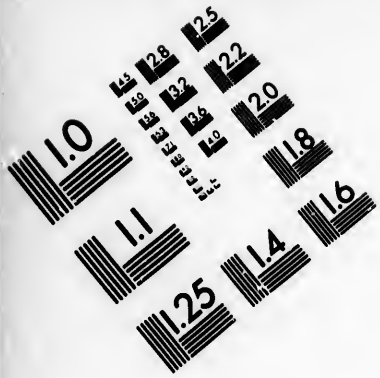

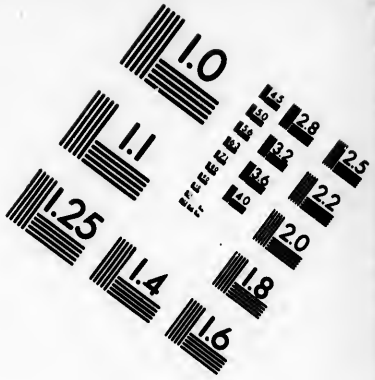

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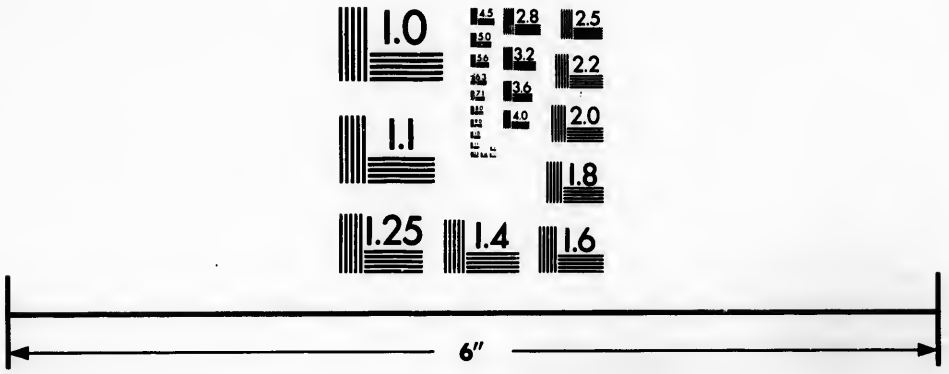

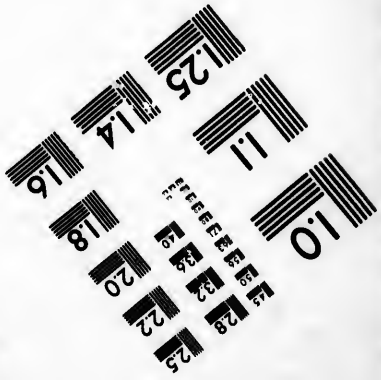

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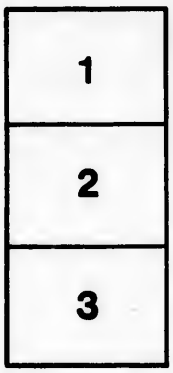

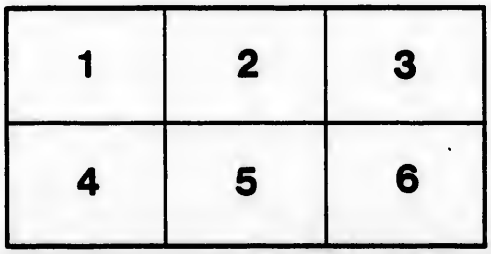

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On Latent Infection and Subinfection, and on the Etiology of Hemochromatosis and Pernicious Anemia

* * *

J. GEORGE ADAMI, M.A., M.D., F.R.S.E.
Montreal, Canada

ON LATENT INFECTION AND SUBINFECTION, AND ON THE ETIOLOGY OF HEMOCHROMATOSIS AND PERNICIOUS ANEMIA.*

BY J. GEORGE ADAMI, M. A., M. D., F. R. S. E.
PROFESSOR OF PATHOLOGY, M'GILL UNIVERSITY.
MONTREAL, CANADA.

I can remember, as well as though it were yesterday, sitting in the large bacteriologic laboratory at the Institut Pasteur, close upon ten years ago, and hearing Roux, that clearest of lecturers, recount step by step the fascinating story of the discovery of the anthrax bacillus and the elucidation of the etiology of splenic fever—the history, in short, of the establishment of bacteriology as a science directly bearing on disease. More especially there remains vividly impressed upon me the almost paradoxic point which Roux then made, that mistaken facts and incomplete observations accepted as facts may be of temporary benefit and may aid advance. As Roux pointed out, the most clinching argument brought forward by Davaine, in favor of regarding the anthrax bacillus as the active agent in infection, was that if a pregnant sheep or cow died of the disease, the maternal blood, which contained abundant bacilli, was capable of causing the disease in other animals, whereas the blood of the fetus, which he found free from germs, was absolutely harmless, even when inoculated in large quantities. We now know that the fetal blood in infectious diseases is not necessarily free from the germs of those diseases; the fetus may suffer from the same infection as the parent. Davaine himself, and those attempting to repeat his observations, might have obtained different

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results; nevertheless, in the then state of bacteriologic science, no surer demonstration of the pathogenetic power of the bacilli could well have been adduced. So also at a later date, when pure cultures of the germ had been gained, the observation made by Pasteur—and the French Commission, of which Roux was a member—that if a broth culture be made of the anthrax bacilli and then the bacilli be filtered off and the clear filtrate alone be inoculated into animals, no results accrue, whereas a minute mass of the residual bacilli surely when inoculated leads to fatal disease in susceptible animals, afforded a singularly powerful demonstration that infection is directly due to the presence of bacilli. As you know, further researches have shown that in connection with very many infectious diseases the fluid of growth contains abundant toxins and, when inoculated, is able to set up the symptoms of disease, and, indeed, had Pasteur employed larger quantities of the filtrate of an old culture of the anthrax bacilli, fatal symptoms might have developed, reproducing to some extent those seen in the natural disease. Fortunately the fluid of growth in connection with anthrax contains but a relatively small proportion of such toxic substances. Without two such *apparently convincing* demonstrations as those above mentioned, it is doubtful whether the world would have become prepared to accept so radical an idea as that bacteria are the essential agents in infection.

In studying and recalling the history of modern medicine, or more especially of bacteriology, not a few other examples of a like nature come to mind. Thus, for instance, very shortly after the discovery of the typhoid bacillus, it was pointed out by numerous observers that these bacilli were present in the stools in enormous numbers and forthwith, in order to prevent the contamination of the water-supply, there came into almost universal employment the method of disinfecting the stools so as to prevent the extension of the disease. We now know that these earlier observations on the stools were incorrect: that what were found in them were the then undifferentiated colon bacilli. For later observations have shown how difficult it is to detect typhoid bacilli in the

feces and how rare it is to discover them after the first fortnight of the disease. But these later observations have also shown that for a period at least they do escape into the feces. Here again, therefore, mistaken observations led to advance, for it is needless to state that, for the health of the public, nothing can be better than the sedulous disinfection of typhoid excreta.

I do not mean, in quoting these cases, to suggest that imperfect observations and premature deductions are commendable. I do but wish to point out that advance in our profession not infrequently follows imperfect knowledge, and that the imperfect knowledge of a great man and a conscientious worker is oftentimes directly productive of good results. We should always keep in mind, as old Sir James Paget indicates in the introduction to his son's "Life of John Hunter"—indicates, though he does not absolutely state it—that facts are not of necessity truths; while true in themselves, they do not reveal the perfect truth; that our science is based on half truths; that however sure we are at a given moment of the facts on which we base our conclusions and determine our treatment, later and fuller studies may well show that those facts are not the whole facts, those truths not the whole truths, and that, just as we, benefiting from the facts accumulated by our predecessors and adding materially thereto, have widely modified the conclusions formed by them and the treatment which they employed, so later generations with fuller knowledge will surely arrive at theories and treatment widely different from ours. "Experience is fallacious and judgment difficult;" we must be prepared as experience grows, to modify our judgment.

Of the generally accepted and basal postulates on which not only is bacteriology founded, but also on which our appreciation and treatment of infection and infectious conditions has been developed, it may safely be said that the foremost, that which has been the fundamental in the application of bacteriologic knowledge to surgery and medicine, has been that in health the organism is free from bacteria, that the tissues are sterile and that infection is due to an abnormal entrance of pathogenetic

bacteria into the body. It is on this assumption that antiseptic and aseptic surgery have their basis, and from it we start in order to explain infection. We assume that the skin and the mucous surfaces of the body form a natural barrier beyond which, under normal conditions, bacteria do not pass; that the presence of bacteria in the deeper tissues is the exception and not the rule. We are forced to acknowledge that, occasionally, bacteria gain an entrance without there being a recognizable external lesion, and we speak of disease developing under these conditions as *cryptogenic*—this very term indicating an ignorance as to the exact mode of origin of such disease. Yet the generally received opinion is, as I say, that the presence of bacteria, pathogenetic or otherwise, in the blood, the lymph and the tissues generally, is the exception and not the rule. To the physician, as indeed to the bacteriologist in general, the primary factor in infection is the virulence of bacteria. The protective powers of the tissues, while they may be important, are a secondary factor; the former we can measure with fair accuracy; we have no means whereby to determine the latter with any precision. Having this view, we find it difficult to comprehend phenomena such as phagocytosis, which we are forced to admit come into play in infectious conditions. We see that the leucocytes and endothelial cells take up and destroy pathogenetic bacteria, but find it difficult to understand how these cells can assume functions which apparently are so totally new to them. Indeed, this difficulty in comprehending the assumption of phagocytic properties by the cells of the body has been, I firmly believe, the great obstruction to the ready or general acceptance of phagocytosis as a factor in the arrest of disease.

It would be absurd to deny that this postulate—that the tissues normally are sterile—has been most valuable. Without it and the theory derived from it modern medicine—I use the term in its broadest sense—would not and could not be in its present position; for working conditions it has been essential. If not true it must be somewhere near the truth, otherwise facts and observations would not confirm in so great a measure thereunto.

But is it the whole truth? Does everything prove that normally the tissues are free from bacteria? Are there conditions only explicable by assuming that bacteria habitually or frequently enter the circulation? If we find that there are, it is of no use to fall back on that weak retort, that the exception proves the rule—a retort weak as in general misconstrued and misapplied. The exceptions prove the rule only in a mathematical sense of testing it. In this sense the exceptions assuredly do prove the rule and this evening I wish to test whether certain facts at our disposal confirm this theory and to determine whether possibly a modification of the postulate is not necessary.

If it does happen that bacteria enter the circulation under ordinary conditions, all will agree that the more frequent regions of entrance are likely to be found, not so much in connection with the denser epithelial surface layers of the body, as in connection with the more delicate mucosæ of the respiratory and alimentary tracts. And it is to the latter of these that I shall more especially confine my attention. In connection with this alimentary tract we have very definite evidence that here bacteria may penetrate the protective barrier of epithelial cells, nay more, that they are constantly being taken into the system.

So long ago as 1882 Schäfer[1] pointed out the possibility that leucocytes played some part in carrying fat from the intestines into the interior of the villi, and the following year Zawarykin[2] laid down that fatty globules only gained their entrance into the lymphatics through this intermediation of the leucocytes. My old master, Heidenhain,[3] while doubting whether the globules which Zawarykin saw in the leucocytes between the epithelial cells were truly fat, could not but agree that leucocytes were to be seen frequently and in considerable numbers between the cells. More recently, A. B. Macallum of Toronto,[4] in studying the absorption of iron by the economy, has published certain very interesting observations. Taking, for example, the lake lizard—*Necturus lateralis*—which had been kept for thirty months without food, and killing such animals eight hours after feeding them

with material containing albuminate of iron, he found that on removing and hardening the intestine intact, then cutting sections and treating them for iron, there, actually within the lumen of the intestine, were numerous free leucocytes crowded with granules of iron pigment; others, free from iron, appeared to be passing out between the epithelial cells, others filled with it, were in the same position, while still others were subepithelial. In higher animals he found that after giving iron, the tips of the villi between the epithelial cells showed the same iron-containing leucocytes and, further, they were present in the venules of the villi; and very shortly after feeding animals in this way, either with peptonate or albuminate of iron, many of the leucocytes in the capillaries of the liver and the spleen were found loaded with it. There can be no doubt then, that under certain conditions leucocytes are constantly passing out on to the free surface of the digestive tract and passing back, and such leucocytes, taking up various food stuffs, are able also to take up bacteria. The researches of Ruffer[5] fully prove this. He took the small intestine of healthy rabbits immediately after death, hardened it in absolute alcohol and cutting sections stained them for bacteria. He found leucocytes present on the free surface, others between the epithelial cells of the mucosa, some of which contained microbes, while, in Peyer's patches, the interior of the individual lymph follicles contained enormous numbers of micro-organisms which, according to him, are without exception in the interior of the lymphoid cells of the tissue. In the rabbit's tonsil he found an identical condition of affairs and, according to his studies, the polymorphonuclear leucocytes wandering on to the surface and there taking up fatty and other particles and occasionally bacteria, pass back again into the lymph glandular areas and are there taken up by certain larger cells—the macrophages of Metchnikoff—cells which, according to Mallory, are of endothelial origin. Here, in these larger cells, they and the contained bacteria undergo digestion. A similar state of things has been recently shown to occur in connection with the lungs, in the peribronchial glands.

Thus, then, under certain conditions bacteria pass into the lymphoid glandular tissue of the pharynx, as of the small intestine, and there tend to be destroyed, and these lymph glands of the subepithelial and submucous areas of the alimentary and respiratory system may be regarded as a second line of defense of the organism against bacterial invasion. But these facts show that at least one tissue is not normally sterile, it is, if you like so to regard it, *potentially sterile; the tendency is for entering bacteria to be rapidly destroyed.* But we can realize conditions under which such destruction is not complete—when, for example, the passage out and the migration and subsequent return of the leucocytes is excessive, or when again the cells of the body are weakened and can not with sufficient rapidity destroy the bacteria, or when again bacteria themselves, happening to be in the intestine, are of peculiar virulence.

We can, however, go beyond the submucous glands. My senior demonstrator, Dr. A. G. Nicholls, has recently made some very interesting observations, which can easily be repeated and confirmed. Killing healthy rabbits, he has immediately stretched the mesentery of the small intestine, rubbed this on either side with a sterile swab, so as to remove the covering endothelium and then stretching the mesentery over a glass slide, has hardened it in formalin and removed it without cutting the intestine, so as to prevent any bacteria contaminating the surface from the intestinal contents. After hardening in this way he has strained with carbol-thionin. A full account of these experiments will be published later; here I need only say that in rabbits which are apparently in perfect health, the mesentery so prepared shows relatively abundant bacteria in various stages of disintegration. Some are in the lymph channels, and it may be in the blood-vessels; others are apparently free in the lymph spaces and others again are in the immediate neighborhood of nuclei which would seem to be those of wandering cells. Nor, as Bizzozero[6] and Ribbert[7] have pointed out, are bacteria absent in the healthy mesenteric gland, and my own observations confirm these statements. Sections of healthy mesenteric glands of man show, in gen-

eral, definite bacteria undergoing degeneration, and occasionally the number is remarkable. Neisser,[8] it is true, found the mesenteric glands of large animals sterile, but, as I shall have occasion later on to point out, his methods of obtaining cultures can not be considered free from objection; nor, indeed, does the fact that he was unable to gain cultures disprove or tell against the fact that sections of these mesenteric glands show the evident presence of bacteria. Here, as in the submucous glands, the tendency is for those bacteria to show marked signs of degeneration. The function of the gland tissue, in fact, is to destroy these bacteria, but that they are continually passing into the gland there can be no doubt.

My own experiments carry this subject one very considerable step further. It has been abundantly noted by a large number of observers—by Borel,[9] for example, in connection with the tubercle bacillus, and by Werigo[10] in connection with the anthrax bacillus—that within a very few minutes after intravenous inoculation of the bacteria, these are to be found already within the endothelial cells of various organs of the body. Werigo has clearly shown, and Lemaire[11] has confirmed, that the hepatic endothelium is especially active in this matter and that the endothelial cells can be seen to give out fine prolongations to which the bacilli become adherent, and later as the processes contract they become actually intracellular.

In my own studies on the colon bacillus, or more correctly on certain members of the group of colon bacilli, I have been able to carry these observations beyond this point. Under certain conditions of modified growth these colon bacilli present themselves as bipolar organisms. In the stumpy bacterial forms the coloring matter appears to collect itself or to contract into two rounded masses, and in this condition the bacillus looks curiously like a diplococcus with a clear space around it resembling a capsule, which is, however, the colorless body substance of the organism. In the longer forms there may be three or four or more of these little masses, while, occasionally, instead of the two polar bodies, there is only a single rather ovoid mass.

In our studies[12] on intravenous inoculation of definitely long bacillary forms of the colon bacillus, it was interesting to observe that even in a quarter of an hour, many of these had been taken up by the endothelial cells of the liver, and now the longer rods evidently tended to break up into short pieces, and in several cases all that could be seen of them were these small diplococci still staining strongly, but absolutely unlike the original ba-

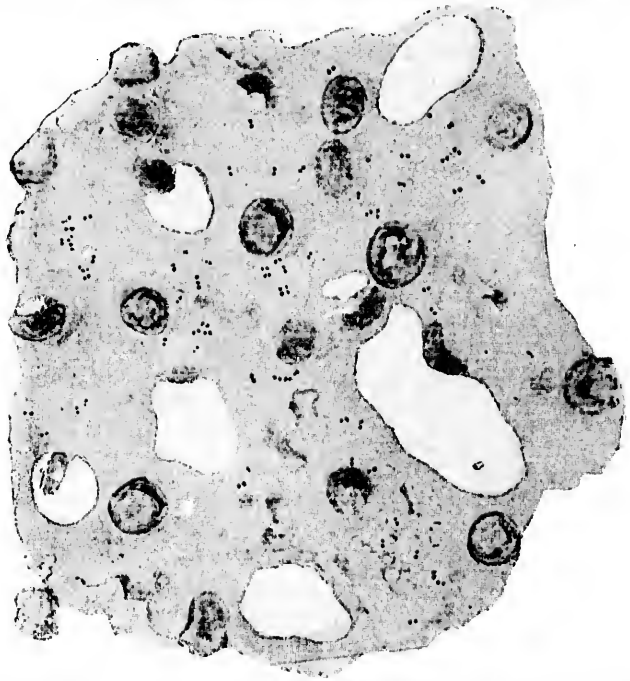

Fig. 1.—From section of liver, stained by carbol thionin, of rabbit dying 16 hours after intravenous inoculation of 0.5 c.cm. of a 48 hour broth culture of a bacillus (B. coli) gained from spleen of case of progressive portal cirrhosis. Drawing made by Zeiss camera lucida, 1/12 in. immersion lens (Winkel), Oc. 4. Sections from liver of rabbit inoculated intravenously with like dose of B. coli from ordinary feces showed identical appearance.

cillary form which had been inoculated. At a still later period—in from two to four hours—we observed that in the liver cells there appeared an increased number of minute slightly brownish diplococcoid forms, and these increased in numbers so that in rabbits killed twenty-

four hours after inoculation, they might be present in very great quantities while at this period not a single bacillus or diplococcoid form was recognizable in the endothelium. Dr. A. G. Nicholls and I were able similarly to recognize an almost identical process occurring in the cells of the tubules of the kidney, more especially in the convoluted ones, though here the brown staining of the coccoid forms was not so marked.

The difficulty in following and recognizing these little bodies is very great; they very soon lose their staining power, but in the liver cell they assume a brownish tinge and thus, if thin sections be taken and treated with weak acetic acid so as to dissolve away much of the protoplasm of the cells and to clear these, the little bodies can be seen without any special staining. They vary considerably in their size, and it would seem that they are in various stages of destruction and dissolution, so that they are apt not to stand out clearly, and unless one studies them carefully and focuses with extreme precision, they appear to be merely small and irregular masses of pigment. But if studied with more care we can recognize a series of forms from those more especially at the outer edge of the cell, which may still take on a faint stain with carbolthionin and which are of the same size as those observed in the endothelial cells, through still smaller ones only possessing a brown color, until the smallest are only just visible as two minute dots lying in a clear space and recognizable only with the 1/18 inch immersion-lens. Nay more, we at times come across little, clear, vacuolar spaces of an oval shape, with no solid contents, but in size and shape resembling the clear spaces around the minute dots. Even now, although I have been looking at these for many months, it often takes me some minutes before I can resolve the bodies, these pigment granules, into their component parts, for I may add that where they are crowded together and where the section is at all thick, it is practically impossible to recognize their nature. Places have to be selected out where they are more scattered, and then their remarkable double nature and the surrounding fine halo are recognizable. These little bodies vary in size, it is true, but were they indiscrimi-

nate pigment granules or particles we would not find as we do that in the pairs the two members should be so remarkably equal; were we dealing with agglomerated independent granules of varying size, it is a mathematical certainty that the particles would not group themselves together in pairs formed of equal parts. This in itself, I can not but take it, is an added proof that we must be dealing with the remains of micro-organisms.

Cohnheim[13] long ago suggested that in the event of bacterial invasion the body protects itself by excreting the living germs through the kidneys and through the liver. But numerous observations, among which must be especially mentioned those of Wyssokowitsch, have thrown very considerable doubt on this theory. Wyssokowitsch,[14] in the course of a very long series of observations carried on with twelve species of bacteria chosen as not causing local lesions in the kidney, was unable in a single instance to gain cultures of the bacteria from the urine, whereas in thirteen out of seventeen experiments, employing species known to be liable to cause local lesions in the kidneys, bacteria passed in smaller or greater numbers into the urine. Sherrington,[15] who gives a very full study of this subject of the escape of bacteria with the secretions, finds that even when every drop of the circulating blood is teeming with organisms there may not be the slightest transit of them into the urine or the bile; nevertheless, when certain pathogenetic species are employed, a considerable number, often very considerable, of the injected bacteria, tend after a time to appear in the secretions of the kidney and the liver, and the escape in the excreta is sometimes accompanied by escape of actual blood. He points out, on the other hand, that sometimes the bacteria are present in the excreta without any detectable presence of blood in the same. He, however, with Wyssokowitsch, concludes that, when this transit occurs, the evidence is against believing that the parts are still normal, although rupture may not have occurred.

It is, however, but right to point out that both older and more recent observers have arrived at different conclusions. Among these may be mentioned: Trambusti and Maffucci,[16] who, in guinea-pigs and rabbits, after

injecting the anthrax bacillus, found it both in the bile and urine; Cotton,[17] who found the pyococcus aureus as also the bacillus prodigiosus in the bile thirty minutes after inoculation, and the bacillus pneumoniæ after 4¼ hours; Pernice and Scagliosi,[18] who, after inoculating anthrax into guinea-pigs hypodermically, found the bacilli in the bile in four hours, the bacillus pyocyaneus and the bacillus subtilis in six hours, while in connection with the kidney Posner and Lewin,[19] after injecting the bacillus prodigiosus into the intestines, obtained it both from the kidney substance and from the urine. Biedel and Kraus,[20] after injecting animals with pyococcus aureus, the bacillus coli and the anthrax bacillus, found these in the urine, which was free from albumin and blood, a few minutes after injection. These last observers also made a series of examinations on the secretion through the liver, and introduced a method of placing a canula into the common duct before inoculating the animal, so as to gain the bile which is in the process of being discharged, from the canula, instead of making cultures from the gall-bladder. By this method they gained from the bile the pyococcus aureus which had been inoculated intravenously, in one experiment in thirteen minutes, in another in twenty, and in another in thirty-five.

But some of the most valuable observations on this subject have been made a Chicago worker, Dr. Fütterer.[21] He was able to gain the bacillus prodigiosus from the pelvis of the kidney two minutes after injection into the jugular vein of the dog, while, inoculating animals with the pyococcus aureus and the bacillus prodigiosus and following Biedel and Kraus, he obtained bile from a canula inserted into the common duct and gained abundant cultures of these micro-organisms within two or three minutes after inoculation into the left side of the heart.

Clearly, from the above observations certain bacteria, at least, are actively excreted, as Cohnheim suggested, through the liver and through the bile. In my own experiments after inoculating the bacillus coli, I have at times found only the minute and apparently dead diplo-

coccoid forms in the bile, and the very appearance of these indicates that they have been acted on during their transit through the liver. That appearance is, I take it, an indication of definite secretory activity on the part of the hepatic endothelium and the hepatic parenchyma. But in addition I have found in other cases attenuated, as again well-developed and thoroughly vigorous, colon bacilli in the bile within a few hours after inoculation of a large quantity of these micro-organisms into the peritoneal cavity or into the blood. Sections of the livers of such animals show the changes in the endothelium, as also in the liver cells, already described. Thus I am led to conclude that where the number is not too great, the liver tissue is capable of wholly destroying and digesting the bacteria. Where, however, this function of the liver cells becomes exhausted by the taking up of excessive numbers of the bacteria, then it is possible for the bacteria to be discharged or secreted into the bile in a still living state.

These observations appear to me to clearly demonstrate that while *one of the functions of the lymphatic glands is to take up and destroy bacteria circulating in the lymph, a function of the liver, both as regards its endothelium and its cells, is to take up and destroy such bacteria as are introduced by leucocytes into the venules of the portal system and gain entrance into the portal blood, while similarly a function of the kidney parenchyma, more especially of the convoluted tubules, is to remove bacteria circulating in the systemic circulation.* I have not as yet been able, for lack of time, to fully study the other glandular and excretory organs of the body. I have, however, made individual observations tending to prove to me that other glands possessing excretory ducts, the pancreas and the mammary glands for example, have identical functions. However, I would as yet make no absolute statement concerning these organs.

But if, experimentally, we can thus demonstrate this remarkable power possessed by the liver and kidney cells, is it likely that these properties are normally in a state of rest and that it is the exception, not the rule, for bacteria to be taken up and destroyed by these cells? As a

matter of fact, I have accumulated abundant evidence that this is not the case. In the liver cells of normal animals, of man and the rabbit for instance, these little brownish diplococcoid bodies are normally present. *They form, indeed, the finely granular pigmented material so frequently met with,* and the reason why this has not been recognized earlier is that the pigment has not been examined with sufficient care and with sufficiently high power. I was much interested, for example, to observe in one or two of Dr. Fütterer's photographs,[22] the appearance of these minute diplococcoid bodies, an appearance, I may add, wholly different from the coarser clumps of inspissated bile lying in the first intra and extracellular bile capillaries of the organ. Upon examining a series of sections of forty livers taken in order from as many different autopsies at the Royal Victoria Hospital, I found bodies present in all but three. Out of these forty sections, which were simply labeled with the number of the autopsy, I selected five in which, without there being any sign of cirrhosis or severe disturbance of the organ, these little brown diplococcoids were present in relatively enormous numbers. On studying the autopsy book to see from what cases these came I was greatly impressed by the fact that in every one of these, without exception, there was a history of extensive abdominal inflammation. From such studies we are bound to conclude that normally a certain number of bacteria find their passage into the portal circulation, and, whether already destroyed by leucocytes or still living when taken up by the endothelial cells, they are arrested from entering the general circulation by this agency of the liver, and further, that inflammation of the intestines materially favors this passage.

But now, as against the conclusions above deduced, we have, I must freely confess, numerous careful studies by trustworthy observers, which would appear to establish a view diametrically opposed. Observer after observer has found the blood free from bacteria, even when there is acute infectious disease, nay more, even when, as in typhoid fever, there is an acute inflammation of the intestine. Observer after observer has

found the normal tissues, liver, kidney, spleen, and so on, absolutely free from bacteria. Is the conclusion which I have reached founded throughout on erroneous observations; is it possible that the negative results of so many good workers are due to imperfect technic; or lastly, is there a *via media,* and can we discover facts which are capable of reconciling the two opposed series of observations?

ON THE PRESENCE OF BACTERIA IN THE BLOOD.

Let me first consider the case of the blood. Long years ago Lord Lister drew attention to the sterility of the blood, but it was he who, later, made, as I shall shortly point out, the first observations on the cause of this sterility. With that unfortunate aptitude which French and German observers have shown to neglect English and American work, the fact has in general been passed over that Lister made the first careful studies on the bactericidal function of the blood outside the body, and, though we owe the first full studies on the subject to an American, Dr. Nuttall, he, working in a German laboratory, did not there have his attention called to Lister's earlier paper on the subject. From Lister onward it has been the custom to regard normal blood as of necessity absolutely sterile. In 1895, however, Nocard[23] called attention to certain facts showing that this view was not wholly correct. For years Nocard had collected his blood serum aseptically without the employment of heat; in some cases he found that the serum so collected did not "keep" and, looking over these cases, he found that these sera had invariably been collected in the afternoon, after a meal; and so he made a series of observations in which he determined that the serum of fasting animals is nearly always sterile as again, to a less extent, is their chyle; after feeding he discovered that microbes were present in the chyle in considerable numbers, being less where lean food had been taken, while after a meal of fatty foods they formed innumerable colonies. The assumption here is that where fat is taken up into the system from the intestines, along with it, by the same route, bacteria gain an entrance. These observations of Nocard

were shortly after confirmed by Porchard and Desoubry[24], who also found that during digestion the chyle of dogs is very rich in microbes, and that these are already less numerous in the heart blood, particularly in that of the left side, as that in the jugular vein they are less numerous than in the carotid artery—an indication that along the course of the circulation the microbes are arrested.

Allied to these results may be mentioned those of Posner and Lewin,[25] who, having tied the rectum in the rabbit, without, however, causing any gross lesion of the mucous membrane, found that within eighteen to twenty-four hours the whole organism, including the heart blood, became infected with intestinal bacteria, and who, in a like manner, conclude that bacteria are capable of invading the whole organism through the intestinal walls, even when there is not the slightest perforation of the intestine.

The above observations of Nocard, it is needless to say, caused considerable interest, though they were received with grave doubt. In Germany, more especially, Max Neisser[26] took up the study. He obtained the mesenteric glands from young cattle and sheep. Taking all precautions against contamination, he made cultures from these and, without exception, save in his earlier observations, in which he alleges poor technic, the glands were found sterile. So also he found that the mesentery with its lymph vessels, from rabbits and guinea-pigs, when placed directly into culture-media, remained absolutely sterile, and from these observations he arrived at the conclusion *that normally by means of the lymph channels, not a single bacterium passes into the circulation either by resorption or by growth.* Further, the same observer, taking a series of fasting and well-fed dogs, to some of which he had given abundant quantities of various pathogenetic and non-pathogenetic bacteria by the mouth, removed the chyle and attempted to gain cultures in gelatin, agar and broth. He found that under all conditions the chyle gave no cultures, or, as he states it, was *absolutely free from germs,* while he concluded from some further observations that normally the chyle is free from

any bactericidal powers. Kühnau[27] obtained similar results.

In America, quite recently this subject has been taken up in a long and most thorough investigation by Franklin Warren White of Boston.[28] He attempted to gain cultures in septicemia and other diseases, and, in order to guard against possible contamination, took the blood direct from the veins by means of a sterile syringe under all aseptic precautions. 0.5 c.c. of this blood was forced in each case into eight tubes of agar kept fluid at the bed side at a temperature of 42° C.; then the blood was thoroughly mixed with the agar.. Two broth tubes were each inoculated with 0.5 c.c. of the blood and those various bloods and tubes so prepared were kept at the body temperature and examined at intervals for several days. The results obtained are rather remarkable: out of 18 cases of septicemia, in 4 only did he gain positive results, specific bacteria being found in the blood during life. Out of 19 of pneumonia, in only 3 were there positive results; in 8 of cerebrospinal meningitis, not a single positive result was obtained, whereas out of 37 of chronic disease (nephritis, tuberculosis, gastric ulcer, myocarditis and pericarditis, etc.), only 5 positive results were obtained. Thus, out of 92 cases altogether, only 12 gave cultures and these in cases of active disease. A remarkable point with regard to these observations of Warren White is that he, like many previous observers, Petruschky, Sittmann, Hewelke, Michaelis, Meyer, Verdelli and yet others, obtained almost entirely, if not entirely, staphylococci, streptococci and pneumococci. The remarkable fact is that whereas bacillary forms are so commonly associated with infection, all these observers with singularly rare exceptions failed to gain bacilli from the blood. This in itself is very suspicious. Warren White did not get the colon bacillus in a single culture, although the colon bacillus was not infrequently found in one or more organs at the autopsy, and, like the other observers, whom he quotes, he can not accept the theory that the normal or nearly normal bowel is easily and frequently penetrated by bacteria.

It is very remarkable that Warren White himself[29]

has pointed out that the blood serum even in healthy individuals is not appreciably germicidal for pus organisms* whereas it is markedly germicidal toward the colon bacillus, and he found further that the serum retained this property even in cases of severe chronic disease up to the end of life, and it may be for several hours after death.

Herein lies, it seems to me, the explanation of the whole matter: Those observers who have most frequently gained positive results are just those who have employed broth cultures and have diluted the blood considerably. Nocard and French observers, as I know from personal experience, still favor the method introduced by Pasteur, of using relatively large quantities of broth for making first cultures, in preference to solid media; whereas German observers, as in private duty bound, follow the methods introduced by Koch and work especially by means of streak and plate cultures of solid media.

Because certain observers have failed to discover bacteria in the blood from cases of infectious disease, it by no means follows that the blood when shed has been free from bacteria. One and all of these observers who have gained so large a proportion of negative results have failed to take into account, or to take any measures to diminish the bactericidal action of the shed blood, and our German colleagues, those who have been foremost in dwelling on this bactericidal action and employing it to explain immunity and arrest of disease, have been the greatest sinners in this respect. I need but refer here

*In this White is in harmony with Nuttall,[30] Stern,[31] and Prudden.[32] Flexner,[33] however, agrees with Rovighi[34] that, normally, human blood serum does possess distinct bactericidal properties for the pyococcus aureus, though this power is absent or diminished in some cases at least of advanced chronic disease. Of nine samples of blood taken from persons suffering from some form of chronic disease, in three only was no appreciable effect exerted on the pyococcus aureus. Flexner found that 1 c.c. of normal blood serum might in four hours kill some 29,000 pyococci, though usually the number destroyed was very much less.

to the fact long ago clearly demonstrated by Lubarsch, that whereas 1 c.c. of shed blood will kill thousands of anthrax bacilli, a much smaller number of the bacilli introduced into the circulating blood will surely cause the death of a rabbit, i. e., will not be killed in the circulating blood but will proliferate abundantly; or to the abundant further evidence that we possess, that the bactericidal powers of the circulating blood are relatively slight, whereas those of the shed blood are remarkably powerful. In the act of coagulation it is that the bactericidal substances are in the main liberated. If but a few bacteria be in the blood removed from a vessel, and a drop of that be smeared over the surface of agar or blood serum, no wonder that the results are negative. That drop of blood alone is capable after coagulation of destroying hundreds, not to say thousands, of such bacteria as the colon bacillus. Even if, as Warren White proceeded to do, 0.5 c.c. of blood be mixed with 5 to 10 c.c. of agar or other medium, the dilution is too slight to greatly inhibit this bactericidal action. No wonder then that in his series of observations, only those forms, and just those, relatively resistant to the bactericidal action of the blood serum, managed to proliferate and to form colonies.

Thus it happens that those who have employed solid media have had a succession of negative results; those who have freely diluted the blood and the chyle have more often gained positive results. It is not that the bacteria have been of necessity absent from the blood, it is that the proper means were not taken to favor their growth.

What is true of the blood is true also of the bile. Compared with the blood the bile has such slight bactericidal effects that most observers have denied that it has any at all. My own observations show me that it has a slight bactericidal and inhibitory action on the growth of bacteria. Here, as with the chyle, if relatively large numbers of bacteria from a pure culture be added, they grow immediately and abundantly, but if the number be small, they tend to be destroyed. Dr. Maude Abbott, working in my laboratory at the Royal Victoria Hospital,

has now repeatedly found that if inoculations of human bile be made simultaneously upon agar or blood serum and into broth, the former tubes may remain sterile, the latter show growth. It is only where relatively abundant bacteria are present that growth occurs on all media. In short, the proper method to test the blood for the existence in it of bacteria, is to take a relatively large quantity of that blood, say about 0.5 c.c.—because no one pretends that in the circulating blood any large number of bacteria is present, and if a small quantity be taken the germs are likely to be missed—and immediately drop that into a Pasteur flask containing 50 or 100 c.c. of broth, shake forthwith so as to distribute the blood through the broth or other fluid culture-media and thereby to dilute it thoroughly. Even with this dilution it is not certain that bacteria present in the blood will grow, but, certainly the growth is distinctly favored as compared with the more common method of the employment of solid media. I do not say that, employing this method, germs are constantly found in the blood; I do say that they tend to grow much more readily.

ON THE PRESENCE OF BACTERIA IN NORMAL TISSUES.

Similar considerations and similar criticisms may be brought to bear on the observations which have been made with regard to the existence of bacteria in the normal tissues. Time and again observers, like Hauser,[35] Neisser,[36] and yet others, have found the tissues of healthy animals so frequently sterile that the occasional gaining of cultures from the organs has been by them referred to contamination in the admittedly difficult task of removal of organs or parts of organs from the body into sterile receptacles. Thus, for example, Neisser, out of some thirty-seven rabbits, mice and guinea-pigs, which he fed with various pathogenic and non-pathogenic organisms and in certain of which he further set up grave intestinal irritation by giving at the same time croton-oil or powdered glass, failed to gain cultures from growths in the liver, spleen, kidneys, lungs, etc., in twenty-four, and only gained cultures, and these in not all the organs, in the remaining thirteen. His

method was apparently most complete; the animals were skinned and then placed in sublimate solution so as to sterilize the surface, then fastened out on sterile boards, the operator himself having his hands sterilized, and each organ was removed in turn by a separate set of sterile instruments and then placed in sterile vessels and melted gelatin or, rarely, melted agar poured over them, while only after two days were they examined.

The results seem most positive, and what is remarkable is that even when cultures did grow in the organs, in general they were not the forms with which the animals had been fed.

Recently Dr. A. G. Nicholls and Dr. Ford, Fellow in pathology at McGill, have been repeating these observations, and they have gained very different results and Ford has discovered wherein Neisser has been led astray. The animals employed by him so far have been rabbits, and he has taken precautions similar to those employed by Neisser to guard against contamination. Immediately after removal of the kidney or portion of the liver with sterile instruments, it has been placed in the flame of a large Bunsen burner and turned around until the surface began to "splutter," if I may so express it, thereby making sure that there should be no surface contamination. The organ or part has then been dropped into a sterilized bottle of special construction, containing melted glycerin or melted agar, so that if there were any subsequent contamination by the air it would first of all show itself on the surface of this medium when solidified. Dr. Ford will publish his whole series of observations later, but he has done sufficient to allow me to state that where organs are placed in gelatin and kept in the cold, a large portion remain absolutely sterile and show no growth, whereas when placed in agar and kept at the body temperature, the majority of livers and kidneys show relatively abundant growth after two days or less.

Here, again, I take it, the bactericidal influence of the body tissues come in. If may be that if the organs be not immediately removed after death, such bacteria as are present undergo attenuation and destruction with fair rapidity, unless, as in cases of disease, they be pres-

ent in relatively large numbers, while at the same time the bactericidal powers of the tissues are depressed. What appears more evident, though, from Dr. Ford's results, is that this inhibitory action of the body tissues upon microbes that are accustomed to live at the body temperature is favored by keeping cool, or more correctly that the activity of growth of the bacteria is depressed. That Dr. Ford's results can not be ascribed to contamination is rendered evident by the fact that where he has found micrococci growing in the normal removed liver, he has found them also growing in the kidney. If certain forms of bacteria be present in one organ, the tendency for them is to be also present in the other; though it should be added that—as might be expected if these have been brought to the organs from the intestines—colon-like forms predominate, and again not infrequently more than one form is present.

Let me, before proceeding farther, gather up and group together the conclusions which may be legitimately adduced from the facts so far brought forward. They are, it seems to me, the following:

1. Normally there is a passage out of leucocytes through the mucosa on to the free surface of, more especially, the alimentary tract.

2. These leucocytes, while in part undergoing a destruction, in part find their way back between the epithelial cells, bearing with them foodstuffs and solid particles, among which may be the bacteria present in the cavity of the gut.

3. During the active congestion which accompanies digestion, the passage out and return of these wandering cells is increased.

4. These cells upon their return find their way either into the lymphatic channels or the venules of the portal system.

5. In either position, they tend to be destroyed and digested by the leucocytes and thus, while preparations of the mesentery and of the mesenteric lymphatic glands may show abundant bacteria, the vast majority of these at the same time show obvious degeneration, while cultures made from the mesentery or from the lymphatic

glands upon ordinary media by ordinary methods as a consequence tend to remain sterile. Similarly, in the normal liver, the same rapid destruction takes place, so that here again, by ordinary methods, no evidence of living bacteria is obtainable.

6. By the employment of adequate methods it can be demonstrated that even in the healthy liver and kidney in a large number of cases, in one animal at least—the rabbit—a certain number of living microbes are present at any one moment so that, if the healthy organ be removed from the body, cultures can be obtained of these living microbes.

7. It is most probable, further, that in ordinary health a certain number of bacteria which have not been destroyed by the leucocytes or removed by the lymphatic glands or endothelium of the portal system, pass either through the thoracic duct or through the liver into the systemic blood. Such bacteria tend to be removed more especially by the kidneys, though it may be by other glandular organs. In any case the ordinary methods at present employed in making cultures from blood are inadequate to detect the presence of such bacteria unless they are of such a nature or are circulating in such quantities that the whole number is not destroyed by the bactericidal action of the shed blood.

LATENT INFECTION.

It follows further, from these conclusions, that there does exist a condition of what the French term "latent microbism," or what I think should be more correctly termed, for my present purposes, "latent infection." We have abundant evidence that even in the healthy feces such forms as the pyococci, streptococci and the bacillus pyocyaneus are to be encountered fairly often. We further know that the commonest form inhabiting the intestine, that which outgrows all other forms, namely the colon bacillus, even when obtained from perfectly healthy feces, may show marked pathogenetic properties when inoculated into the lower animals.

We also know as a common fact in pathology, that just as one swallow does not make a summer so an isolated

microbe gaining entrance into the system, does not usually set up disease. Save when we are dealing with the most virulent forms of pathogenetic micro-organisms and with animals which are peculiarly susceptible, it requires numerous bacteria entering at the same time to so lower the resisting powers of the tissues as to there survive and proliferate. Even with the tubercle bacillus it has been calculated that, in the very susceptible rabbit, at least from twenty to thirty have to be inoculated subcutaneously before the disease can surely be set up; any lesser number is destroyed. If, therefore, in the intestine, here and there at scattered points, individual bacteria are being introduced into the system from time to time, that does not necessitate proliferation and consequent infection; we can easily understand that if the tissues there possess their normal powers, isolated bacteria tend to be destroyed by the cells or the containing leucocytes at the immediate point of entry; and, as a matter of fact, study of the mesenteric glands and the difficulty in obtaining cultures from these, even when sections of the same show relatively abundant bacteria, is clear evidence that this is the case.

ON CERTAIN CASES OF SURGICAL INFECTION.

Only the other evening I was talking over these matters with my colleague, Dr. Armstrong, surgeon to the Montreal General Hospital, and he put to me certain very pertinent questions. "Why," said he, "do we surgeons dread operating upon the robust city man apparently full of health and vigor, who wants to rush in upon us on the Friday or even upon the Saturday afternoon, to have some such small operation performed upon him as, for example; the removal of hemorrhoids, in order that he may be back again at his business on the Monday morning? Why is it that the chances are so greatly against such operation being safe? Why, on the other hand, if we coop up that man for two or three days previously and thoroughly purge him, is the operation a trifle, and we can be practically sure that there will be no complications? The sudden change in his diet and habits can scarce improve the vitality and resisting

power of his cells. Why, again, is it our common experience that our best cases, upon which we can operate with the certainty of gaining good results, are those who have been almost bedridden with chronic disease and have been in a condition of invalidism for long months and living upon a restricted diet? Why, again, do we fear to operate upon cases suffering from chronic constipation? Can any more satisfactory explanation of these facts be given than this theory of latent infection and of the possible infection of wounds, not from outside or from the skin, but from bacteria circulating in the tissues, which, under normal conditions, are destroyed and rendered harmless, but which under the abnormal traumatic conditions of the operation are now able to proliferate and set up local disturbances?"

TERMINAL INFECTION.

But, in addition, we can equally well understand that if from some cause or other, as for example, from inflammation along the intestinal tract, whereby excessive numbers of bacteria are introduced, or again in conditions such as are afforded toward the conclusion of long-continued chronic wasting disease, in which the reactive powers of the tissues are greatly lowered, or again where there is temporary lowering of the vitality by injury or operation, then everything favors the multiplication of bacteria so introduced and the development of either localized—so-called cryptogenetic infection—or of general septicemic disturbance.

The admirable and, I would say, classic observations of Flexner,[37] on terminal infections, show in the most vivid light how common it is to have death preceded by such general or local infection by germs totally foreign to the main morbid condition, and amply confirm Osler's[38] well-known remark that "persons rarely die of the disease with which they suffer."

POST-MORTEM INFECTION.

If we accept the conclusions above mentioned, we gain a more correct understanding of what I may term "post-mortem infection" of the body. The usual explanation of the abundant growth of bacteria in the various organs

after death is that while there may oftentimes occur an agonal invasion of bacteria, the essential cause of such infection and subsequent putrefaction is the entry of bacteria, more especially through the intestines after death. Birch-Hirschfeld[39] has lately reaffirmed this, and has brought forward certain observations of his own in favor of such a conclusion. While he admits that the agonal invasion may occur even in the absence of demonstrable lesions of the epithelial layer, he concludes that a post-mortem invasion of the internal organs by intestinal bacteria is a constant phenomenon, occurring in the majority of cases about ten hours after death, with especial frequency in the liver, but also met with in the kidneys, spleen, portal and heart blood and bile. It is an interesting point that Birch-Hirschfeld, in this supposed invasion, admits that the various organs show no constant sequence of infection, as again that morbid changes in the intestine have no influence on the time of the appearance of the bacillus coli in the internal organs. It is most interesting to further observe that this period of ten hours mentioned by him corresponds singularly with the maximum period, mentioned by Flexner, at which the blood of the cadaver was found to lose its bactericidal power; and lastly, it is of importance to notice that those who have explained post-mortem infection by this method have never demonstrated, what ought, according to this view, to be most clearly demonstrable, namely, the existence of masses of bacteria in special abundance in the intestinal wall and appearing to be growing through that wall into the blood-vessels and surrounding tissues.

It is impossible from the above observations that I have recorded to come to any other conclusion than that at the moment of death, or shortly before, the lowering of the vitality of the tissues permits a larger number of bacteria than normal to be present in the living state in the blood and lymph. Just as when one removes the blood or takes the tissue juices outside the body and adds to certain quantities of these fluids a fair number of bacteria, the tendency is for certain of those bacteria to be destroyed during the first few hours, then gradually

for the remainder to multiply; so in the dead body, after death there would seem to be often, but not always, a preliminary period in which the bactericidal action of the tissues continues and the number of bacteria to be obtained from the tissues by ordinary methods is singularly small: following this there is multiplication. In short, our ordinary methods are imperfect, inasmuch as they only give us results when bacteria are present in relative abundance. As a consequence, it is possible for us, fortunately, often to determine what is the main invading microbe, but even with them, as shown by Flexner's results, the greater the care that is taken, the greater the variety of bacteria which may be found in the body after death.

SUBINFECTION.

But apart from this latent infection and the sudden and acute one to which it may at times give rise, if we admit this normal passage in, and normal destruction of, bacteria by the tissues, there is possible, it seems to me, an intermediate condition which I would term "subinfection," a condition in which, as a consequence of chronic inflammatory disturbance in connection with the gastro-intestinal tract, there may for long periods pass in, through the walls of the stomach or of the intestine, a greater number of ordinary bacteria inhabiting the tract, and, while the bacteria undergo the normal and inevitable destruction by the cells of the lymph glands, the liver, the kidney and other organs, nevertheless, the excessive action of these cells and the effect on them of the bacterial toxins, liberated in the process of destruction, may eventually lead to grave changes in these cells and in the organs of which they are part—changes of a chronic nature. At no individual moment may we find evidence of the presence of large numbers of living bacteria in such organs, but we may find the evidence of their presence in the cells, and may find certain chronic inflammations associated with, or the result of, this overwork of the bacteria-destroying cells. It is possible, I would urge, that there may exist a morbid condition, the existence of which has not so far, to the best of my knowledge, been fully recognized. We must, I

think, admit the existence of the following forms of infection:

1. *Fulminating Infection*—In which, from the onset to the conclusion, the tissues are unable to overcome the virus.

2. *Acute Infection*—In which, while at first the bacteria gain the upper hand, the tendency is for the tissues to be stimulated eventually to counteract the germs and their toxins.

3. *Chronic Infection*—In which the tissues have not the power of wholly destroying the bacteria, although they may arrest their activity, and thus the bacteria constantly but slowly gain the advantage.

4. *Subinfection*—In which the tissues readily destroy the invading bacteria, but in which, just as water constantly dropping makes a hole in the stone, eventually, with recurrent invasion, the tissues become worn out, whereupon chronic or acute infection may supervene.

The absolute recognition and determination of this last condition is rendered peculiarly difficult by the fact that any chronic catarrhal or inflammatory condition of the intestines is accompanied by abnormal fermentative changes therein. And thus at the present time it is almost impossible to distinguish and divide conditions which might be due to this combined cell exhaustion and cell intoxication from the intoxication and the disturbances due to increased absorption of soluble poisonous products through the intestinal wall.

Yet certain observations that I have been making during the last two years do, I must confess, lead me to believe in the existence of such a condition of subinfection. In the first place I found these minute diplococcoid bodies peculiarly frequent in the liver cells in cases of hepatic cirrhosis, and since finding these, the more I have myself made autopsies in cases of this condition, and the more I have carefully studied the records of others, the more it has been brought home to me that accompanying ordinary progressive cirrhosis there is a chronic catarrhal condition of the intestines, together with a definite enlargement of the retroperitoneal and mesenteric lymphatic glands. Here it is more especially

in the cells at the periphery of the lobule that this presence of these bodies is noticeable, in those cells, that is to say, which are first fed from the blood coming from the portal vessels, and which are again most liable to undergo atrophy and to be affected by the fibroid change occurring in the interstitial tissues.

My first view that these little bodies either taking on a slight or an intensive stain, or seen purely as fine double pigment granules, were directly associated with cirrhosis and indicated a specific micro-organism, was rapidly modified by the discovery that cultures from the cirrhotic livers and from the bile in such cases, while at first tending to give a form of diplococcus, upon subseculture and passage through animals, developed into a form morphologically unrecognizable from the colon bacillus, while frequently absolutely typical colon bacilli were obtained from these organs and from the rest of the body.

But while this is the case, the frequency with which the colon bacillus has been found by other observers, associated with more acute hepatic disease, and with which, in one form—the so-called hypertrophic cirrhosis—other observers have noted its presence, renders it not impossible that this bacillus may have some part to play in connection with the condition.

HEMOCHROMATOSIS.

Recently there came to us a case of well-marked hepatic cirrhosis associated with great pigmentation of the skin and the intense development of the condition known as hemochromatosis. In this, as in other cases of hemochromatosis, there was iron-containing pigment in the liver, the mesenteric glands, the pancreas, and to a less extent in the spleen, kidneys and the heart. What is the cause of this hemochromatosis has been a matter of very considerable conjecture of late years. There is a very full paper on the subject in the last issue of the *Journal of Experimental Medicine,* by Dr. Opie, of Baltimore, a paper so full and thorough that here I need not go into the various theories that have been adduced; I will only say that Dr. Opie comes to the conclu-

sion that the condition is a distinct morbid entity characterized by the wide-spread deposition of the iron-containing pigment in certain cells, and the association of iron-free pigment in a variety of localities in which pigment is found in moderate amount under physiologic conditions. With the pigment accumulation there is degeneration and death of the containing cells, and consequent interstitial inflammation, notably of the liver and pancreas, which become the seat of inflammatory changes accompanied by hypertrophy, while, when the chronic interstitial pancreatitis has reached a certain grade of intensity, atrophy and diabetes ensue, and this last is the terminal event in the disease.

Dr. Maude Abbott, who has been working in my laboratory, on this subject, for some months, has reached somewhat different conclusions. She called my attention to the fact that where there is marked destruction of the blood the spleen may also be the seat of pigmentation, whereas in the diabetic and cirrhotic cases, as again in pernicious anemia, the spleen is not implicated. Examining some of these typical cases of hemochromatosis she reported to me that in some instances, she noted frequent diplococcoid bodies. To a slight extent the deposit of iron-containing pigment is present in a large number of cirrhotic livers which she has examined, and she has been especially struck by the fact that one and all have shown either marked inflammatory disturbance in cases in which such occurs unassociated with cirrhosis, it also occurs in cases unassociated with cirrhosis either of the liver or pancreas. Examining the records of the connection with the intestines or some chronic suppuration elsewhere in the body—conditions in short leading to more or less chronic destruction of the blood. When now I come to study her material more fully, and with the highest power, to my astonishment I find that where this pigment has not clumped together into too large masses, in the liver cells for example, as again in the abdominal lymphatic glands, there are, in a very large proportion of the ultimate fine masses of pigment, reacting to Perl's test and containing iron, distinct diplococcoid forms or bodies. Of this there can be no doubt.

In short, the condition of hemochromatosis is of bacterial origin and, just as Hintze,[40] and before him, von Recklinghausen,[41] pointed out that the slightest case of hemochromatosis presents itself merely a brownish coloration of the intestinal walls, so here we may have a succession of cases in which at first only the intestinal walls and the mesenteric glands become the seat of the deposit of this pigment, and to a slight extent the liver, through cases in which the liver is involved and there is associated or accompanying cirrhosis, to cases in which the pancreas also becomes the seat of this abundant deposit of the minute pigment granules, of modified "corpses" of bacilli in the cells. I have no doubt concerning this; the diagram is a faithful reproduction of a portion of one of these livers of hemochromatosis, from a case described by Kretz,[42] which has come through several hands into that of Dr. Abbott. You will see that whereas in certain regions it is dense and it is impossible to make anything out, there are other parts in the cells where these little diplococcoid bodies definitely take on the reaction for iron.

Where we have *diabète bronzé,* or again extensive cirrhosis of the liver with hemochromatosis but without diabetes, there deposit of this iron is so extreme that certain of the cells, more especially at the periphery of the lobules, become little more than a mass of agglomerated iron-containing pigment, and what is more, this pigment is now to be found in the connective tissue at the periphery of the lobule and, as Dr. Abbott points out, and as others have also concluded, the little masses of pigment indicate the remains of liver cells. In fact, the condition is a very extreme one.

PERNICIOUS ANEMIA.

The nature of this deposit of pigment in the liver in conditions of hemochromatosis is identical with, though more extensive than, that first recognized by Quincke, and of later years more especially dwelt on by Wm. Hunter, which is found in the liver in pernicious anemia. There is the same finely granular nature, the same tendency for the pigment to be accumulated in the cells in the

immediate neighborhood of the bile capillaries, and here again there is the same reaction with ammonium sulphid, and by means of Perl's test with potassium ferrocyanid. Examining a series of livers from cases of pernicious anemia, I find in them identically the same condition, namely, that whereas under the ordinary high power, or even the ordinary 1/12 oil-immersion, all that one sees is an irregular massing of fine granules in the liver cells, if one examines carefully and conscientiously by means of a yet higher power of immersion-lens, these irregular granules resolve themselves into irregular clumps of stumpy ovoids, as again of minute diplococcoids, and again into isolated diplococcoid bodies which may or may not show a fine halo round them, situated in the liver cells. Nay more, in advanced cases of pernicious anemia, one finds the same bodies also crowded in the very much swollen endothelial cells. In both positions these take on a reaction for iron, but even when stained for iron, as by Perl's test, the diplococcoid nature can be made out in a large number of the isolated masses on careful focusing.

I do not mean to say that all show themselves as diplococcoids; there are numerous isolated granules as again bodies of a more oval shape, and again certain bodies, roughly the same diameter, which often appear to be definitely bacterial in form. But on careful study the number of double bodies, of dots of the same size, is so remarkable and so frequent that the diplococcoid nature of the granules is their especial characteristic.

It is now more than a year since my attention was called to the fact that the colon bacillus when virulent is especially liable to set up hemorrhagic inflammation in the lower animals, as again in certain cases in man, so that in hemorrhagic peritonitis we very frequently come across abundant cultures of this form. As Sidney Martin has pointed out, parallel inoculations in lower animals, of the closely allied typhoid bacillus, lead to a non-hemorrhagic disturbance. Thinking over this it occurred to me that very possibly the toxins of the colon bacillus might have some peculiar action on the blood and on the vessels, and by following this train of thought

it occurred to me that the toxic substance which Hunter concluded must become absorbed from the upper portion of the gastro-intestinal tract, to explain the pronounced destruction of red corpuscles in pernicious anemia, might possibly be of bacterial origin. The point, I believe first drawn attention to by von Jacksch, and more recently corroborated by Dr. Finley of Montreal, that in

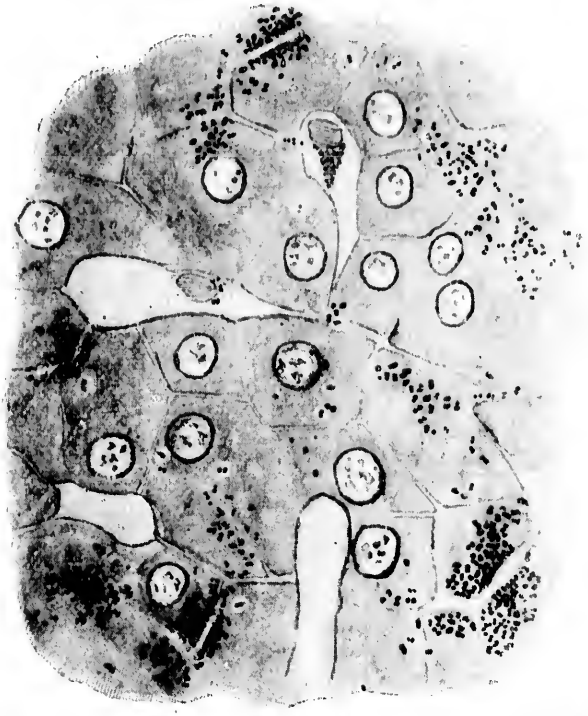

Fig. 2.—Section of liver from case of hemochromatosis (pigmental cirrhosis) stained with alum carmin, then treated with weak hydrochloric acid and later with dilute potass. ferrocyanid solution. Drawn under camera lucida, Reichert 1/18 immersion-lens, ocular 4.

typical cases of pernicious anemia there is an absence of hydrochloric acid in the gastric juice, an observation since confirmed by other observers, seemed again to render the abnormal multiplication of bacteria within the stomach extremely probable. With this end in view I suggested to one of my demonstrators, Dr. D. Anderson,

that he make a special study of the bacteriology of the stomach in cases of pernicious anemia. This disease is not very frequent, and it is difficult to accumulate any large number of cases, but during the year, Dr. Anderson has studied three of these in the laboratory at the Montreal General Hospital. He has found in all a complete absence of hydrochloric acid, with the presence, however, of considerable quantities of lactic and some butyric acid, and in all three, to my great astonishment, he has obtained by plating pure cultures of the colon bacillus. This colon bacillus has been haunting me these last years, appearing to reveal itself everywhere, and I could hardly believe these results, but Dr. Anderson obtained similar ones in connection with a test-breakfast on one of the patients during life, and was absolutely convinced as regards the correctness of his results; and what is more, on making sections from one of the stomachs, he found numerous diplococcoid forms in the submucous tissue. This I should add was long before I had realized the nature of the pigment in the liver. In order to confirm the result, I asked Dr. Ford to make an independent examination of a case at the Royal Victoria Hospital, under Dr. James Stewart. He gave a test-breakfast to the patient and absolutely confirmed the findings of Dr. Anderson in every respect. In this fourth case plates made from the breakfast gave abundant and pure cultures of the colon bacillus. The form was at first a little abnormal, the colonies were of a more opaque white than usual, but later separate cultures from several colonies gave a perfectly typical form, endowed with motility, and in every respect corresponding to the tests for the colon bacillus.

Thus, then, we have in these cases of pernicious anemia in the first place some chronic inflammatory condition of the mucous membrane of the upper gastro-intestinal tract, leading often to atrophy. In the second place we have the abundant presence of the colon bacillus here in the upper intestinal tract; in the third we have Dr. Anderson's observation of the presence of the modified form of the colon bacillus within the walls of the stomach, and in the fourth, the dead unstaining forms of bacilli—these minute brownish diplococcoid bodies present in the

endothelium of the liver capillaries and again heaped up in the liver cells. My own opinion on examining these specimens is that in the majority of cases the bacteria are already dead when taken up into the liver cells, and that we are dealing, as I say, with the corpses of bacteria.

There are very many points in connection with these thoroughly surprising observations which need further elucidation. I have throughout this lecture already referred so frequently to the work of those in my laboratory that I dare say no more; it would be unfair to Dr. Anderson and to Dr. Ford to prematurely publish more concerning their work. There is one point that will probably come to everyone's mind, to which I must briefly refer, that is, why do these colon bacilli in the liver cells and elsewhere in this broken-down form take on the curious brown pigmentation, and actually take up iron? Only last Saturday Dr. Ford showed to me cultures that he had made of the colon bacillus outside the body, which were becoming diplococcoid in shape and which took on this brown staining. He has been able, in short, outside the body, to reproduce both the appearance and the properties of these modified colon bacilli in the tissues. He will later describe his methods.

I am now very careful not to state that the colon bacillus is the primary or the essential cause of either cirrhosis or pernicious anemia; indeed, I think that it is probably not, that in either case there is some primary and underlying factor favoring its entrance into the economy: this, however, I do say, that a study of these conditions does confirm me in the belief that the constant destruction and taking up of excessive numbers of these, and it may be other bacteria of similar pathogenetic powers, does affect the cells and does affect their activity. These observations, therefore,, in my opinion. confirm a belief in the existence of the condition of what I have termed subinfection. Nay more, I believe that in the development of many chronic fibroid conditions, this subinfection will be found to play a definite part. "But," as Plato was wont to remark in a manner strangely and suggestively modern, "this is calculated to afford the subject-matter of another dissertation."

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