the foot or at the ankle, or even the popliteal, be examined, the pulsation will be found feeble or utterly extinguished, while higher up at the seat of the obstruction the artery will be changed into a moderately firm but very tender cord, in which we may some-

* Partly quoted from my Toner Lecture.

times differentiate the obstructed artery from the non-obstructed vein — an important point in prognosis. Week by week, sometimes day by day, the growth of the secondary coagulum may be traced upwards by the progressive abolition of the arterial pulsation and by the upward march of the gangrene. If old cicatrices from burns, or unhealed eczematous ulcers, old fractures or varicose veins exist, all *loci minoris resistentiæ*, they will be among the earliest parts to yield. Blebs may form in the early stages, but most frequently they will dry up and the parts will mummify, although, as already indicated, moist gangrene may supervene if a large clot form much higher up, or if, in addition to the artery, the vein also becomes extensively obliterated, thus involving great masses of moist tissue, such as the thigh, in sudden ruin.

As is generally seen in cases of dry gangrene, days or weeks will elapse, if the patient lives so long, during which nature as usual makes a powerful effort to rid herself of the dead parts by the establishment of a line of demarcation. On the establishment of this, the pain often ceases.

In case the primary obstruction is in the vein and it becomes obliterated, extensively and completely, by a thrombus or by a simultaneous venous and arterial thrombosis, then the gangrene will be of the moist instead of the dry variety. It will present the usual appearance of moist gangrene. The vessels at the the seat of the obstruction will be very tender and can be felt as hard cords. The clot will extend sometimes rapidly and widely, and the gangrene will be more extensive in the area involved and far more acute in its disastrous clinical course, as would naturally be expected.

In the variety of gangrene beginning in the peripheral vessels, the symptoms will vary somewhat. It is not so uniformly in the lower extremity, and is much more frequently symmetrical. If small in extent, pain is not

apt to be a leading feature. The onset is often earlier, and from the nature of the case its progress is more acute and its limits more quickly defined, so that usually, within a few days at least, the boundary of the gangrene is well defined. Its area also is usually much less than in those cases in which a perceptible coagulum exists, not often extending in the leg beyond the foot or ankle; and if it occur in the nose, ears, genitals, etc., it rarely involves surrounding parts to a large extent. Sometimes, however, it may extend more widely, as in a case of typhus and starvation, mentioned by Lyons,* in which the patient walked to the workhouse, and on baring his chest the whole of the right side was "a dark, olive-green, jelly-like, tremulous mass." The abdominal wall is sometimes similarly involved. The probably irregular area in which the stasis of the blood will take place in this form, also accounts for the great irregularity generally seen in the line of demarcation; whereas, if a well-defined thrombus exists in a large vessel, the gangrene is apt to be fairly evenly bounded. This sudden history is usually followed by a speedily decided issue. Death follows quickly, or reaction and recovery set in within a short time, instead of long hanging in the balance.

In my Toner Lecture, I collected in all 113 cases of gangrene, to which Dr. Westcott has added 90, making 203 in all. Excluding from the former collection 34 cases of typhus reported by Estlander in Finland, of the remaining 169 cases 115 followed typhoid fever and 40 typhus fever. Some of the latter were undoubtedly really typhoid. In the following *résumé* I shall combine the results of the former and the later series together.

The influence of age is not very marked. Of 140 cases, 26 appeared before fifteen years of age, 64 from fifteen to twenty-five, and 50 after twenty-five years of age.

* On Fever, 191.

This will not differ much from the normal age-distribution of typhoid.

But sex seems to have a marked determining influence. Of 155 cases, 90 were males and 65 females, or about three to two.

The site of the gangrene is more striking than either age or sex. In six cases it attacked the ears, in 10 the nose, in 47 the face, neck and trunk; in 5 the arms, in 20 the genitals, and in 126 the legs; that is, of 214 cases in which the location is stated, in 146 it was in the lower extremities and genitals, and in 16 more in such peripheral districts of the vascular system as the ears and the nose.

I have found in the two series 128 cases of venous coagula following typhus and typhoid, especially the latter, in which the site is stated. Only four cases involved the upper extremity alone, two of which were followed by gangrene. Two involved both arm and leg, but all the other 124 cases were limited to the lower extremities. Gangrene of both venous and arterial origin (including both thrombosis and embolism) form most frequently during or just after the period of greatest cardiac weakness, a weakness felt most at such distant points as the legs. Of 41 arterial cases, 18, and of 107 venous cases, 40, occurred in the second and third weeks of the fever — that is to say, of 148 cases 58 (39.2 per cent.) occurred in the second and third weeks.

These figures, it seems to me, are most instructive. In discussing the pathology, I gave marked prominence to the sluggish peripheral circulation as a mechanical factor in the production of the gangrene. Even though we admit in many cases the determining influence of the bacilli of typhoid, the striking clinical fact above established must be explained by any accepted pathology. If arteritis or phlebitis or emboli of cardiac origin, whether bacillary or not, were the sole or even the preponderating cause, then gangrene

certainly should attack the upper extremities, the head, the neck and trunk with far greater frequency than is seen by these statistics. Just as in gangrene from other causes, often of non-bacterial origin, such as ordinary senile and diabetic gangrene; or of bacterial origin, as in scarlet fever, measles and the other exanthemata, the legs suffer so much more than all the other parts of the body put together; so in typhoid grangrene the familiar rule holds good.

It is also in the lower extremities that venous thrombi causing phlegmasia alba dolens are most frequent in other diseases of microbic origin, as in puerperal fever, pneumonia, septicemia, pyemia and even in tuberculosis and malarial fever. In both classes of diseases arising from half-a-dozen or more different bacteria or entirely apart from any bacterial influence, the one striking fact is that the legs suffer far more frequently than all other parts of the body put together. It is, it seems to me then, good common sense and good pathological sense to seek for the efficient, the exciting, the actual cause determining the location of the thrombosis and the frequent gangrene in legs themselves as legs, that is, as distal parts of the circulatory system.

The distribution as to left- and right-sided gangrene is very striking. In the early series, I did not make such a differentiation, but in the present series of 90 cases I have found that of 46 cases of arterial gangrene, eight occurred on both sides, 19 were right-sided and 19 left-sided, showing an exactly even distribution. In the veins, however, the facts are strikingly different. Both sides were affected in only four; the right side alone in 10 and the left side alone in 38. This, as we know, is in accordance with the usual experience in other diseases. Why the left side should be so much more subject to gangrene due to venous obstruction, as also to phlegmasia alba dolens,

than the right side, has been a subject of speculation for many years. My own conviction is that the obstruction to the return of the venous blood by reason of the compression of the left common iliac vein where it passes under the right common iliac artery is the most potent factor, slight in itself it is true, but when the blood is in unstable equilibrium between fluidity and coagulation, this slight retardation is in most cases just sufficient to precipitate the coagulation upon the left rather than upon the right side.

The same predominance of the left over the right side holds good in cases of venous obstruction, and the same balance of the two sides in cases of arterial obstruction, when they are not followed by gangrene. Excluding three involving the Sylvian artery, all of which occurred upon the left side, producing right hemiplegia,* and one of the right brachial artery, of the cases of arterial thrombosis without gangrene, six were right-sided, and five left-sided, while four were bilateral. Of the cases of venous thrombosis without gangrene, three were bilateral, 13 right-sided and 31 left-sided, or combining together the cases of venous obstruction, whether followed by gangrene or not, seven were bilateral, 23 right-sided and 69 left-sided, while in arterial obstruction the bilateral cases number 12, the dextral 25 and the sinistral 24. This extraordinarily even distribution would seem to suggest that the cause in cases of arterial obstruction is much more frequently embolic than has been hitherto believed.

While the male genitals and perineum are attacked by gangrene occasionally, it is in women especially that we find the widest spread havoc. I have found in all 20 cases, of which 16 followed typhoid and four followed typhus.

* For an important contribution to this rare sequel of typhoid see Osler, Recent Studies in Typhoid Fever, Johns Hopkins Hospital Reports, vol. v., and in the Journal of Nervous and Mental Disease, May, 1896, p. 295.

Fourteen cases were in young persons from seventeen to twenty-seven, except one child of five and five women of thirty-two years of age and over. In 17 of these cases, there was gangrene of the labia extending sometimes to the perineum and the thigh.

The disorder manifests itself either as a distinct gangrene of the external genitals or by gangrenous ulcers forming in the vagina. The former occasionally is followed by complete closure of the vagina and retention of the menstrual flow as in a case reported by Martin* in which sloughing of the upper vagina and the entire cervix uteri occurred. The vaginal ulcers appear usually on the posterior wall and lead occasionally to recto-vaginal fistula as in two cases reported in my former table, one case of vesico-vaginal fistula in the present table reported by Schick,† and in the fourth, my own case, both recto-vaginal and vesico-vaginal fistulæ occurred.

A *résumé* of this unique case, of which I quote the earlier part from my former lecture, is as follows:

Mrs. M. D. was under my observation in St. Mary's Hospital from 1873 to 1876, and is the only case I have found of both recto-vaginal and vesico-vaginal fistulæ. Up to March, 1872, she was perfectly healthy, when, at the age of thirty-four, she had a severe attack of typhoid fever for four months following exhaustive nursing during her husband's fatal illness also from typhoid. About the fourth week the labia minora sloughed away to a large extent and both water and feces passed by the vagina. In October, 1872, she was admitted to the hospital, under the care of my colleague, Dr. Grove, with two large vesical openings (separated by a slight bridge of tissue), which had destroyed the posterior part of the urethra and the floor of the bladder up to the uterus, and one rectal opening an inch in diameter, and one and a half inches above the anus. Dr. Grove operated on her three times unsuccessfully;

* Centralb. f. Gynekol., 1881.

† Wien. klin. Woch., 1892, vi., 413.

once on the rectal opening by the rectum, when he divided the sphincter, and twice by the vagina. From December 1873, to December, 1875, I did nine operations. Thrice unsuccessfully I attacked the fistulæ proper, when, becoming convinced that the attempt to close them was hopeless, with her entire consent after a full explanation of the consequences of the operation, I proceeded to close the vagina. At first I attempted to preserve and utilize the remnant of the urethra, which gave me great trouble and necessitated several operations; but at the twelfth operation, December 28, 1875, I gave up the attempt, excised the useless urethra and closed the entire vulval aperature by ten silver sutures. The operation was a complete success. At the time of the delivery of that lecture, nearly seven weeks after the final closure of the vulva, I stated that she defecated, menstruated and micturated entirely by thé rectum, and without the slightest trouble. She rose usually once, sometimes twice, in the night, and micturated only five or six times during the day. My greatest fear was that the feces softened by the urine would pass into the vagina or bladder and give trouble, but up to that time at least none had arisen, and she was happily rid of the annoyance which had continued four years. Soon after this, however, a small fistulous opening appeared in the cicatrix, caused probably by the feces. This healed after a thirteenth operation, and when my lecture was printed (May, 1877) she had remained entirely well for over fifteen months. In the last four operations, instead of the usual sigmoid female catheter to empty the bladder, I inserted the curved branch of a pocket-case male catheter into the bladder and the vagina through the recto-vaginal fistula, thus draining these cavities, while I drained the rectum below the eye of the catheter, by an ordinary drainage-tube inserted into the rectum, lest the feces should be softened by the urine and then pass into the vagina. They answered admirably. The difficulty in obtaining a cure, I believe, lay partly in the inherent difficulty of the case, and partly in her deteriorated health ever since the fever.

Her later history is as follows:

Menstruation ceased in February, 1887, over eleven years after the closure of the vagina. December 11th,

1888, she again came to me complaining of pain in her rectum and vagina, and stated that the urine was intermittent, sometines escaping and sometimes not. She told me that for the thirteen years since the last operation she had been absolutely comfortable, that she was only obliged to rise about twice in the night to evacuate the rectum and that neither the urine nor the menstrual flow, while it had continued, had irritated the rectum, nor had the feces annoyed her by gaining access to the vagina so far as her sensations went. By inserting a finger into the rectum, I found the old fistula between the vagina and the rectum had so contracted that it would barely admit the point of my forefinger. This examination showed at once that there was a calculus formed in the vagina, which acted like a ball valve. I readily, of course, crushed it by means of a pair of curved forceps introduced through the rectum. The portions I secured uncrushed weighed 70 grains and measured $\frac{3}{4}$ by $\frac{5}{8}$ of an inch. She made an entire recovery in three or four days.

A month ago, on May 7, 1896, she called again to say that while she had been perfectly comfortable for the seven years since the removal of the stone, three weeks ago a small abscess had formed at the former outlet of the vagina and that that morning the urine had commenced to dribble away. Examination showed the orifice of the vagina firmly closed excepting one small point just admitting a probe, through which some urine was escaping. Rectal touch showed that the recto-vaginal fistula was the same as before. I advised her to keep the parts clean and wear a napkin, and wait to see whether the small fistula would not close spontaneously. In two weeks this hoped-for result followed, and she is again entirely relieved of her distressing disability.

The case is particularly interesting, not only for its unusual character and its cause, but I believe it was possibly the earliest case in which the urethra itself was entirely removed and the vagina closed, the rectum thus being made to serve the triple purpose of a reservoir for the urine, the menstrual discharge and the feces. It is an encouraging fact that in any case requiring similar treatment, the later

history shows that for over twenty years she has only twice had the least trouble, once from a small calculus forming in the vagina and once from a small abscess forming in the cicatrix, which abscess has spontaneously closed. Instead of being a constant source of disgust to herself and every body about her, a hospital patient dependent upon charity, as she could not earn her daily bread, and a pariah cut off from all society, she has been enabled to become self-supporting as a nurse, and to enter freely into her wonted social relations.

Gangrene extends to the perineum or arises primarily around the anus in a few cases. I have notes of eight men and six women, the sex not being given in two cases. Excepting three cases of eighteen, twenty-one and twenty-two years of age, they all occurred, when the age is stated, from thirty-nine to seventy-four years of age, later in life than most of the other sequels of typhoid. This is presumably due to the fact that in later life the nutrition of the perineum is apt to be less vigorous than in early life. Excepting one in the second week, they all arose rather later than other cases of gangrene; namely, from the third to the seventh week — in other words, during distinct convalescence; and to this is probably due the fact that ten recovered and five died. In a number of cases the bones of the pelvis were involved as well as the soft parts. This also probably partially accounts for the later occurrence of these cases.

Occasionally gangrene attacks very unusual regions or organs. Thus single cases are reported of gangrenous suppuration of the gland of Bartholin (Spillman);* of the tongue (Gaston David);† of the uvula (Freudenberger);‡ of both ears (Sanda);§ of the lips (Spillman).‖ The

* Arch. Gén., 1881.

† Quelques consid. sur la gangrène typhoide, Thèse de Paris, 1883.

‡ Aerzlich. Intelligenzbl., 1879, xxvi., 542.

§ Rev. Gén. de Clin. et de Thérap., 1892, vi., 401.

‖ Marc. Méd. 1895, No. 131, 145.

cheeks are attacked more frequently, and noma and cancrum oris are noted in my table as having been observed nine times, and as usual is very fatal, five of the nine having succumbed, the result in one being unrecorded. The lungs also suffered from gangrene in five cases, of which three died. As to all of these, there is nothing peculiar calling for more than their mention as indicating the protean manifestations of typhoid gangrene.

III. TREATMENT.

To the treatment which I advocated twenty years ago little can be added. The preventive treatment is the most important, such as good food, fresh air, the best hygienic surroundings. Should the heart flag, the stimulation must be maintained at all hazards; alcohol in liberal doses is perhaps the best remedy. Digitalis, strychnine, spartein, strophanthus and other cardiac tonics of the later pharmacopœia may be added. The body should be carefully examined, especially those parts of it which experience has shown are most likely to be attacked, pre-eminently the lower extremities and the genitals. The arms, neck and head being exposed are much more likely to attract attention should they be attacked by gangrene than those which are covered by the bed-clothes. If baths are used, care should be taken that no mechanical injuries are inflicted, especially on the legs. Chapman's ice and hot-water bags, alternate heat and cold, with very moderate friction and stimulating liniments should be advised and the use of the constant current as a means of stimulating the collateral circulation, both in the deep as well as the superficial parts, will be of service. If gangrene is not only threatened, but actually sets in, the gangrenous parts should be kept as aseptic as possible by the free use of antiseptic dressings.

The question of amputation naturally is one of the most important that is raised. In gangrene of the genitals,

head, neck and trunk, operation of course is limited to the removal of the dead and sloughing tissues and especially in the promotion of the utmost cleanliness, particularly in parts of the body soiled by urine, feces or the menstrual dischaage. Detergent washes and stimulating douches, the keeping of the rectum free from accumulated feces and thorough and free incision in abscesses in the vicinity of the anus are to be especially commended.

In the extremities if amputation is necessary, the time when it shall be done depends largely upon whether the gangrene arises from distinct obstruction by a palpable thrombus or embolus, or whether it arises in the peripheral vessels without such an appreciable mechanical obstruction of the main vessels. In the latter case, the line of demarcation is usually established pretty early and the disease is generally unlikely to advance beyond this line. Amputation, therefore, should be done as soon as the line of demarcation is well pronounced, and it may be done but little above this line, since there is no obstruction in the vessels higher up which would threaten the integrity of the flaps.

In the cases where a distinct thrombus or an embolus has formed, however, the obstruction is very apt to extend farther and farther as time goes on by secondary thrombosis. At what level, therefore, the limit between the tissues which must necessarily die and those in which nature can still keep up a healthy life will occur, cannot be stated definitely until the line of demarcation is well established. But the facts obtained by a study of my two series of cases aid us very distinctly in this matter. When the clot extends only up to the popliteal, the leg may escape gangrene altogether, and should it follow I have found it limited in 21 cases to the foot six times, to the lower half of the leg once, and to the upper calf in 14 cases. When the clot extended into the femoral, the gan-

grene extended to the upper calf in 11 and to the thigh in eight cases. When the clot extended above Poupart's ligament, the gangrene was limited in 15 cases, to the foot in one, the calf in eight, and extended above the knee in six. Amputation in these cases, therefore, should not be done, as a rule, until a well-defined and probably final line of demarcation has been formed. When operating, the leg should be made bloodless by elevation and kept so by very careful digital compression. The Esmarch bandage, as pointed out by Quervain, should not be used, partly because it may injure the vessels of the stump and so favor a new arterial or venous thrombus, partly because it may break up an existing venous thrombus and give rise to a dangerous embolus. To this I would add another evident objection, that the septic fluids in the tissues should not be forced into the general circulation. The hemorrhage will be slight, since certainly the artery and often both artery and vein will be obstructed, so that the "muscles will look like meat soaked in salt and water, and there will be no oozing from the marrow of the bone."*

Quervain's method of operating was both ingenious and useful. After forming an anterior flap and before making the posterior flap containing the vessels of the lower thigh, he disarticulated only the bones at the knee joint, dissected the femur loose for twelve centimetres above the joint, and divided the bone, then exposed the vessels and ligated them, and last of all formed his posterior flap. The wisdom of ligating the artery before dividing it was shown by the fact that in the amputated part it was found to be filled with a loose clot, which would almost certainly have been dislodged by the manipulation if the flap had been made prior to ligation and so have caused considerable hemorrhage. Such patients have not a drop of blood to spare.

As a general rule, therefore, we should wait for the line

* Drewitt, Lancet, 1890, ii., 1023.

of demarcation, but the operation should not be deferred long after its appearance. If danger of septic infection or speedy exhaustion should appear, immediate amputation at or above the probable limitation of the disease should be done. The extension of the disease, if the femoral be free, will not be, in the majority of cases, above the tubercle of the tibia. If the femoral be involved, necessitating an amputation of the thigh, the resources and the safety of modern antiseptic surgery would lead us in general to amputate, but in some cases it may be a serious question whether expectant treatment and a relatively long-subsequent amputation might not be less dangerous than an earlier operation.