ON SOME POINTS IN THE ETIOLOGY AND PATHOLOGY OF ULCERATIVE ENDOCARDITIS

BY WILLIAM OSLER, M.D.
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Ulcerative, infectious, or diphtheritic endocarditis is an affection of unusual interest to the profession, both on account of the serious nature of the malady which it excites and of the illustration which it offers of many points in the pathology of infective processes.

Ulceration, loss of substance, on the endocardium occurs under a variety of conditions. Clinically we should, I think, recognise three classes of cases. First, those in which the disease appears without any obvious cause, either spontaneously or in connection with rheumatism or some other affection, as pneumonia, chorea, &c. These cases present a remarkable set of symptoms, very variable in character, but of which two chief types have been recognised—the typhoid and the pyæmic. This is the preliminary form of some writers. Second, those cases which arise during the existence of some local inflammatory process, as puerperal endometritis, acute necrosis of bone, &c., and in which the endocarditis is usually regarded as part of a pyæmic state and secondary to the local disease. And, third, the cases of ulcerative affection engrafted upon valves the subject of chronic sclerotic changes. In this latter variety no special symptoms necessarily accompany the process; the patients are usually in the last stage of chronic valvular disease.

I propose to consider briefly in the following paper some of the conditions under which the disease arises, some points in the morbid anatomy, and, lastly, make a few remarks on the supposed relation of micrococci to the disease.

Of the conditions under which the disease is met with.—(a.) Rheumatic fever.—It is very generally stated by writers on the subject that the "great majority" of the cases of the ulcerative form of endocarditis occur during the course of this affection. While it undoubtedly holds good that the verrucose or plastic variety is met with most frequently in patients the subjects of rheumatism, my own experience, as well as an examination of the literature, leads me to believe that the above statement requires reconsideration. Of twelve cases of the acute primary form which have come under my observation, in only three was there any history of rheumatism, and in all only as indefinite painful conditions of the joints, not as acute rheumatic fever. Of sixty-seven cases of the primary form, the reports of which I have gone over, in only nineteen was there any mention made of acute rheumatism or of previous rheumatic attacks. It may be
I think, safely stated that ulcerative endocarditis does not occur frequently in rheumatic fever.

(b.) Pneumonia.—A very considerable number of cases are associated with this disease. Thus, in seven of the twelve cases which have fallen under my notice this obtains, and in twenty-four of the sixty-seven cases which I have analysed. As this relationship has not, so far as I know, been specially noticed by any other writer, I append condensed reports of these cases.

I.—Mary D., aged twenty-nine, admitted October 22nd, 1878, in an unconscious state. No history of onset of attack. Dulness and blowing breathing at right apex; systolic murmur at left nipple. Temperature range from 104° to 107°. Death on the fifth day in hospital.

Autopsy.—Ulcerative endocarditis of anterior segment of mitral; red hepatization of upper half of right lung; purulent meningitis; infarcts in spleen, which was enlarged.

II.—James B., aged thirty-eight, a healthy man, admitted January 1st, 1880. Had pneumonia ten years before. On evening of 4th, got feverish, had pain in the side and cough. On admission all the signs of consolidation of right lung, lower three-fourths. During first week in hospital delirium set in with prostration. Patient lived for forty-two days, during which time he was in a low typhoid state, had chills, profuse sweats, and a parotid abscess. The temperature range was from 100° to 104°. After the second week the lung symptoms subsided, though the dulness never quite disappeared.

Autopsy.—Extensive ulcerative vegetations on mitral segments; tissue of right lung firmer than that of the left, but not granular; infarcts in spleen, which was enlarged.

III.—M. W., aged forty-three, a well-built man, the subject of syphilis, admitted February 26th, 1880. In October, 1879, he had had a severe attack of inflammation of the right lung. On February 23rd, had a severe rigor, followed by fever, pain in left side and cough, and examination showed signs of pneumonia of lower half of left lung. Up to March 3rd, patient, though delirious at times, appeared to be doing well. Temperature on that date was normal. On the 4th he had a chill, and became feverish and delirious. From this time until his death on the 14th, the chief symptoms were prostration, delirium, occasional chills, and profuse diarrhoea. Temperature range from 101° to 104°. Lung never became clear.

Autopsy.—Small vegetations on mitral segments; large vegetations in right posterior aortic cusp, with destruction of tissue; base of left lung airless and solid; purulent meningitis; spleen large; small infarct in kidney.

IV.—Robert L., aged twenty-nine, admitted June 4th, 1880, with a history of diarrhoea of several days' duration, chills, fever, and cough. Signs of consolidation at left base, with blowing breathing. He was known to have aortic valve disease, and there was a double murmur at the base. The inflammation extended and involved nearly the entire lung. It did not run a typical course, but a low typhoid state supervened, with chills and sweats. Temperature range from 99° to 105°. Death on July 1st.

Autopsy.—Old sclerotic endocarditis with fusion of two segments of aortic valves; small ulcerative vegetations; extensive ulcerative disease of aorta with vegetations and four aneurisms; lower lobe of left lung showed signs of a resolving pneumonia; infarcts in spleen and kidneys; superficial meningeal haemorrhages.

V.—M. G., a young girl aged nineteen, jumped during a fire from a three-
story window, and sustained a fracture of both legs and of the lumbar vertebrae. She did very well for a week, when the temperature rose, and she had cough, shortness of breath, and pain about the heart. Delirium came on with prostration, and death occurred on the sixteenth day after admission.

**Autopsy.**—No suppuration about the fractures, which appeared to be doing very well; a large endocardial outgrowth, with destruction of substance on anterior curtain of mitral valve; hepatisation of central portion of right lung; infarcts in spleen and kidneys; patches of membranous (diphtheritic) colitis; purulent meningitis.

VI.—Edward B., aged sixty-three, admitted to surgical wards March 31st, 1881, with carbuncles on buttocks. They were freely lanced, and though he was much debilitated and had an irregular temperature, he improved considerably, and on April 27th the wounds were doing nicely, and the temperature was normal. Then signs of inflammation of left lung were detected; temperature rose, and there were rapid breathing, cough, and rusty expectoration. The whole organ became involved, and the patient became greatly prostrated. Death on May 8th.

**Autopsy.**—Body wasted; bed-sore on sacrum; carbuncles had almost healed; grey hepatisation of three-fourths of left lung; ulcerative and supplicative endocarditis of top of one of divisions of anterior papillary muscle with exudation in contiguous chordae tendineae; numerous infarcts in the kidneys.

VII.—James H., aged forty, drayman, large and powerfully built. Admitted May 13th, 1881, with pneumonia. Had had two previous attacks of inflammation of the lungs. Rigor on the 11th, followed by fever, cough, and pain in right side. When admitted, consolidation of lower two-thirds of right lung was determined. Delirium set in early. Resolution did not supervene and the fever did not abate at the usual time. Patient fell into a low typhoid state, with delirium and free diarrhoea. Temperature range from 102° to 105°. Petechiae appeared in the skin. Death on the thirtieth day. There was no heart murmur.

**Autopsy.**—Extensive ulcerative endocarditis of mitral segments and of two of aortic cusps; lower top of right lung airless, heavy, firm, and on section granular; spleen large; infarcts in kidneys; numerous infarcts in intestines; purulent meningitis.

Of these seven cases, in five the endocarditis came on during the course of simple pneumonia. Cases V. and VI. were complicated by surgical disease. In the girl with fractured legs the endocardial mischief appeared to develop with the inflammation of the lung, and not to be secondary to the fractures. The patient with carbuncles was much debilitated and succumbed to an extensive pneumonia. Whether the endocarditis was present before the onset of the pneumonia remains doubtful, but I think it scarcely could have been, as the general condition of the man was improving before it came on. The association of these conditions in such a large proportion of cases is very striking, but the relationship between the processes is not easy to trace. So far as one may judge, the pneumonia in the above cases was the primary morbid change. In all it was of the ordinary lobar variety. Cases of ulcerative endocarditis of the right heart have been described, with extensive secondary changes in the lungs, but in none of my cases was the pulmonary process of a pyemic character. I have not specially stated it in the condensed reports of the cases, but it is worthy of remark that all the patients were either debilitated at the time of the attack, or were hard drinkers. Many constitutional affections predispose to endocardial inflammation, notably rheumatism, less frequently some of the exanthems, and to these we may
now add pneumonia, which is regarded by many as a constitutional disease. Unfortunately the form of endocarditis which accompanies it appears to be more often of a serious nature, judging at least from the evidence before us. With our present knowledge, the most, I think, that can be said on this point is, that in certain cases of inflammation of the lungs there is a tendency to ulcerative endocarditis. In a former paper * on this subject I called attention to the fact that inflammation of a diphtheritic character had been observed in other organs in pneumonia, particularly in the colon, in which region Dr. Bristowe met with diphtheritic exudation in four out of sixteen cases. There was purulent meningitis in four of the seven cases above reported, which was doubtless secondary to the endocarditis.

(c.) A very considerable number of all the cases of ulcerative endocarditis occur in connection with local inflammatory processes of an unhealthy type. In this group the *endocarditis puerperalis of Virchow is most conspicuous, and not unfrequently complicates the endo- and peri-metritic disorders following parturition. It is further met with in acute necrosis of bone, occasionally in gonorrhoea, and in pyæmic states. In some cases it is very difficult to say whether the pyæmia has excited the endocarditis, or whether the former has not been determined by the latter; indeed, the relation may be reciprocal. This form is often referred to by writers as “secondary,” the exciting cause being, in most instances, obvious. There are some peculiarities in the endocardial lesions, which will be referred to later.

(d.) The valves of patients who die of chronic heart disease present very diverse anatomical pictures. There may be—(1.) Simple sclerotic changes with great deformity; (2.) the same with small bead-like vegetations; and (3.) sclerotic and deformed valves with recent ulcerative changes, destruction of tissue, and valvular aneurisms. Probably the great majority of ulcerative processes on the valves occur in this connection. These cases usually proceed as ordinary examples of heart disease, with little or no fever, in fact, none of the severe typhoid or pyæmic symptoms so striking in other instances. In one or two cases I have seen slight, irregular fever, or signs of extensive embolism, which may indicate the nature of the process going on, but the clinical picture is not that of the primary infectious form. It has long been recognised that ulcerative changes appear with special proneness on damaged valves. In two of the cases of pneumonia with this complication, the valves were the subject of that peculiar malformation by which two of the segments had fused together; and in two instances of chronic heart disease, with extensive ulcerations and aneurisms, the same condition of the segments was met with. Interference with the vessels and consequent defective blood supply may, as Virchow suggests, have something to do with this tendency in sclerotic valves to ulcerative changes.

It occasionally happens that ulcerative endocarditis arises as a complication of one of the acute exanthemata. According to Lancereaux + chronic malaria is also a predisposing cause.

Morbid anatomy.—I shall only deal in this place briefly with a few points in the cardiac lesions. In the great proportion of cases the affection is valvular and confined to the left side. The changes met with are by no means uniform, but a remarkable variety prevails. There may be—(1.) Superficial losses of substance, not extending much deeper than the endocardium, the surface rough, without

* Archives of Medicine, Feb. 1881, New York.
+ Archives Générales, 1873.
much exudation, nothing deserving of the name of a vegetation. My experience has been that this variety is most common in the puerperal state and in pyæmia. Sometimes it is difficult to make out the erosion, particularly when post-mortem staining of the membrane has taken place. In only one of the twelve cases of the primary form was the lesion of this nature, and in this there was also a good deal of swelling and infiltration about the base of the ulcer. It is natural to suppose that lesions of this kind would prove more dangerous by the rapid infection of the blood with small emboli; and in the case just referred to, the infarcts were more numerous than in any other instance, scarcely an organ being free. (2.) For the great majority of the cases of the primary form, the term "ulcerative" hardly expresses the precise anatomical condition. The expression used by French writers is more correct, "Tendocardite vegetante ulcerose," for there are both loss of substance and vegetative outgrowths. The affected valve presents irregular nodular excrescences of a greyish-white colour, often fissured, cauliflowerike; the surface either quite smooth and covered with a thin fibrinous lamina or granular from exposure of the texture of the mass. On section the cut surface may be uniform and fleshy, or broken and granular. The consistence is not very great, the masses crumbling on firm pressure. They are intimately united with the tissue of the valve, which, if the vegetation is large, is usually indistinguishable at the site of attachment; indeed, the whole thickness of a segment may be involved and the mass spring from both sides. In two instances the vegetations were of a fleshy character, not friable. The ulcerative outgrowths, which develop on the sclerotic valves of patients the subject of chronic heart disease, resemble closely in coarse features those met with in the more acute process. Small calcareous concretions are not uncommon in them, and they are, I think, more frequently accompanied by perforations and aneurisms of the valves. (3.) In a small group of cases the endocardial process is supplicative and the tissue is bathed with pus corpuscles. An abscess may be formed, and after discharging, leave an ulcer. In Case VI. of the group of cases occurring in pneumonia, the tip of one chorda tendinea was soft and bathed with pus; in another case there was a purulent deposit at the base of a large vegetation in a sinus of Valsalva.

In my previous paper I have dealt with the histological characters of the vegetations, and would here simply state that the micrococci have been present in all the cases examined by me. A peculiar arrangement of them was noticed in a specimen obtained from a cow. In addition to the usual forms there were definite spherical bodies of various sizes, looking like aggregations of micrococci enclosed in capsules.* In two specimens from man I have met with somewhat similar appearances. I have not seen the chain-like filaments described by some writers.

In this connection I may state that micrococci are not peculiar to the vegetations of the ulcerative form of endocarditis, but exist in the small bead-like outgrowths of the rheumatic and other varieties of the disease, as Klebs was the first to point out. My experience tallies with his; in seven specimens of verrucose or plastic vegetations which I have examined, all contained micrococci.

The relation of the micrococci to the disease has been very fully discussed by Virchow, Eberth, Klebs, and others, most of whom hold that they are the specific elements which account for the peculiar malignancy of the disease, and that they stand in the same position in this affection as the baccillus in anthrax. There

* Vide plate illustrating my previous paper already quoted.
are some points which should, I think, make us hesitate to accept this view without further evidence. Micrococci abound in all forms of endocardial vegetations—in the warty outgrowths of rheumatic endocarditis, in the vegetations of old sclerotic valves, as well as in the excrescences which develop in the acute ulcerative form. This latter is a malady which runs the course of an infective disease and may destroy life in four or five days. The micrococci are supposed to gain access to the blood and to excite in some way endocarditis; at any rate they flourish in the vegetations which are regarded as centres for the distribution of the germs throughout the body. In the majority of cases emboli are carried away from the vegetations and infarcts produced in the different organs. In other cases, equally malignant, the vegetations may remain unbroken and no emboli are found in the viscera. So far as my observation goes, the micrococci do not exist in the blood during the course of the malady. Nor are they constantly found in the infarcts. The occurrence of micrococci in the warty vegetations of rheumatic endocarditis and in the extensive ulcerative outgrowths so frequently met with in old sclerotic valves are facts strongly opposed to the view of their specific poisonous nature. The micrococci appear to be identical in these cases, though Klebs states that those of rheumatic endocarditis are larger and have a brownish tint. I cannot say that these differences have been constant in the specimens which I have examined. It seems a pertinent question to ask, if in the malignant form of endocarditis, the micrococci are so potent, why in other cases in which they are equally prevalent, should they be inert? Of course it may be urged that the micrococci may be of different kinds or possess diverse qualities, or that the resistance offered by the tissues to their penetration varies in different cases, or that it is only in weakened and debilitated states that these little bodies thrive. There is, I think, something worthy of attention in this latter view. If we study the conditions under which endocarditis develops, we find almost invariably that the patients are the subject of some other constitutional affection which, as we say, predisposes to it. What determines the precise form of the endocarditis, we do not know, but the soft endocardial vegetations form a suitable nidus for the development of micrococci. They appear in fact to be just as much normal components of endocardial outgrowths as the fibrin fibrils which are usually deposited and among which the micrococci abound. It is evident that these structures are common elements in a series of endocardial processes which display totally different symptoms and arise under different conditions. How far they are responsible either for the development of the endocarditis or for the subsequent characters which, in the grave form it assumes, the evidence does not, I think, warrant as yet a very positive opinion.
ON CERTAIN
Parasites in the Blood of the Frog

BY WILLIAM OSLER, M.D.

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ON CERTAIN PARASITES IN THE BLOOD OF THE FROG.*

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In my Practical Histology class, during the winter of 1881–82, while the students were working at the blood of the frog (*Rana Musiens*), I noticed in one of the slides a remarkable body like a flagellate infusorian. I thought that it was one which had got into the blood at the time of withdrawal, from the water on the web of the foot. Meeting with examples in the slides of several other students, my attention was again directed to it, and I made several sketches and wrote down the following description:—"Finely granular protoplasmic body, somewhat triangular in shape, about the size of a colorless corpuscle. The narrow end is prolonged into a cilium, while the other presents a broad band of rapidly undulating protoplasm, which at one angle is prolonged into a long lash-like process. The undulating fringe and the cilia are in constant motion, giving the appearance of rapid waves passing from one corner to the other, the waves of protoplasm gradually increasing in length and tenuity until they have the appearance of projecting cilia."
No nucleus can be seen. Though in constant action no change of locality takes place.” Fig. 1.

On looking up the subject I found that the little organism was the *Trypanosoma sanguinis* which had been described originally by Gruby as an entozoon in the blood of frogs, and by Ray Lankester (not at the time knowing Gruby’s observations) as *Undulina*, the type of a new group of Infusoria.

Though a trifling little object it possesses considerable interest as there is still a doubt concerning its real nature and the movement which it displays is unusual, being neither the slow, creeping rhizopodal motion, nor yet truly ciliary. Minute protoplasmic organisms usually display one or other of these types of movement, but in the object under consideration, there is a peculiar wavy undulation along one margin of the creature together with a lashing vibratile action. Studying the margin under a high power a rapidly succeeding series of waves is seen to pass from one side to the other, increasing in length until at one corner the wave is extended into a lengthened cilium resembling the whip-like flagellum of an infusorian. In the specimens which I examined the undulations always passed in one direction and it appeared as if from the tips of any of the waves the protoplasm could be extended into cilia, though usually only those at one end presented them. It is this latter feature, together with the peculiar wavy character of the motion that gives the creature a special interest and makes it quite an exceptional one among organisms of its class. A fine hair-like extension from the narrow end was also in constant motion and appeared to vary considerably in length, as if it were only a delicate process of the protoplasm, and, unlike a true *cilium*, capable of elongation or retraction. I kept one under observation for over an hour, during which time the movements kept up, but got slower towards the close. The undulatory motion at last ceased, but the tail-like
projection and the flagellum at the margin of the broad end continued to move (the appearance is represented at fig. 2.)

and were evident after motion had ceased. This would favor the view that these processes were "cilia," and not merely temporary extensions of the protoplasm, though the remarkable manner in which the cilia were extended and retracted shows that they were not similar in all respects to the cilia of Infusoria or of various animal cells. Professor Lankester speaks of it as "a mouthless infusorian, closely allied to Opalinidae, from which, however, it differs essentially, as well as from Infusoria ciliata generally in possessing no cilia." Gruby described it as a parasitic entozoon, while Siebold* states that it is not an independent organism, but simply an undulating membrane swimming freely. Dr. Gaule † has advanced some rather startling views concerning this little body which he believes originates in, or is a transformation of a colorless blood corpuscle. He states that on the warm stage the process of conversion of the white blood corpuscle into the Trypanosoma may be readily followed and takes place by the development at one margin of a vibratile cillum and a rapidly undulating membrane. He recognized four or five types of these transformed blood corpuscles and calls them "Kymatocytes." They may return to their original corpuscular condition. I have tried to follow these observations of Gaule but without success and adhere to the opinion that we have to deal here with a minute parasite, the affinities and life history of which have yet to be worked out. They were not abundant in the blood of my frogs and were only met with in two. I have not found them this season in any of the frogs in my tanks.

This session my attention was called by a member of my Histology class to what he thought was a peculiarly elongated white corpuscle in the frog's blood, but which I recognized as another

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* Micrographic Dictionary—Undulating Membranes.
parasitic form. The blood examined by the student on that day was taken from two bull frogs ("Rana Mugiens"), but only one contained the parasites. The organism presents the following characters:—Body an elongated oval, sausage-shaped, ends conical, one sometimes narrow and prolonged. Length somewhat more than half a red corpuscle. The protoplasm is homogeneous and more translucent than that of colorless corpuscles and shows two or more small central vacuoles (?) with a few granules. Movements slow and creeping, accompanied by an occasional bend or twist of the body, go on at ordinary temperature; a little accelerated but not altered in character on the warm stage. The tail-like end though produced does not terminate in a cillum. Fig. 3.

This parasite was originally figured by Ray Lankester, when describing the Undulina (Trypanosoma) but he has only recently, in the Quarterly Journal of Microscopical Science, for January, 1882, given a full description of it, and established its position. He calls it Drepanidium ranarum. Dr. Gaule, of Leipzig, has studied these bodies and has come to conclusions as remarkable as those at which he arrived concerning Trypanosoma. He calls them "Wurmchen," vermicles, and believes that they are protoplasmic portions of the corpuscles of the blood which assume an elongated form and display movements. He has found them within the cells not only of the blood but of the spleen, kidney and liver and has seen them penetrate and enter blood corpuscles by their active movement.

Dr. Lankester shows very clearly that these organisms are truly parasites belonging to the Gregarinidæ or Sporozoa, those lowly protozoal forms, many of which at some time of their existence are parasitic in the interior of cells. He suggests that it is a young stage and the more developed or Gregariniform condition of the parasite exists in some part of the body of the frog. He points out that these bodies have a striking resemblance to those figured by Lieberkühn, as spores or pseudo-navicula from
the kidney of the frog. Within the cells they can best be seen on the addition of salt solution 3%. I have found, after trying a number of solutions, that Pilocarpin ½% brings them out very clearly. In one frog the red corpuscles contained, in addition to the Drepanidia, smaller irregular masses, fig 4.

Fig. 4.

In blood from a small frog they were very abundant, and could be seen well without any reagent. Fig. 5 a represents a corpuscle with one inside which travelled round the cell four or five times, and then migrated from it as shown at Figs. 5 b and c. This curious phenomenon was witnessed several times, and did not seem to injure the corpuscles very much, some presenting no trace of the point of exit, others a slight depression.

Fig. 5.
THE THIRD
CORPUSCLE OF THE BLOOD,

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FROM
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THE THIRD CORPUSCLE OF THE BLOOD.

In addition to the red and white corpuscles, there are in the blood granular bodies of various size, from that of a red corpuscle to masses ten to twenty times as large. These were first described by Max Schultze, and they may be called very appropriately, as I have been in the habit of doing for years, "Schultze's granule masses." In healthy adults they are not abundant as a rule, though exceptionally in persons in apparently good condition they abound. In all cachectic states the granule masses are large and numerous. They form notable features in blood specimens from cases of chronic phthisis, cancer, and wasting diseases generally; also in leukaemia and symptomatic anaemia; but it is not a little remarkable that in pernicious anaemia they are scanty, or even absent. In the lower animals the masses are met with in variable numbers. The blood of the young contains them in larger proportion than in adults. The new-born rat, kitten, rabbit, or guinea-pig may be used with advantage for their study. So common are they in the blood of hospital patients that it is not to be wondered at if mistakes have arisen concerning the signs of their presence in certain diseases. Thus, in The Lancet a few years ago, a gentleman described them under the heading of "a new feature in leucæmic blood," regarding them as specific or characteristic elements.

I have been told of a somewhat prominent London physician, connected with one of the special hospitals for chest diseases, who found them so constant
in the blood of phthisical patients that he regarded them as peculiar to the disease, until advised by a colleague of their wide distribution. The most extensive observations upon their presence in disease were made by Dr. Reiss.\textsuperscript{1} The common opinion regarding them has been that they represent degenerated white blood-corpuscles, or a granular detritus resulting from their decay. I first showed that they were composed of distinct corpuscles, and that the masses did not preëxist in the blood, but were formed at the moment of withdrawal by the aggregation of the corpuscles. At the edges of large groups, the disk-like corpuscles can be distinctly seen, and in the sulphate of soda solution, such as used for mixing the blood in hæmocytometer work, the corpuscular nature of the masses is quite clear. But what led me to this point was the fact of the impossibility of supposing that masses of the size of some of these could pass through the capillaries. Reiss felt the same difficulty, and suggested that in some cases they might produce embolism. In the blood of the new-born rat they are most abundant, and the subcutaneous tissue was employed to investigate the condition of the masses within the vessels. It was then found that they do not preëxist as aggregations in the blood, but are in the form of isolated corpuscles floating free with the other forms. By far the simplest way of demonstrating the isolated corpuscles in the vessels is to snip a small bit of the subcutaneous tissue from a young rat, and examine in salt solution.

In a small artery or vein, there will be seen with the red and white cells small, pale corpuscles about one-fourth the size of the red ones, often in extraordinary numbers (Fig. 1). A drop of blood from the tail of the same animal will show numerous granule masses, at the edges of which the corpuscles can be

\textsuperscript{1} Reichert u. DuBois Reymond's Archiv, 1872.
seen. The corpuscles swell in water, and become pale: dilute acetic acid renders them more distinct;

FIG. 1.

they stain with carmine and methyl-violet. The corpuscles are discoid, pale, structureless (Fig. 2),

FIG. 2.

and often undergo peculiar alterations in shape, elongating or presenting two or three fine hair-like extensions. They measure from \( \frac{1}{8000} \) to \( \frac{1}{12000} \) of an inch. The largest I have measured was \( \frac{1}{5000} \); and the smallest are from \( \frac{1}{15000} \) to \( \frac{1}{20000} \).

The facts above given are from my paper before the Royal Society in 1874, which was published in the *Proceedings* for June 18th of that year. A considerable part of that communication was taken up with describing the changes in form which the corpuscles undergo when kept for some hours at the temperature of the body, and examined in blood-serum; but the corpuscles were described and figured, and a true explanation given of the structure and formation of Schultze's granule masses. These bodies are undoubtedly the same as those described by Zimmerman¹ as elementary corpuscles which he found when blood was let flow into a solution of a neutral salt; after the subsidence of the colored elements, the supernatant serum contained, in ex-

¹ Virchow's Archiv, Bd. xviii.
traordinary numbers, small, round, colorless corpuscles with weak contours.

In 1877–79, Hayem, of Paris, investigated these bodies very carefully, and by special modes of preparation and examination was enabled to isolate them and prevent their aggregation into masses. He called them hæmatoblasts and believed that they represented embryonic red corpuscles.

From this time on, until last year, little or nothing new concerning these bodies is met with in medical literature, when in a series of papers in the Centralblatt f. d. medicinischen Wissenschaften, and more fully the November number of Virchow's Archiv (Bd. xc.), Prof. Bizzozero, of Turin, described anew the corpuscles and advanced important views concerning their connection with the process of thrombosis and coagulation. His account of the corpuscles, which he calls "Blutplättchen" (blood-plates), differs in no essential particular from that which I had already given, and his figure of them in a small bloodvessel (Pl. V., Fig. 2, Virchow's Archiv, Bd. xc.) is similar to my original one reproduced here in Fig. 1. The observations upon the connection of the corpuscles with thrombus formation are novel and important. When a vessel-wall is injured, or when any foreign body is introduced, the earliest observable phenomenon is the collection of the blood-plates on the wounded spot or on the foreign substance. The white corpuscles appear later and are much less numerous. The blood-plates rapidly change, becoming fused or united together and converted into a granular substance, and this dissolution or disintegration appears intimately associated with fibrin formation. In a portion of a vessel sutured between two ligatures the blood remains fluid so long as the blood-plates retain their normal form and appearance.

The influence which Schmidt and others attribute to the white corpuscle in coagulation, Bizzozero
believes is due to these smaller elements. Certainly no such rapid disintegration of the colorless corpuscles takes place, as is spoken of by some writers. Under favorable conditions they may retain their vitality, as shown by amöeboid movements, for twenty-four or thirty-six hours after withdrawal, and many hours after coagulation has occurred. If freshly-drawn blood is whipped with a bundle of threads, the "blood-plates" first adhere to them, and afterwards a few white and red corpuscles. If the threads are then, before fibrin is deposited, washed in salt solution, they will, when placed in a suitable liquid (proplastic of Schmidt), induce coagulation, which, as Bizzozero has shown by other experiments, cannot be attributed to the few red or white corpuscles adhering to the threads. Several facts have come under my observation which corroborate the views of the learned Italian professor. I have been struck with the density and richness of the fibrin network in blood specimens in which Schultze's granule masses were abundant. As is well known, the distinctness with which the fibrin filaments can be seen in blood slides varies very much, and I think the variations will be found to have a close connection with the abundance or paucity of these elements. As one watches the process of coagulation, the filaments first seen are invariably in association with small granules—which represent disintegrated blood-plates—or larger Schultze's masses. In cases of extensive atheroma of the aorta, the thrombi which form in the small breaches of the intima may consist entirely of these corpuscles, and in aneurisms they occur on the surface of the fibrinous laminae. So, also, in the vegetations of endocarditis, these little corpuscles are found associated with the fibrin layers so commonly deposited in these structures.

So far as I can make out, the corpuscles here described are different from the invisible corpuscles
of Professor Norris, of Birmingham. The origin of the corpuscles remains a problem—one of many connected with the blood which await solution at the hands of histologists.

To conclude: 1st. There is in mammalian blood a third corpuscular element, one-eighth to one-half the size of the red corpuscle. It can be clearly seen in the bloodvessels of the living animal or in the vessels of freshly removed bits of tissue. It may be called appropriately the third corpuscle, or "blood-plate," though the latter expression is not a very satisfactory one.

2d. In blood withdrawn from the vessels these corpuscles aggregate together and form the well-known granule masses in which the corpuscles rapidly degenerate and lose their outlines. These masses, first described by Max Schultze, should be known by his name.

3d. There is evidence to show that the third corpuscle plays an important rôle in coagulation.
ON THE USE OF ARSENIC
IN
CERTAIN FORMS OF ANÆMIA.

BY

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Read before the Philadelphia County Medical Society, Sept. 22, 1886.

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ON THE USE OF ARSENIC
IN
CERTAIN FORMS OF ANÆMIA.

In an address last year, Dr. Wilks remarked that in therapeutics we do not so much need new remedies as a fuller knowledge of when and how to use the old ones. I do not know a more striking illustration of this than is afforded by arsenic, a good old remedy, for which an almost new use has arisen in certain cases of pernicious anæmia. The attention of the profession was directed to the subject by Bramwell in 1877, and although various reports bearing witness to the value of this drug have appeared from time to time, the knowledge of its efficacy does not appear to be very wide-spread, and there are still points in connection with its employment upon which we need information. These, I trust, discussion may bring out, and render clear the direction which future observation should take.
In treating a case of anaemia, it is of the
first importance to ascertain, if possible, the
cause. For convenience, and until the pres-
ent complex pathology is simplified, we may
classify the anaemias into secondary and pri-
mary; the former induced by causes acting
upon the blood itself, the latter the result of
disturbance in the blood-making organs. This
distinction, not always clear, serves to sepa-
rate two clinical and pathological groups of
cases.

The secondary anaemias are the most com-
mon, and arise from a variety of causes, as
hemorrhage, prolonged drain of albuminous
material in chronic disease, and the action of
toxic agents on the blood. In very many of
these conditions a return to the normal state
follows naturally upon removal of the cause,
and the regeneration of the corpuscles may
take place with extraordinary rapidity, as
after a copious bleeding or a sharp fever;
but, as a rule, iron in some form will be
found useful or indispensable. In three of
these secondary anaemias I have found arse-
nic very beneficial.

1. *The Anaemia of Heart-Disease.* — In
chronic valvular trouble we not infrequently
meet with an impoverished condition of the
blood, which materially aggravates the car-
diac distress. The comfort of such patients
is in direct proportion to their corpuscular
richness, and without any apparent increase
in the valve mischief, a reduction in the
ratio of the corpuscles is followed by short-
ness of breath, palpitation, and signs of
heart-failure. The value of iron in this con-
dition is well known, and its combination
with digitalis a universal practice. Arsenic is also indicated in these cases, particularly in children, or if, as sometimes happens, iron does not agree. In June of this year I saw a lad, J. W., æt. 14, who had had chronic valve-disease for four years. He had been wintering in the South, and went afterwards to the Arkansas Hot Springs. When I saw him the anæmia was very marked, and he suffered from breathlessness on the slightest exertion. There was no cardiac distress, and the compensation was not seriously disturbed. At the Hot Springs he had several chills, with fever, for which he had taken quinine. He was ordered Fowler's solution of arsenic, beginning with \( \frac{1}{33} \), three times a day, and increasing to \( \frac{1}{6} \), if well borne. He had been taking an iron and strychnine pill for several weeks, and had with him a boxful, which he was advised to finish. Digitalis was prescribed, but was not to be taken unless there were signs of heart-failure. The diet was carefully regulated. The lad improved rapidly, and within six weeks had a good color, and had gained several pounds in weight. He had not needed the digitalis. The arsenic was well borne. The improvement had continued on the 3d of this month. Possibly here there was a malarial taint; but, in any case, if medicinal agents had anything to do with the rapid improvement, the credit is due to the Fowler's solution.

2. In Malarial Anæmia.—The value of arsenic in chronic ague-poisoning is so well recognized that I need scarcely detain you with the narration of cases in support. There
have been several at my clinic during the past year in which the improvement in the blood condition, as tested by the hæmacytometer, has been very remarkable. One case in particular, from Cape May, I may refer to, as the patient, with enlarged spleen, had on two occasions hemorrhage from the stomach. The arsenic in this case was pushed for several months in increasing doses. At one time he took \( \times \text{xxxvi} \) of the Fowler’s solution daily. When last heard from, in July, he was at work, and had gained in flesh and strength. On May 12, the date of the last blood count, the percentage was over eighty (it had been scarcely fifty), and the spleen had diminished materially in volume. In certain of these cases the ratio of the corpuscles may increase rapidly without any essential change in the volume of the spleen. In the case of M. D., a girl of 15, who has been in the University Hospital on several occasions for the past two years, the arsenic, which was very persistently employed, does not appear to have reduced the spleen in the slightest degree, and yet under its use the corpuscles rose to eighty-five per cent. In this instance, with a history of malaria, there is evidence also of congenital syphilis, to which may possibly be due the splenic enlargement. Injections of arsenic into the substance of the organ were tried without benefit.

3. Certain Anæmias of Gastric Origin.—As a tonic in debilitated states of the stomach, arsenic has long been a favorite remedy with many practitioners. It is sometimes also of great service in the anaemia of chronic gastric catarrh, particularly in alcoholic patients.
A good illustration of this was under my care at the Philadelphia Hospital this spring. W. G., aged 25; waiter; hard drinker; history of dyspepsia for several years. Admitted April 5 with anæmia and attacks of giddiness. Ill for ten days; vomiting, pain in stomach, and fainting spells on attempting to stand. Had been failing in strength for some time and getting pale. Had suffered from palpitation, and said he had vomited blood. He was profoundly anæmic, and could not stand without danger of fainting. Tongue coated; great irritability of stomach; vomiting on the slightest provocation; great throbbing of abdominal aorta. He was kept at rest, given a milk diet, and Fowler's solution in 3-drop doses. The red corpuscles were not more than twenty-five per cent., and the coloring matter about the same. The improvement was rapid, and by the 21st the corpuscles had risen to over forty per cent., and the gastric irritation had almost disappeared. The arsenic was well borne, and was gradually increased to mxi t. i. d., and on May 4 he was ordered small doses of nitromuriatic acid. On May 17 he left the hospital with a fair digestion and, for him, tolerably good color. On June 24, when readmitted with extensive pleuro-pneumonia, he stated that he had recovered strength rapidly, and had been at work. Possibly, in this case, there was ulceration of the stomach in addition to the chronic catarrh; but, whatever the condition, it was one in which the arsenic seemed to be highly beneficial, and, as he received no other medication, we may reasonably attribute to it the stimulation of the
blood-making function. As we shall see, there are anæmias of gastric origin in which this drug is powerless. These are some of the secondary anæmias which have, in my experience, been apparently benefited by the use of arsenic.

Turning now to the primary group, we have here again for convenience to make a division of the cases. There is, first, a large section of what may be called cytogenic anæmias, in which the reduction and alteration in the corpuscles is associated with evident changes in the hæmatogenous tissues,—the spleen, lymph-glands, and bone marrow. Sometimes these changes are accompanied by an increase in the colorless corpuscles of the blood; and, depending on the organ involved, we then speak of splenic, lymphatic, or medullary leu-kæmia. If there is no marked increase in the white corpuscles we call the cases splenic anæmia, lymphatic anæmia (Hodgkin's disease), and medullary anæmia. The pronounced leucocytosis in certain of the cases, which gives a special character to the blood, is probably not such an important factor as we have hitherto supposed, and there are such insensible gradations between the cases that in a strict classification they may be appropriately grouped together. Secondly, there is the curious primary anæmia known as chlorosis, characterized by well-marked etiological and anatomical peculiarities; and, thirdly, we have the much-discussed affection, perni-cious or essential anæmia.

The anæmias of this primary group offer a remarkable therapeutic study, embracing cases of the most hopeful and the most hopeless
character. A clearer knowledge of the etiology and pathology of certain of these forms may give a clue to lines of treatment more fortunate than those we now possess; for, if we except chlorosis, the majority of the cases of this class of anæmias prove fatal. Leukæmia, splenic anæmia, when non-malarial, Hodgkin's disease, are considered incurable affections, and very many of the cases of pernicious anæmia prove obstinate to all treatment.

The relation of arsenic, as a remedy, to this group of primary anæmias is worthy of our closest study, more particularly as of late years remarkable results have been reported from its use. Chlorosis may here be excluded from our consideration, as it would only be in a strangely obstinate case that a practitioner would require to employ arsenic. The specific action of iron in increasing the defective hæmoglobin of the corpuscles, and doubtless, also, in stimulating the formation of new ones, is one of the few instances in therapeutics in which definite tissue-changes, under the influence of a drug, may be followed with scientific accuracy from day to day and from week to week.

In leukæmia and Hodgkin's disease arsenic has been extensively tried, occasionally with temporary success. We must bear in mind in these affections that there are natural periods of improvement without any special medication. I have met with this in leukæmia, and it must be taken into account in our estimation of the effect of a remedy. Personally, I have not seen any benefit from the use of arsenic in this disease. It was given in several of the eleven cases which I saw in
Montreal, all of which were fatal. In Hodgkin's disease the report is more favorable. In 1883 I had two cases, both in women, in which the large glands of the neck and armpits reduced materially under the prolonged use of Fowler's solution, but I do not know the subsequent history of the cases. Several writers have reported most satisfactory results. Karewski* had three recoveries, and of eleven cases treated at the Stockholm Hospital five were benefited.† The persistent use of it in full doses for many months is probably the most efficacious remedy we possess in this disease.

In cases of splenic anæmia of non-malarial origin, I cannot say that I have seen any special benefit from arsenic.

We come now to pernicious anæmia, in which so much has been gained by the judicious use of this drug. Pernicious anæmia includes cases of very diverse etiology. Any severe anæmia tending to a fatal termination may well be termed progressive and pernicious. In a considerable proportion pregnancy and parturition appear to have been determining factors, while others can be directly traced to defective food, as in many of the Zurich and Bern observations. Excluding these, we have a group of cases of which the etiology is obscure, and to which, in our present knowledge, the terms idiopathic of Addison and essential of Lebert are applicable. Every year, however, we are reducing the number of cases which we can strictly call

† Abstract in Year-Book of Treatment for 1884.
idiopathic. It is reasonable to suppose that the extensive changes in the bone marrow found in certain instances are directly related to the profound disturbance in blood formation, just as is the case in hyperplasia of the spleen or of the lymph-glands. An anæmia medullaris is now very generally recognized. Then, there are the cases of pernicious anæmia in which the primary disturbance seems to be in the gastro-intestinal canal, and the condition of the blood the direct consequence of the impaired nutrition. There remain cases in which none of these conditions prevail, and neither during life nor after death do we find any clue to the origin of the anæmia. To such, for the time, the designation idiopathic is applicable. Clinically, it may be impossible to distinguish between these various forms, and the etiology is often very obscure and gives us no help. The cases which come on during or after pregnancy, or which result from inanition, are readily recognized, and offer, as a rule, a more hopeful prognosis; but we cannot yet with any accuracy separate during life the cases in which there is atrophy of the mucous membrane of the stomach, or extensive medullary changes, from those in which these conditions are absent. A more careful study may in the future enable us to do so, and I have laid stress upon these differences in etiology and pathology because in them will possibly be found the explanation of the success or failure of certain remedies.

Prior to 1877 arsenic was not systematically employed in pernicious anæmia, and to Bramwell is undoubtedly due the credit of its intro-
duction. Neither Müller* nor Eichorst,† in their elaborate monographs published in 1877 and 1878, speak of its use. Padley,‡ in an interesting review of the question, has carefully analyzed the cases in which arsenic was not employed, and finds that of forty-eight, forty-two were fatal, while of twenty-two cases treated with arsenic sixteen recovered, two improved, and four proved fatal; and he remarks, that “in the whole list there is not, with one exception, a single authentic case of recovery in which arsenic did not form the chief part of the treatment.” Certainly the reports of this affection since 1880 have been much more encouraging, and it need not necessarily be regarded as “almost invariably fatal,” to use the words of a leading textbook. Of three cases of pernicious anæmia which I have seen this year two have already proved fatal, and one is in a fair way to recovery.

**Case I.**—A man, aged 42, I saw with Dr. Henry. We reported it in full in the April number of the *American Journal of Medical Sciences*, and it is remarkable as an instance of pernicious anæmia, with advanced atrophy of the mucous membrane of the stomach. Arsenic was given during the course of the disease, but not for any length of time, as it seemed to bring on diarrhoea.

**Case II.**—A woman, aged about 45, I saw with Dr. Weir Mitchell on January 20. She had been the subject of dyspeptic attacks

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* De Progressive Perniciose Anæmie. Zurich, 1877.
† De Progressive Perniciose Anæmie. Leipzig, 1878.
‡ *Lancet*, 1883, ii.
for some years, and had become very pale, and during last year the anæmia reached an extreme degree. With rest, systematic feeding, iron, and arsenic she improved, and was able to go home and attend to her household duties. I saw her in January on her way South. She returned in March very much worse; was again placed on the plan of treatment which had proved so successful in the first attack, but the stomach was so irritable and the digestive power so enfeebled that she sank, and died on the 18th of April. The improvement in her first attack was attributed by Dr. Mitchell to the careful feeding and rest as much as to the medicine.

Case III.—An active business man, aged 43; seen March 4. History of dyspepsia, and for the past six months failure in strength. Shortness of breath on the slightest exertion, and at times attacks of agonizing pain at the heart resembling angina. He had not lost much flesh; indeed, as is usual in these cases, the subcutaneous fat was well developed. When first seen, the anæmia was marked; lips and tongue very pale, and sclerotics pearly. The general surface did not look so pale, on account of his dark color and a decided saffron-yellow, sub-icteroid tint of the skin. The temperature was a little elevated; pulse 100, and of moderate volume. With the exception of heart-murmur, there were no symptoms elicited in the examination of thoracic and abdominal viscera. The blood showed in a marked manner the corpuscular changes of advanced anæmia. The blood count could not be made at the time, but when I next saw him, two weeks later, there
were only 700,000 red corpuscles to the cubic millimetre, and the color percentage was only about twenty. He was put to bed, absolute rest, given a milk diet, ordered massage once a day, and as medicines bismuth and carbonate of sodium, with Fowler's solution \( \frac{m}{y}v \), three times a day, to be increased one minim daily at the end of a week. He had been taking, by the advice of his physician, an elixir of iron and strychnine, which was continued. For two months there was not much apparent change, though the ratio of the colored corpuscles increased to over 1,500,000 per cubic millimetre. The arsenic had been pushed to 15 drops three times a day, when puffiness of the eyelids and forehead came on, and it was omitted for a week, and started again with \( \frac{m}{y}v \). On reaching \( \frac{m}{x} \text{iii} \) a slight red rash appeared, and it was stopped, and, after beginning at \( \frac{m}{y}v \) again, he reached \( \frac{m}{x} \text{xx} \) t. i. d. On these large doses he seemed to improve more rapidly, and he bore them for two weeks or more, when gastric irritation supervened, with diarrhœa. The drug was then stopped for ten days, and pills of \( \frac{1}{10} \) of a grain of arsenious acid ordered. On January 31 he was allowed to get up. By June 13 he was able to move to Cape May. The blood condition has rapidly improved, and at the last count the corpuscles were nearly 4,000,000 to the cubic millimetre. When seen on September 7 he looked remarkably vigorous, had a good appetite, was at business, and feeling very well. It would be incorrect to attribute the success in this case entirely to the arsenic, but rather to the plan of treatment, in which it was a
very important factor. It will be found, I think, that absolute rest in bed, with daily massage, and the strictest attention to feeding, are most important features in the successful management of these cases.

Arsenic has been spoken of as a specific in pernicious anæmia. This is a mistake. The disease, as I have indicated, is so varied, and results from the operation of such diverse causes, that we cannot expect any one remedy to be uniformly active. In a majority of the cases iron is useless, but it sometimes succeeds after arsenic has failed absolutely. Such a case was reported by Finlay* last year, which was cured by iron after a thorough and but ineffectual use of arsenic. I do not think we understand fully the conditions in which it is most serviceable, and for the time we must be content to employ it empirically, on faith of the success which has attended its administration in so many cases. Ultimately, we may hope to be able to discriminate between the cases which call for iron and those in which arsenic is indicated, and with this object in view the cases which come under observation should be carefully studied.

Mode of Administration.—I usually give the liquor arsenicalis (liquor potassii arsenitis), beginning, in an adult, with miv three times a day. Occasionally this is found too much, and I reduce the amount to 2 or 3 minims. After ten days, if well borne, I order an increase of a minim each day, so that by the end of the second week the patient is taking

* Lancet, 1885, i.
10 or 12 minims three times a day. This is kept up for a week, and then gradually increased until the physiological effects are obtained. The amount which will induce these varies with different individuals, and those who bear it best seem to improve the most rapidly. I have thought sometimes that the small doses are not so well borne as larger ones, and are more likely to cause gastric irritation. Young people bear it remarkably well. Within the physiological effects there is no special limit to the quantity, and, as in chorea, I make them my guide in the administration. A very important point is the continuous use for many weeks or months, omitting for a few days if unpleasant effects arise. Even after apparent recovery I advise the continuance of the drug. When the liquor arsenicalis is not well borne, the arsenious acid in pills may be tried, or the solution may be given hypodermically. In these cases of severe anæmia I never care to use hypodermic injections systematically, as I have seen ecchymosis of the tissues follow, and in several instances distressing small abscesses. By the rectum, it is usually well borne.
ANTIFEBRIN.

BY

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Professor of Clinical Medicine in the University of Pennsylvania.

[Reprinted from The Therapeutic Gazette, March, 1887.]

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GEORGE S. DAVIS, PUBLISHER.
1887.
A FEW months ago Drs. Cahn and Hepp announced from Kussmaul's clinic the discovery of a new antipyretic, which they named antifebrin. A full account of their observations has more recently appeared in the *Berliner Klinische Wochenschrift*, Nos. 1 and 2, 1887.

The drug is known chemically as phenylacetamide or acetanilide \((C_6H_5C_2H_9OHN)\), and is formed by the action of heat upon aniline acetate. It is a neutral body, and in this respect it differs from all other antipyretics, which are either phenols, like salicylic acid and resorcin, or bases of the chinoline series, as thallin, antipyrin, and quinine. It is a white crystalline powder, insoluble in cold water, but readily dissolving in hot water or alcoholic solutions. The taste is not unpleasant. The dose is from 8 to 12 grains. In larger amounts it is not poisonous, though it is advisable not to exceed 30 grains in the day. Usually 8 grains will be found an effective dose. It is conveniently given in spirit and water, or in whiskey, or, for children, in warm sweetened water.

During the past three months I have used it in my wards at the Philadelphia Hospital and at the Hospital of the University of Pennsylvania in the following 29 cases: typhoid fever, 7; pneumonia, 6; phthisis, 8; erysipelas, 4; pleurisy, 1; peritonitis, 1; rheumatism, 1; intermittent fever, 1. As a rule, 8 grains were given when the temperature rose above \(103^\circ\), and hourly observations were made for six or eight hours. In several cases of phthisis 4 grains were given four or five times a day. The maximum amount given in one day was 32 grains (Case II.). For brevity, the effects of the drug may be noted under the following heads:

1. **Reduction of Temperature.**—This is the most marked and characteristic action, beginning usually within an hour. In eighteen administrations the fall was over \(2^\circ\) in this time; in three instances a fall of \(3^\circ\), on two occasions a fall of \(4^\circ\). In thirteen instances the temperature was reduced \(4^\circ\) in two hours, in sixteen administrations \(3^\circ\), and on four occasions \(5^\circ\). The greatest drop within this time was in Case XXIV., in which the fall was \(6\frac{2}{3}^\circ\). The greatest reduction was in the following: Case I., \(8^\circ\) in five hours; Case X., \(6\frac{2}{3}^\circ\) in five and a half hours; Case XVIII., \(7\frac{2}{3}^\circ\) in two and a half hours; Case XX., \(7^\circ\) in seven hours; Case XIX., \(7\frac{3}{2}^\circ\) in ten hours.

In seven administrations the temperature was unaffected by the eight grains. Cases VII. and XIII., both of pneumonia; Case XXIII., peritonitis; and Cases IX. and XVIII., erysipelas.

The duration of the reduction was variable, usually from three to six hours. The following cases illustrate well the antipyretic action of this drug:

**Case XI.** (Chart I.).—Man, aged 32, admitted to the drunkards' ward of the Philadelphia Hospital. A few days after admission he was noticed to be a little short of breath, and, on examination of the lungs, there was dulness, with râles and feeble blowing breathing at the right base. On January 3, at 5 P.M., the temperature was \(105\frac{5}{6}^\circ\). Antifebrin, gr. viii, was given, and the fever gradually fell, as the chart shows, until midnight, reaching \(100^\circ\). By 3 A.M. it had risen to \(101\frac{4}{6}^\circ\). At 7 P.M. on the 5th the temperature was nearly \(104^\circ\), and another dose of the antifebrin was given with good effect.
Antifebrin.

**Case XI.**

January 3.

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**Pneumonia.**

**Case IV.** (Chart II.).—Rachel C., aged 21, admitted November 3 with typhoid fever. On the 4th the temperature was 104°, but from this date until the 13th it did not rise above 103°. At 8 P.M. on the 13th the temperature was 103°, but there was no collapse. The thermometer did not again register above 103° in her case.

**Case X.** (Chart III.).—J. B., aged 35, with chronic phthisis and high fever. The chart shows how rapidly the antifebrin in three suc-

104°. Antifebrin, gr. viii, was given. By ten o'clock there was a fall of 5°, with profuse sweating. At 11 P.M. the temperature was 97°. At 12 A.M. it began to rise, and by 2 A.M. was 99.4°. Between eleven and twelve o'clock she complained of slight chilliness, but the general condition was good, and there was no collapse. The thermometer did not again register above 103° in her case.

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**Case XVIII.** (Chart IV.).—F. H., aged 31, was trephined for mastoid disease in Philadelphia Hospital January 15. On the 20th he was attacked with erysipelas. On the 23d, at 10 A.M., the temperature was 106°; at 11, 105°.

Typhoid fever.
He was given antipyrin, gr. xv, and quinine, gr. xx. At 3 p.m. the temperature was still above 103°, and a second dose of antipyrin was given. At 5 p.m., quinine, gr. xx. He had had also quinine, gr. v, every four hours. At 8 p.m. the temperature had fallen to 100.4°, at 11 p.m. to 99°, and at 3 a.m. to 98°. On the 24th the fever was again 105°, and antipyrin and quinine were given, with a reduction of 4° in five hours. On the 25th antipyrin and quinine were twice given, without any effect. He was transferred to the medical ward, and the antifebrin was used as shown by the chart. The last dose caused a fall of 7.8° in two and a half hours. The patient subsequently did well. The chart is of interest, as it affords a comparison between the action of antipyrin with quinine, and that of antifebrin.

In several cases the dose of gr. viii did not seem sufficient. In seven administrations little or no effect followed. This was particularly noticeable in the pneumonia cases. In Case XIII., with almost complete involvement of the right lung and affection of the left base, the temperature from the 5th to the 10th ranged from 102° to 105°. Antifebrin was given six times, thrice without effect, and on three occasions it only reduced the fever a degree or a degree and a half. Thallin, gr. iv, twice brought the temperature down 3° and 4°; but the most effective agent in this case seemed to be the cold pack, which reduced the temperature from 105° to 98.8°.

This patient had delayed resolution, and the fever did not subside until the thirty-ninth day from the initial chill. In other instances, a second dose repeated an hour or more after the first produced the full effect, as in Cases XI. and XVIII.

In typhoid fever the action was usually prompt and satisfactory. In Case II., a young man, aged 25, with persistently high temperature and marked nervous symptoms, the drug was given on fourteen occasions, and after each dose there was a drop of from 3° to 5°. In the milder cases the effect was more striking, as in Case IV.

In the erysipelas cases the action was in each instance most decided.

In phthisis, with high fever, the drug was usually given in a single powder of gr. viii, when the temperature was above 103°, but in three cases the plan was tried of giving gr. iv four or five times a day. This did not seem very successful, and the patients did not feel so comfortable as with the single dose.

In a remarkable case of quartan ague antifebrin in 8-grain doses given before or during the paroxysm seemed to be without effect. One curious circumstance, however, is worth mentioning. The lad had always with the fever the most intense general urticaria, which the antifebrin seemed to prevent, much to the patient's comfort.

2. Action on the Circulatory System.—Usually with the reduction of the fever the pulse would fall, and a drop of 20 or 30 beats in two or
three hours was frequently noted. Thus, in Case II., with a pulse-rate of 112 per minute, and the temperature at 105°, the pulse fell to 84 in four hours. In another case the pulse fell from 130 to 90 in four hours. A marked increase in the pulse-tension was observed in several cases. Even with a rapid fall of from 5° to 7° in two or three hours, there was no evidence of heart-weakness. Slight cyanosis, which is mentioned by one or two German writers, did not occur in any instance.

3. Sweating.—As with thallin and antipyrin, the action of antifebrin is almost invariably accompanied with profuse perspiration, which is often the first effect of the drug. Repeatedly I have seen the forehead beaded with sweat half an hour after the administration of 8 grains. This is sometimes a most unpleasant feature in the employment of the drug, and is the only one of which the patients have complained. In several instances the drug was combined with atropine, but without much effect. It does not seem to increase the night-sweats in cases of phthisis; indeed, under its use, one patient, who sweated much with the afternoon dose, had drier and, in consequence, more comfortable nights. In the severe typhoid case already referred to, I stopped its use, as the sweating seemed to weaken the patient.

4. On the Urine.—The only change noted was a marked increase in the amount in some of the cases. This is probably a direct result of the increased arterial tension.

5. The effect on the general condition seemed usually beneficial. A quiet sleep often followed an hour or so after its administration. The phthisical patients expressed themselves more positively than the others in this matter.

There were none of the disagreeable effects which we sometimes see follow the use of antipyrin and thallin. There was no instance of vomiting; and, with the exception of Case IV., there was no shivering or chilliness, such as is so common after antipyrin.

These limited observations confirm those of Cahn and Hepp and others, and I think that we have in antifebrin a prompt and powerful antifebrile agent, easy to take, and free from unpleasant effects. It has the advantage also of cheapness. Merck's article, which I have used, is only sixty cents an ounce, wholesale.
CASE OF ARTERIO-VENOUS ANEURISM OF THE AXILLARY ARTERY AND VEIN OF FOURTEEN YEARS' DURATION.

By WILLIAM OSLER, M. D.,

PROFESSOR OF MEDICINE JOHNS HOPKINS UNIVERSITY, AND PHYSICIAN IN-CHIEF TO JOHNS HOPKINS HOSPITAL.

The following case is worth placing on record, partly on account of its rarity, but more particularly on account of the long duration without serious symptoms, and the admirable illustration which it affords of the propriety of non-intervention in certain instances of aneurismal varix.

On December 28, 1888, I saw in Hamilton, Ont., with Dr. Malloch, H. B. T., aged twenty-five, who presented the following condition: He is a strong, healthy young man, with a fresh complexion, well developed muscles and a well-shaped thorax.

Inspection.—The apex beat of the heart is in the fifth interspace inside the nipple line. There is a slight fulness beneath the outer half of the left infra-clavicular space, and pulsation is seen in this region; there is also slight, but not nearly such marked, sub-clavicular impulse on the right side. The carotids do not throb visibly, but on the left side above the clavicle there is fullness in the lower cervical triangle, and a distinct impulse. The position and appearance of the left clavicle are normal. It is not elevated. There is perhaps slight fulness in the first intercostal space, near the sternum; there is no special prominence of the first rib, or of the manubrium sterni.

Palpation.—The cardiac impulse at the apex has moderate force; there is no thrill. There is no impulse upon the sternum, or beneath the inner half of the left infraclavicular region. There is a very distinct impulse in the prominence above referred to in the outer half, upon the clavicle itself, and upon the sub-clavicular fulness. There is a continuous vibratory thrill communicated to the hand, which is felt over the whole
region of pulsation, and the entire left side of the root of the neck. It is not felt on the right side, nor over the sternum, nor on the precordia. There is no definite tumor to be felt either below or above the clavicle; the enlargements referred to are soft, and yield readily to pressure. High up in the axilla there is a fulness in the course of the artery. To the touch it does not give the sensation of a distinct tumor; there is a remarkable continuous thrill in this region which is obliterated here and in the subclavian region when the axillary artery is compressed. The left arm looks normal, the veins are not distended, the finger-nails are neither blue nor incurved, and the tips are not clubbed. The pulse in the left radial is not so strong as in the right; there is no perceptible retardation.

Percussion.—The cardiac dullness is normal. Percussion over the manubrium and on the inner half of the infra-clavicular region is clear; the outer half is distinctly resonant.

Auscultation.—The heart sounds are clear at apex and base. There is no special accentuation of the aortic second sound; no murmur in the right carotid, or in the right sub-clavian arteries. Over the outer half of the left infra-clavicular area, on the corresponding portion of the clavicle, over the lower cervical triangle from the sterno-mastoid border to the attachment of the trapezius there is a loud continuous bruit. This murmur is also heard with great intensity in the axilla, down the inner surface of the arm, and on the front and back of the fore-arm. It is very loud and distinct in the palm of the hand and in the finger tips. In all of these regions the murmur resembles an intense bruit de diable, or a venous hum at the root of the neck. At one point only, just below the clavicle, there is a slight systolic intensification of the murmur. Posteriorly the bruit is heard in the sub-scapular space and feebly upon the scapula. Subsequently, when the patient came under my care in Philadelphia, he was seen by Professor Ashhurst, who noticed that pressure upon the axillary artery high up in the arm-pit caused complete disappearance of the thrill and the murmur in the clavicular region. The diagnosis of arterio-venous aneurism was made.

The history of the patient is as follows: When fifteen years of age in running down a sloping grass plot he fell and forced a lead pencil, which was in his watch-pocket, into his side high up
in the axilla. When pulled out this was followed by a gush of blood, which instantly ceased. Shortly after, the arm began to swell and was subsequently black and blue to the wrist. His physician kept him in bed for two days and in the house for ten days with his arm in a sling. He does not seem after this to have had any special trouble. He has been accustomed to take a great deal of athletic exercise; rows in the summer, and has worked hard in the gymnasium during the winter months. He consulted Dr. Malloch for occasional pain in the lower portion of the chest and sleeplessness, but all this time he was keeping up his athletic sports and the condition above described was only discovered accidentally by Dr. Malloch, who stripped him to examine for the cause of the pain. He has had no serious interference with the use of the arm, but considered himself in perfect health. Since the discovery of the condition he has been somewhat nervous and uneasy and says that the pain has been aggravated.

The most careful examination of the axilla fails to discover the point at which the lead pencil entered. The patient was shown at a meeting of the College of Physicians in Philadelphia, in January, 1889, and the general opinion of the surgeons present was that, as the condition had lasted for so many years, and had not seriously interfered with the use of the arm, nothing should be done.

Unfortunately the friends of the patient became uneasy, and not satisfied with the opinions which had been given them, and he returned to the old country, and there sought advice in several quarters. In Dublin he very narrowly escaped operation, and even the day was set, but relying, as he said, on my strong statement, he, to use his own expression, escaped to London, where both Sir Joseph Lister and Sir Wm. Savory counselled non-interference, the former stating that life might not be curtailed at all by the affection, and that if at any time inconvenience arose, the artery might be tied above and below the orifice of communication.

I have heard from this patient within the last six months, and he continues well.

Arterio-venous aneurism of the axillary and sub-clavian vessels is rare. Bramann, in his exhaustive article, (Langen-
beck's Archiv. Bd. 33) was able to collect only ten cases. In several of these the condition lasted for a long time; in one five; another seven; and in a third thirty-three years. In the latter, after persisting for all this length of time without anything more than slight painful sensations in the fingers, the left arm increased in volume, became œdematous, and the veins were distended, a condition which necessitated ligation of the sub-clavian artery.

In this case the lead pencil, in all probability, perforated the artery and vein high up in the axilla, and it is evident that the opening is in the axillary artery, and not in the sub-clavian, for the thrill and pulsation above and below the clavicle disappear when this vessel is compressed high in the arm-pit. The remarkable thrill and fullness in the sub-clavian triangle and the sub-clavian space is associated probably with distension of the sub-clavian vein and its branches. An interesting point in the purring murmur was its intense transmission to the peripheral vessels, and it could be heard loudly even in the finger tips.
Caecal and peri-caecal inflammations are described under the various terms typhlitis, peri-typhlitis, para-typhlitis, peri-caecal abscess, and appendicitis. I think we may clinically, and for practical purposes, distinguish two groups of cases, to the first of which the name typhlitis may be restricted, and to the second appendicitis, or, perhaps, better, as Dr. Fitz suggests, perforative appendicitis.

Typhlitis.—By this we understand inflammation of the caecum. The term has also been used to designate inflammation of the contiguous parts as well; but it may be limited to the cases in which the caput caeci and the adjacent portion of the ascending colon are involved. Unfortunately, we know nothing of the anatomical condition described under this term. I have myself never seen a post-mortem, nor do I know of a report in which the disease was confined strictly to the walls of the intestine in these regions.

The cases are commonly met with in young persons, particularly in young males. The attacks are very often associated with errors in diet. In the majority of cases there is a history of constipation. The symptoms are very distinctive. The patient complains of pain in the right iliac fossa; there is constipation and often nausea—sometimes vomiting. At first there may be no fever, but subsequently the temperature rises from 100° to 102°. On examination, the patient is usually found with the right thigh flexed on the abdomen. There is slight fullness in the right iliac fossa; tenderness on pressure, and, often, dullness on percussion. In the majority of instances there is distinct induration, which may have a rounded outline, so that the expression “sausage-shaped tumor” has been applied to the condition. Such cases are extremely common, and are usually regarded (no doubt properly) as the result of faecal impaction—typhlitis stercoralis. With proper

treatment, recovery is the rule. Local applications—the ice-bag, turpentine stupes—are usually found sufficient to allay pain. To break up the fecal masses, large injections should be used. Purgatives may be administered, but I prefer, as a rule, to rely on large injections.

Attacks of this kind may repeatedly occur in the same patient; I have known of four or five recurrences within four years. There can be very little doubt that this local inflammation is due to faecal impaction. The inflammation is confined to the intestinal wall, and rarely extends to the tissues in the neighborhood. It is true, that occasionally there may be more serious disease of the caecal coats. I have put on record two instances of round ulcer of the caecum, in both of which perforation occurred, with the production of peri-caecal abscess. It is quite possible, of course, that inflammation may extend to the loose connective tissue behind the caecum—when that organ is attached—and even go on to suppuration. But, with the exception of the cases of ulceration, I have no personal knowledge of instances in which there has been peri-caecal abscess apart from disease of the appendix.

The opinion has been expressed, and is I believe widely held, that the cases such as I have here described are also in reality due to appendix disease; that typhlitis and peri-typhlitis mean in all cases tubal affection. I confess there is often great doubt as to the true nature of a case, but, clinically, I believe we can recognize a sterical typhlitis. There is at present in my wards at the Philadelphia Hospital a case in illustration. Lad, aged 22, admitted 22nd, with temperature of 102°, a furred tongue, constipation and abdominal pain. On examination, there was tenderness in the right iliac fossa, the thigh was drawn up and everted; the right iliac region was dull, tender to the touch, and presented a distinct induration, without definite outlines. He had nausea and vomiting on admission. Stupes and poultices were applied,
and large enemata were given; no opium, as the pain was not excessive. The injections brought away a number of hard fecal masses. The temperature on the third day was normal, the induration and tenderness gradually disappeared, and on the sixth day the sense of resistance in the two sides was equal, and the patient said that he felt quite well. He had had a similar attack six weeks before. Such cases we have all seen, and whatever the morbid condition may be, I think they possess features which separate them from the next group.

Appendicitis.—In the second group of cases the lesion proceeds from the appendix vermiformis, which is liable to various affections—catarrhal inflammation, catarrhal ulceration, obliteration, obliteration of the proximal end, dilatation of the tube, and perforation. Foreign bodies may also lodge in it, and feces moulded to the tube may become hardened and calcified so as to form small enteroliths.

In a recent report (Med. and Surg. Rep., Oct. 6th, 1888) I gave notes of eleven cases in which I had met with ulcers in the appendix, usually in connection with phthisis or typhoid fever. I have never met with foreign bodies in the appendix. On one occasion five apple pips were brought to me as having been found in, and removed from the tube, in a dissecting-room subject; and in one of the cases in the post-mortem books of the Montreal General Hospital, Dr. Sutherland (who was acting as Pathologist in my absence) records the presence of six or eight snipe shot in the appendix of a man dead from Bright’s disease. The resemblance of the small enteroliths to date-stones, frequently leads to error.

Inflammation and ulceration of the appendix vermiformis (so long as it is confined to this tube) may produce no definite symptoms. There may be the most extensive ulceration, the lumen may be completely obliterated, there may be extreme distention, without the patient manifesting any signs of abdominal disorder.

If the appendix is quite free, it is possible that ulceration may go on to perforation, without the tube forming attachments. This, however, is very exceptional. More commonly adhesions form and the perforation leads to localized abscess, the situation of which will depend upon the position of this extremely variable structure. It is most commonly situated in the right iliac fossa, and is either within the peritoneum, when the appendix is entirely surrounded by this membrane, or it is behind the peritoneum, when the appendix (which is rarely the case) has only a partial serous covering. I have seen perforation occur with the formation of localized abscess, within the pelvis in the neighborhood of the broad ligament; in another instance immediately upon the sacrum, the tip of the appendix lying to the left of the middle line; and, in a third instance, the abscess was high up behind the mesentery upon the psoas muscle.

I do not think that sufficient stress has been laid upon the fact, that this local inflammatory process almost invariably precedes the graver manifestations. That healing may take place at this stage, is shown by the occurrence of an obliterated tube closely adherent with fibroid thickening and much pigmentation of the surrounding tissue. Once perforation has occurred with abscess formation, the course is extremely variable. It is within the experience of almost every physician to have seen the pus appear anteriorly in the neighborhood of the groin, where it may open spontaneously. The presence of gas, or even small fragments of feces, may show that there is open communication with the bowel. Two such cases I saw with my preceptor, Dr. Holford Walker, of Dundas, in 1868 and 1869. One of these cases made a good recovery; the other, with much more extensive abscess formation and perforation in several places (through which gas discharged), succumbed to septic fever. That the tube of the appendix is not always obliterated at its cæcal end before perforation occurs, as is claimed by some writers, is shown by such cases. The pus may burrow and appear in the lumbar region, or it may pass down and appear in the peritoneum and form a peri-rectal abscess. A more favorable event is, when the abscess perforates into a neighboring viscus—the colon, the cæcum, the rectum or the bladder. In a recent report of a case in a French Journal, in which the abscess perforated into the bowel, the characteristic oval enterolith was found with the discharged pus and feces. Perforation into the bladder is less common. At the Montreal General Hospital, in the Summer session of 1882, I lectured upon two cases in which this event occurred with
recovery. I met with a curious sequel in a case of peri-cecal abscess which perforated into the bowels. The patient had for some years after, and may still have for aught I know, persistent enlargement of the right leg, due, undoubtedly, to chronic venous stasis consequent upon the narrowing of, or perhaps the obliteration, of some of the large veins in the pelvis. A third and almost necessarily fatal mode of termination, is when the local circumscripted abscess perforates the peritoneum, setting up a diffuse; virulent and septic inflammation.

I have never yet seen instances of perforative appendicitis in which there were not attempts made to limit the inflammation. Even when the appendix has been free in the peritoneum, walls circumscribing the abscess are formed by the adherent mesentery, retro-peritoneum and intestinal wall. Symptoms of perforative appendicitis are fairly well defined. A number of cases begin with intestinal trouble, constipation or pain in the ilio-cecal region, lasting for a variable time. A more characteristic mode of onset is a sudden, sharp pain in the right iliac fossa. This may be followed by collapse symptoms, or more usually by an aggravation of the intestinal disturbance. It is worth noting, that strain, such as sudden lifting or jumping, may be followed by an acute pain, and may, apparently, be the starting-point of appendicitis. The local symptoms are rarely as well marked as in typhilitis. Tenderness is usually present; there may be fullness, or even induration, but in my experience, these signs are more frequently absent. The leg is usually drawn up, thereby relaxing the psoas muscle. Irritability of the bladder, as shown by frequent micturition, not infrequently occurs. The fever is moderate; the tongue is furred, but constipation is not so constant a feature as in stercoral typhilitis. Abdominal distention (typanites) comes on early, and may interfere with proper examination. A rectal examination may indicate fullness towards the roof of the pelvis, but unless the whole hand is used, the ordinary digital exploration is practically worthless. Practice on the cadaver, with the pelvis exposed, shows how futile is the attempt to reach, even with the longest finger, those higher portions of the pelvis which the peri-cecal inflammation usually affects. Increasing typanites,

diffuse tenderness on palpation, aggravated constitutional symptoms, indicate the spread of the peritonitis. It must not be forgotten that the peritonitis may be limited to the lower portion of the abdomen, even confined to the coils of the small intestines situated within the pelvis. Such abdominal distention may be extremely slight. I saw, with Dr. Musser, last year, a case of perforation of the appendix with peritonitis, in which the abdominal walls were flat and presented a hard, board-like resistance to palpation.

In a considerable majority of cases, I think the sudden onset with sharp intense pain, indicates, not the perforation of the appendix, but the extension of an already existing inflammatory process. As I have stated, extensive ulceration, distention, adhesion and obliteration of the tube, may occur in persons in whose history there is no account of localized abdominal inflammation. It is not impossible that ulceration, leading to perforation and local abscess, may occur without exciting severe symptoms. I have so often seen, about the perforated appendix, signs of chronic inflammatory mischief indicated by fibrous bands and pigmentation, that the process has certainly ante-dated the onset of the acute fatal illness of only a few days duration. Marked tendency to recurrence finds also its explanation here, in the temporary aggravation of the condition. Surgeons have repeatedly, in these cases of recurring attacks in the peri-cecal region, cut down and removed an adherent, chronically inflamed and even perforated appendix.

In many instances the diagnosis of perforated appendix presents great difficulties. Perhaps, of all the symptoms, the most important is the sudden agonizing pain occurring either at first, or after gastro-intestinal symptoms have lasted for some days. Its importance may be gathered from the fact, that of 257 cases analyzed by Fitz, it was present in 216. Abdominal pain and distention are more marked, and occur earlier than in ordinary typhilitis. Induration in the iliac fossa is also less common; indeed, a very considerable proportion of the cases present no local tumor. The diagnosis in such cases rests largely upon the mode of onset, the development of symptoms, the previous history of the patient, the absence of signs of hernia or of internal strangulation. The occurrence of frequent micturition and the characteristic
decubitus of the patient, are highly suggestive symptoms. Cases occur in which it seems impossible to accurately determine the condition, and the patient presents the picture of general peritonitis, which has started from some unknown locality.

Treatment of peri-cæcal abscess from appendix disease has made great progress within the past few years, and the operation devised by Willard Parker has now become, not only a very frequent, but a most successful one. As I have already stated, there are many instances of spontaneous recovery, even when extensive suppuration has occurred. We all have seen, in the recurring attacks of this disease, the gravest symptoms disappear and the patient rapidly convalesce. The medical treatment is much the same as I have spoken of in typhlitis. Opium, in some form, has almost always to be used to relieve pain. For constipation, large injections may be employed. In the early stage I never use purgatives. I would hesitate to employ even a saline cathartic, which moves the bowels with very little disturbance of the peristalsis. Not that I would hesitate when general peritonitis is established, as I believe this method of treatment to be in a high degree rational. A concentrated saline purge produces local depletion of the intestinal vessels from duodenum to cæcum, and removes in great part the interstitial oedema of the intestinal wall upon which, chiefly, the paralysis depends. But, in the early stages of the affection, our means should be directed towards limiting the inflammatory process, and favoring those conservative barriers which nature invariably sets up against extending inflammation. I have been so much impressed with the fact, that in these cases the dangerous symptoms seem to originate by the extension of the disease from a localized peri-cæcal abscess—the walls of which may be in part mesenteric, or, as I have seen, intestinal—that I dread the disturbing influence of purges. The indications for surgical interference are not always clear; but my experience has taught me that the abdomen is much more frequently left untouched than it should be, and that an operation is too often deferred until practically useless. Local indications may be very positive, particularly when the perforated appendix lies behind the peritoneum, in the iliac fossa spine above Poupart’s ligament. But when the abscess is high on the psoas muscle, or lies within the brim of the pelvis, or far over towards the middle line, these symptoms are absent, and in such cases, from the general condition alone, the indications for operation must be gathered. We may say, as a general rule, that in young persons, in whom the attack has set in with severe pain in the right iliac fossa (whether preceded or not by previous digestive disturbance), and in whom the constitutional symptoms, as shown by rapid pulse, fever and coated tongue, indicate a serious lesion—when tympanites and abdominal tenderness exist, it is better in these days of safe laparotomy to give the patient the benefit of any diagnostic doubt, even without the existence of local tumor, and to explore thoroughly the peri-cæcal region. Still more urgent would such indications be, if the patient had had previous, though less severe attacks.