

CULTURES FROM THE BLOOD IN SEPTICÆMIA, PNEUMONIA, MENINGITIS AND CHRONIC DISEASES.

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The value and significance of bacteriological examination of the blood are so evident that many observations by this method have been made in the last twenty years in an endeavor to throw light on the etiology and course of infectious diseases. The object of such investigations is not wholly theoretical, but is also practical as a means of diagnosis, prognosis, and, possibly, treatment. The results obtained have been varied and contradictory, which is probably due in part to faulty methods. The old method of pricking the skin and using a few drops of blood for culture has the disadvantage that too small an amount of blood is used to find the bacteria if they are few in number, and that it involves great danger of contaminating the cultures with bacteria from the skin. The later method of aspiration of a superficial vein by cannula or sterile syringe has the advantage of furnishing a satisfactory amount of blood for examination and lessening the dangers of contamination. The method of Petruschky (47), namely, blood-letting by means of a wet cup, is more complicated and less satisfactory than the latter method. Direct animal inoculation with blood from a patient, as used by Petruschky and others, is not always reliable as compared with cultures on suitable media.

Until recently post-mortem findings have been considered of equal significance with intra-vital ones, but there is no question that cultures during life, in spite of incompleteness of methods, furnish a better indication of general blood invasion during disease than autopsy reports, as the latter do not exclude agonal and post-mortem invasions. Wyssokowitsch (62), as a result of his studies on the filtering of bacteria out of the blood by the liver and kidneys, stated that in

any ordinary course of infection the invading bacteria would be so quickly and completely separated from the blood that there would be very small chance of finding them by methods of blood culture. Many other observers, on the contrary, have found bacteria in the blood in a large percentage of cases examined and have probably overestimated the significance of these results and the value of blood cultures as a means of diagnosis in infectious diseases.

Our own observations extend over a series of 92 cases, consisting of 18 cases of severe sepsis, 19 cases of lobar and lobular pneumonia due to the pneumococcus, 8 cases of epidemic cerebrospinal meningitis, 37 cases of severe chronic disease, and 10 miscellaneous fatal cases. Cultures were made during life, usually in the later stages of disease, and in many of the cases as soon as possible after death (one-half hour). The cultures in cases of septicaemia, pneumonia and meningitis were made in order to find out, if possible, how frequently, in addition to toxine absorption, the blood was invaded by the specific organism of the disease; also the time of occurrence of such general invasion, and its relation to mortality.

In the cases of chronic disease the cultures were made both before and after death to determine the frequency of general blood invasion in the late stages of disease, and during the last few hours of life—the so-called “terminal infections” and “agonal infections.”

Methods.—The blood was obtained during life as follows: The skin about the elbow was carefully scrubbed with soap, water, alcohol and ether and a tight bandage was tied around the upper arm to distend the veins about the elbow. One of the large superficial veins was aspirated with a sterile glass syringe (an ordinary glass antitoxin syringe, with asbestos packing and a two-inch needle of rather small bore, was used) and 5 cc. of blood withdrawn. The aspiration was rendered practically painless by use of an ethylchloride spray; 0.5 cc. of the blood was forced directly from the syringe into each of eight tubes of agar, kept fluid at the bedside at a temperature of 42° C. The blood was thoroughly mixed with the agar and four of the tubes slanted and cooled. The other four were plated. Two bouillon tubes were each inoculated with 0.5 cc. of the blood. The plates and tubes were kept in the thermostat at body temperature and examined at intervals for several days.

Blood was obtained after death by aspiration of the heart. The skin was prepared in the same manner as during life and the same syringe used, with a longer ($3\frac{1}{2}$ inch) needle, which was thrust through the 4th costal interspace close to the sternum (to avoid the lung) into the right or left ventricle of the heart and 5 cc. of blood withdrawn and planted in cultures as just described. As the needle in this method passes through the pericardial and probably the pleural cavity on the way to the heart, blood was taken after death only in cases where these cavities were not infected. One to three specimens of blood were taken in each case. The time of taking the blood was from 10 days before to one-half hour after death in the fatal cases, or at intervals of several days during the height of disease in the cases which recovered.

The bacteria found in the cultures were identified by microscopical examination, growth on various media and a comparison with the organisms found in metastases or at autopsy. In the large number of cultures made contaminations were relatively few and easily recognized by their distribution and character of growth on the media.

I.—SEPTICÆMIA. PNEUMONIA. MENINGITIS.

Before describing our own results we will briefly review the more important previous work on these subjects. Septicæmia has furnished a fruitful field for observation.

Garré (25), Rosenbach (51), Brunner (10), and Blum (7) report single positive results of blood cultures in cases of septicæmia. A few drops of blood were taken during life by pricking the finger. Brieger (9) in six severe cases of puerperal sepsis took blood from a vein during life and obtained in each negative results. Czerniéwsky (16), using blood from finger and vein, in 370 cultures from 37 cases of puerperal sepsis obtained positive results in only 15 tubes from 10 cases; all the severe cases gave pure cultures of streptococci. Sängner (52) found staphylococci in blood taken from a vein in four cases of sepsis.

Later observers urged the necessity of using larger quantities of blood (1 to 5 cc.) for cultures owing to the small number of bacteria present in the blood. The method of venous aspiration with a syringe was introduced with varying results. Blum found *Staphylococcus albus* in two cases of sepsis several days before death. Canon (11), in addition to positive results in 40 out of 70 cases of sepsis, pyæmia, and osteomyelitis, where blood was taken several hours after death from an arm vein, obtained 11 positive results in 17 of these cases during life, usually 2 or 3 days before death in fatal cases. He believes that bacteria are present in the blood of almost all cases of sepsis in the late stages of disease,

and grow and increase in the blood in some cases. Microli (39) found *Staphylococcus pyogenes albus* in each of his four cases of septicaemia during life. Parascandolo (46) examined eight cases of pyaemia and found pyogenic streptococci in blood during life in each. Hirschlaff (31) in eight cases of local and general sepsis found staphylococci or streptococci in seven. Sittmann (53) found staphylococci or streptococci in each of nine cases of septico-pyaemia from six hours to fifteen days before death, and believes that pus organisms are always present in the blood in such cases, and that blood cultures are the surest means of diagnosis. He concludes that Canon's observation that streptococci are found in the blood only a few days before death was due to faulty methods.

In contrast to these abundant positive findings other observers using larger amounts of blood and better methods have found specific bacteria present in the blood in a smaller percentage of their cases. After allowing for individual differences in patients, the suspicion of contamination in the earlier cases is inevitable. Many of the observers have not taken into consideration the demonstration by Welch (58) of the frequent, if not constant, presence in the deeper layers of the epidermis and in the glandular appendages of the skin of the white staphylococcus and of the inability to destroy this organism by ordinary methods of cutaneous disinfection. Welch has called attention to the absence of diagnostic significance attaching to the demonstration of ordinary cutaneous bacteria, particularly white staphylococci, in blood withdrawn by cutting or pricking the skin.

It is interesting to note that Petruschky (47) using a rather objectionable method, obtaining the blood for cultures by means of wet-cupping, in 59 cases of sepsis obtained only 17 positive results: streptococci 15 times, staphylococci twice. Neumann (42) in 5 cases of pyaemia, using large amounts of blood from an arm vein, obtained negative results. E. Grawitz (26) in 7 cases of endocarditis found pyogenic cocci in the blood only once. Kraus (33) in 88 cases of infectious disease (puerperal fever, endocarditis, tuberculosis) found staphylococci or streptococci in the blood in 17 cases. In a second series of 104 cases of infectious disease using a pointed bent hollow needle and taking the blood directly from the vein to the culture media, he obtained only 12 positive results; 22 of these cases were septicaemia, erysipelas and endocarditis, and these gave 7 positive results. He emphasizes the fact that positive blood cultures to be of diagnostic value must be of "specific bacteria," whose nature excludes the possibility of their being contaminations. Kühnau

(34), using 10 cc. of blood taken from a vein through a cannula directly to the culture media, in 45 cases of septicæmia and local purulent infections obtained 4 positive results, and in 76 cases of endocarditis 2 positive results. In a considerable number of cases he made cultures of blood obtained by the old method of pricking the finger, as well as by aspiration of a vein. The results obtained furnish an interesting commentary on the unreliability of the earlier method. In 23 cases of septico-pyæmia three positive results were obtained by the venous aspiration method; in 18 of these cases the finger blood was examined, in 12 staphylococci were found. In 12 cases of ulcerative endocarditis, *Staphylococcus pyogenes aureus* was found once in venous blood, while bacteria were found 11 times in the finger blood. Hewelke (30), in examining febrile cases of phthisis, found pus organisms in blood from the finger in 14 cases out of 27, and 3 times out of 27 where the blood was taken by puncture of a vein.

In contradiction to the belief of these last-named authors, that even in severe septic cases only a relatively small number of bacteria circulate in the blood, is the statement of Nocard (43) that directly after taking food an abundant passage of bacteria occurs from the intestinal canal to the blood by means of the chyle. This was confirmed by Desoubry and Porcher (17) in experiments upon dogs. A number of clinicians have considered the intestine the starting point of bacteria in various infections through the blood. Tavel (55) in strumitis, A. Czerny (15) in certain skin diseases, Posner and Lewin (48) in "cryptogenetic septicæmia," and Fischl (18) in septicæmia in infants. The passage of bacteria into the blood by means of the chyle has been disproved, however, by the later work of Neisser, Kühnau and others. Neisser (40) investigated the chyle of large dogs by tying a cannula in the thoracic duct and found it uniformly sterile even after feeding the dogs abundantly with bacteria. Kühnau obtained a similar result in five dogs. Neisser found the mesenteric glands of large animals sterile. Fodor (20) has shown that the blood of normal animals is sterile and Meissner (37) and Hauser (28) that the organs are sterile.

Blood cultures made in cases of pneumonia by several authors indicate that a general blood invasion by the pneumococcus occasionally occurs during life. Belfanti (4) in "many" cases (number not given) obtained 6 positive results; five of these proved fatal. Boulay (8) of four cases found pneumococci in two a few hours after death. Friedländer (23) in 6 cases had one positive result. Sittmann (53) in 16 cases obtained 6 positive results (in 2 of which pneumococci were found only

in stained specimens of blood, not in cultures). Of the 18 negative cases 2 died; of the 6 positive cases, 4 died. The positive results were obtained from one to seventeen days before death in the fatal cases. Kraus (33) in 12 severe cases of pneumonia found the pneumococcus once, one day before death; of 11 negative cases 10 recovered. Kohn (32) in 32 cases found pneumococci in the blood of 9: 7 of the positive cases died and 2 recovered after metastatic pneumococcus infections; of 13 negative cases, 8 recovered. Excluding two cases dying of complications, we find that a considerable majority of the negative cases recovered and of the positive cases died. He concludes that the presence of pneumococci in the blood gives a very unfavorable prognosis. The positive results were obtained only 24 to 48 hours before death in the fatal cases. Kühnau in 9 severe cases found pneumococci in two cases, both fatal. Another fatal case was negative.

An epidemic of cerebrospinal meningitis was in progress at the time of our blood investigation and cultures were made in eight cases. Weichselbaum (57), Netter (41), Heubner (29), Councilman (14) and others have studied the disease and do not find the specific organism, *Diplococcus intracellularis*, at autopsy, except in connection with the lesions of the disease, and conclude from post-mortem cultures of the blood, liver, spleen, and kidneys that it never produces septicaemia. The abdominal and thoracic organs are frequently found sterile at autopsy.*

My own observations embrace 18 cases of severe *sepsis* (7 appendicitis with general peritonitis, 2 phlegmon of leg, 2 septic wounds, 1 osteomyelitis, 1 suppurative periostitis, 1 suppurative nephritis, 1 facial erysipelas, 1 abscess of the appendix, 1 empyema), all of which were fatal, and eight of which were autopsied. They are chiefly cases of severe local septic infection without formation of metastatic abscesses, only one case being pyæmic. In the 18 cases, 37 blood cultures were made and specific bacteria were found in the blood during life only four times—*Streptococcus pyogenes* in pure culture three times and *Staphylococcus pyogenes aureus* in pure culture once. We give a brief description of the four positive cases:

* Since the completion of this article Gwyn (*Bulletin of the Johns Hopkins Hospital*, 1899, x, 112) has reported a case of epidemic cerebrospinal meningitis in which during life he obtained in pure culture *Diplococcus intracellularis meningitidis*, not only from fluid withdrawn by lumbar puncture, but also from the blood and from the fluid aspirated from an inflamed joint.

Case I.—Phlegmon of both legs following amputation of feet. Culture from leg showed *Streptococcus pyogenes*. Temperature 104° to 105° F.; death in 9 days. Blood culture 6 days before death, negative; 4 days before death, 40 to 60 colonies of *Streptococcus pyogenes* per cubic centimetre. No autopsy.

Case II.—Suppurative nephritis. Renal symptoms for 4 weeks; pyuria. Temperature 102° to 103° F.; death. Blood culture 3 days before death, 2 to 15 colonies of *Staphylococcus pyogenes aureus* per cubic centimetre. Autopsy, 58 hours after death, showed prostatic hypertrophy, cystitis, pyelonephritis, ureteritis, acute pleuritis, abscess of lung. Cultures from heart, liver, kidney, spleen, lung, ureter showed *Staphylococcus pyog. aureus*.

Case III.—Phlegmon of arm. Culture showed *Streptococ. pyog.* Temperature 100° to 103° F.; cervical adenitis; death after 2 weeks. Blood cultures 10 days before death, negative; 2 days before death 50 to 60 colonies of *Streptococ. pyog.* per cubic centimetre; one-half hour after death 1200 to 1500 streptococci per cc. No autopsy.

Case IV.—Erysipelas. Acute intestinal obstruction, laparotomy. One week later facial erysipelas, local peritonitis and otitis media. Temperature 103° to 104°; death. Blood cultures 5 days before death, negative; 2 days before death, 15 to 20 colonies of *Streptococ. pyog.* per cc.; three-quarters of an hour after death 20,000 *Streptococ. pyog.* per cc. Autopsy 13 hours after death showed malignant adenoma of sigmoid flexure, circumscribed peritonitis with multiple abscess formation, double purulent otitis media. Cultures from scalp, ear, peritoneum, liver, showed *Streptococ. pyog.*; spleen sterile.

In each of the foregoing cases the species of bacteria causing the initial lesion produced also the general invasion, no heterologous organisms being found. In the two positive cases in which an autopsy was performed the bacteria found in the blood during life were also found distributed through the organs at autopsy. The blood cultures in the other 14 cases were negative, in two cases one or two cultures being contaminated with cocci from the skin or air. In the 6 negative cases in which an autopsy was performed, while scattered germs were found in certain of the organs, there was no evidence of a general infection. These facts speak well for the method of blood culture employed in detecting a general bacterial invasion when it occurs.

The number of bacteria found per cubic centimetre during life

was never large, at most 50 to 60 streptococci. In two cases (III and IV) there was a great increase in the number of bacteria found immediately after death over the number found two days before. This may be interpreted to mean either that a growth of bacteria occurred in the blood during the last two days of life, or that a largely increased number were able to enter the blood during the last days or hours of life as a result of diminished body resistance.

The time of bacterial invasion of the blood was late in the disease, cultures from the fifth to tenth day in three of the subsequently positive cases being negative. The probable explanation of this is that the bacteria did not succeed in invading the blood till the body resistance was much reduced, this general spread and growth of bacteria, accompanied by an increased production of toxins, together with the lowered body resistance, leading speedily to a fatal ending.

In 7 cases in which the blood was negative before death it was examined also after death. The cultures were negative in each of these instances. An autopsy was performed in 6 of these cases and showed absence of any general invasion and several sterile organs at each autopsy. No general agonal invasion occurred in any of these patients.

Our 19 cases of *lobar pneumonia* were all at least moderately severe, and 10 were fatal. Of the latter 9 were autopsied. Thirty-two cultures were made, and in three fatal cases *Diplococcus pneumoniae* was obtained from the blood during life. We will briefly describe the 3 positive cases:

Case V.—*Lobar pneumonia*. Temperature 103° to 104° ; delirium; death. Blood cultures, 3 days before death, negative; one day before death, 40 to 60 colonies of the pneumococcus per cc. Autopsy $2\frac{1}{2}$ hours after death: consolidation of right lower and middle lobes, right pleuritis with effusion. Cultures from liver, lung, heart and spleen showed pneumococci; kidney sterile.

Case VI.—*Acute bronchopneumonia*. Duration 2 weeks; temperature 100° to 101° ; cough, dyspnoea, orthopnoea; slight oedema of ankles; vomiting; three general convulsions, death. Blood cultures 4 days before death negative; 2 days before death, 18 to 30 pneumococci per cc. Autopsy 3 hours after death: acute bronchopneumonia, acute fibrinous

pericarditis and peritonitis, acute glomerulonephritis. Cultures from lung, heart, pericardium, peritoneum, spleen, liver and kidney showed pneumococci.

Case VII.—Lobar pneumonia. Duration 8 days; temperature 101° to 103°; delirium; death. Blood cultures 5 days before death, negative; 2 days before death, 10 to 15 pneumococci per cc.

In two of the positive cases at autopsy a general pneumococcus infection was found; in the third case no autopsy was performed. In the 8 negative cases in which autopsy was performed, pneumococci were found in the lung, but there was no evidence of a general infection. No organism save the pneumococcus was found in the blood in any case. The number of bacteria was not large, from 10 to 60 per cc. The time of general infection was always late in the disease, negative results being obtained on the 3d to 5th day before death, and positive results one to two days before death.

Our 8 cases of *cerebrospinal meningitis* were all severe and 6 of them fatal. An autopsy was performed in 4 cases and diplococci found in the meninges; in one case they were identified as *Diplococcus intracellularis meningitis*. No pathogenic bacteria were found in the blood cultures. In 5 cases blood cultures were made shortly after death, and all proved sterile. The thoracic and abdominal viscera were found sterile in three out of four autopsies. In the other case (No. II), a culture shortly after death was sterile, while at autopsy miscellaneous bacilli and cocci were found in the organs. Their presence was probably the result of post-mortem invasion.

In reviewing our cases with reference to frequency of invasion, it is seen that our results in septicæmia are in accord with those of later observers, such as Neumann, Kraus, and Kühnau; we have not obtained the frequent positive results of the earlier investigators. Our series of fatal septic affections proved to be, for the most part, cases of intoxication, with resorption of toxins produced by bacteria growing in a local primary focus, and only in a small proportion of cases did the organisms enter the general circulation. The frequency of general invasion in our pneumonias is similar to that in the cases of Kohn, Kühnau, and Kraus.

Regarding the relation of general infection to mortality, no conclusion can be drawn from our septic cases, save that a large percentage may die without general infection. On the other hand, several authors have found bacteria in the blood in cases of septicaemia which ultimately recovered. Bernheim (5), in 2 such cases, found streptococci; Sittmann, in 5 cases, found staphylococci; Petruschky, in 8 cases, found streptococci of "high virulence." All our cases of pneumonia with positive blood cultures died, while 9 negative cases recovered and 8 negative cases died; or, to put it in another way, a general invasion was found in less than one-quarter of the fatal cases. Ordinarily, pneumococci have been found only in the severest cases, but Sittmann and Kohn each report two instances, and Belfanti one, where recovery followed a positive blood culture.

I believe that the value of blood cultures as a means of diagnosis in obscure cases of so-called "cryptogenetic sepsis" has been overestimated. Positive results during life are always interesting and valuable, and, when secured by proper methods, are removed from the suspicion of agonal or post-mortem invasion which sometimes obscures autopsy findings, but it is evident, from the large percentage of negative results even in the severest types of disease, that the search for the specific causes of disease by this method will often prove futile. As regards prognosis, it is evident that a negative culture does not give much assistance, while a positive result gives a very unfavorable prognosis in the majority of cases. We have never noted any marked change in the clinical course coincident with the occurrence of a general infection.

In our patients the time of general infection in both septicaemia and pneumonia has been late in the disease, only a few days before death. This has been the experience of Canon, Czerniéwski and Kühnau in cases of septicaemia, and of Kohn in cases of pneumonia. This, in my opinion, is either because the occurrence of a general infection led speedily to a fatal termination, or because the general infection was in itself an index of weakened body resistance and general breakdown. Sittmann, on the contrary, has obtained positive results in sepsis from 5 to 25 days before death, and found the pneu-

mococcus in the blood in pneumonia from 1 to 18 days before death. (Compare also the positive cases of blood culture followed by recovery mentioned above). The length of life after general infection depends on the virulence of the germ and the degree of body reaction, and it is evidently possible that the body may eliminate all germs from the blood and recover, or may eliminate a part and then succumb, as is seen in A. Fränkel's (21) case where 200 pneumococci per cc. were found in the blood four days before death and a much smaller number two days before death. Wyssokowitsch, in his experiments of injecting cultures of various bacteria into the veins of animals, found that the bacteria disappeared more or less completely from the blood after injection and were deposited in the liver, spleen and bone marrow, where the non-pathogenic bacteria were killed off as a rule, while the pathogenic bacteria increased and re-entered the blood.

I wish to say a word concerning the mode and cause of general blood infection. Kraus, in an article upon the resorption of micro-organisms into the blood from various organs, as the lung, intestine, bladder, tonsils and gall-bladder, after a careful review of the literature, concludes that in general the organs of the body are permeable for bacteria, some under normal conditions, some after damaging of tissue, and from all these organs with greater or less difficulty a resorption infection of the blood may occur. The exact factors concerned in producing a lessened body resistance, an increased susceptibility, are not known, but undoubtedly the chief defences against the invasion of pathogenic micro-organisms are the body fluids and cells. It thus becomes of great interest to know whether the normal blood is destructive to pyogenic organisms and loses its germicidal power under conditions which predispose to a general infection. It was my intention to test the germicidal power of the blood for pyogenic cocci in cases of septicæmia in order to determine whether general invasion could be traced to a loss of germicidal power. A review of the literature showed that this property of the blood varies in man and animals, both among themselves and for different species of bacteria. Nuttall (44), Stern (54) and Prudden (49) have concluded from their experiments with human blood and normal body fluids that they

possessed little or no effect upon pyogenic cocci. A series of experiments by the author (60), which were recently published, confirm this belief that normal human blood serum is not actively germicidal for pus organisms. Thus it is evident that there are factors other than the germicidal power of the blood which play an important part in protecting the body against general infection and that the solution of this problem must be sought along other lines.

II.—CHRONIC DISEASES.

It is a well-known fact that local infectious processes are of frequent occurrence in patients afflicted with chronic diseases, and autopsy findings indicate that general infection occasionally occurs as a cause of death. Believing that in many cases results obtained during life have more significance than those obtained at autopsy, we have used the method of blood cultures during life to determine the frequency of general terminal infections. Osler (44) says: "It may seem paradoxical, but there is truth in the statement that persons rarely die of the disease with which they suffer. Secondary infection, or, as we are apt to call them in hospital wards, terminal infections carry off many of the incurable cases in the wards." Flexner (19), in an analysis of the autopsy reports of 225 cases in which occurred chronic cardiac, vascular or renal disease, alone or in combination, found 213 cases in which bacteriological examination gave positive results. Local infections were found in a large proportion of all his cases of chronic nephritis, arteriosclerosis, hepatic cirrhosis and other chronic diseases. Acute infections of the pericardium, pleura, peritoneum, meninges and endocardium were most frequent. In 163 cases of chronic nephritis, either single or combined with other chronic disease, 38 cases were found with a general distribution of bacteria in the organs. In 63 cases of cardiac and arterial disease he found 14 similar cases. These were considered instances of general infection during life, and in many a local lesion was present, such as erysipelas or peritonitis, which was looked upon as the source of the general infection. In a large proportion of the cases, visible focal lesions were not present in the organs at autopsy. The pyogenic cocci were

usually the infectious agents. He believes this susceptibility to infection in chronic disease to be a result of changes in the blood occurring in cachexiæ, weakened body resistance being due to a loss of germicidal power of the serum. These are very interesting and significant results, yet it is only fair to say that a general distribution of bacteria at autopsy does not always mean general infection during life. If all the cases could be excluded where the bacterial invasion of the blood and tissues may have occurred not during life, but during the death agony or after death, the list of "general infections" would undoubtedly be smaller.

Of particular interest also are the general blood infections, which have been demonstrated during life in chronic diseases by means of blood cultures. Petruschky examined the blood in 8 cases of advanced pulmonary tuberculosis and found streptococci present once during life. In 8 of 14 cases which came to autopsy, streptococci were found in all the organs. Sittmann obtained positive results in 3 of 4 cases of phthisis, finding *Staphylococcus pyogenes aureus* twice in the blood and *Staphylococcus pyogenes albus* once. The number of bacteria was only 2 or 3 per cc., and they were found from 2 to 30 days before death. Hewelke, in 27 cases of phthisis, found pyogenic cocci in the venous blood in 3 cases. Michaelis and Meyer (38), in examining the blood in 10 cases of phthisis, found pyogenic cocci in 8 cases from 2 to 9 days before death. Hirschlaff (31) obtained staphylococci from the blood in 4 out of 25 cases of phthisis. Fränkel (22) found colon bacilli in the blood during life in a case of leukæmia. Gabbi and Barbacci (24), in 2 cases of pseudo-leukæmia, obtained the same result. Verdelli (56), in 2 cases of pseudo-leukæmia, found *Staphylococcus pyogenes aureus* and *albus*. As an analogue to this class of cases, many observers have demonstrated the occurrence of secondary infections by pyogenic cocci in cases of acute disease, such as typhoid fever and diphtheria.

Turning from this subject for a short time, I wish to speak of another which is rather closely allied to it and upon which we have also made some observations. There is a certain amount of evidence drawn from blood cultures made at the time of death, from the bac-

teriological examinations at autopsies, and from experiments upon animals, that during the last few hours of life the bacteria which are present in certain organs, more especially the bowel, are able to overcome the weakened powers of resistance of the individual and to get into the blood stream, and are distributed by means of the circulation to the various organs, and may grow in these organs after death. This process, which is termed "agonal invasion," naturally has no influence on the course of disease in the individual, it being a result rather than a cause of disease, but it has a very important bearing on the value and significance of positive bacteriological findings at autopsy. If an "agonal invasion" of bacteria is a frequent occurrence, it is very evident that the bacterial contents of organs at autopsy do not represent the conditions present during life; that cultures alone are not sufficient to put the organism found in causal relation with the pathological changes present, and that our conclusions as to the causes of disease from post-mortem bacteriological findings must be much restricted. To throw light on this subject of agonal invasion we have made blood cultures before and after death in our chronic cases, and in a series of miscellaneous fatal cases, and post-mortem cultures in some cases of septicaemia and meningitis already referred to. We will give a brief summary of the more important literature before speaking of our own results.

The first observations of the general invasion of internal organs of the body by the colon bacillus were made by Welch (59) and reported in 1890. He reports that this organism was found in 33 autopsies out of about 200 at the Johns Hopkins Hospital, with especial frequency in cases with lesions of the intestinal mucosa. He regards it as in most instances a harmless invader without influence upon the course of the disease and without pathogenic effects. Many observers have since noted the frequency of occurrence of the colon bacillus in organs at autopsy. Intestinal bacteria have been sometimes reported as present in the blood very shortly after death. Beco (3) in studying the bodies of patients who had died of chronic disease found the colon bacillus present immediately after death in the liver in 11 cases and in the heart in one case; also the colon bacillus and *Staphylococcus pyogenes aureus* together in the liver in 3 cases. Létienne (36) found the colon bacillus in

the gall-bladder 11 times in 48 cases, in 3 cases 45 minutes after death. Achard and Phulpin (1) obtained blood from the veins and liver during the death agony, and also made cultures at autopsy in 43 chronic cases. In no cases were bacteria found in the blood before death, in 8 cases bacteria were found in the liver from 10 minutes to 10 hours ante mortem (*B. coli* 6 cases, *Staph. pyog. aureus* and *Staph. pyog. alb.*, each one case). In 24 cases no bacteria were found before death, but *Staph. pyog. aur.*, colon bacillus and putrefactive bacteria were found in the organs at autopsy. In 11 cases no bacteria were found either before death or at autopsy. They conclude that agonal invasion occurs, but is rather rare and that the intestine is the chief source of the germs. Hanot (27) in a case of jaundice, obtained a culture of colon bacilli from the liver during life.

Wurtz and Herman (61) froze small animals to death and obtained cultures of intestinal germs from the organs during the death agony in 21 out of 33 cases, while control animals rapidly killed remained sterile. Other animals poisoned with arsenic or killed by asphyxiation gave similar positive results. Beco killed rabbits slowly by poisoning with tartar emetic and cantharides and found intestinal germs present in the organs immediately after death in most of the cases, while animals rapidly killed remained sterile. His method of culture by means of bouillon tubes is objectionable. Chvostek and Egger (13), repeating Wurtz and Herman's work, froze 13 animals and obtained positive results in 30 per cent of the cases, while control animals were all negative. Later they froze 50 animals, and examination of the heart's blood immediately after death gave 44 per cent of positive results. Another series of animals frozen and similarly examined two hours after death gave 16 per cent of positive results. He explains this lower result by saying that the germs which invaded the blood were partly killed off by the serum on standing two hours. Starved animals gave negative results. Animals which were stabbed gave 20 per cent positive results, which can hardly be due to agonal invasion and are not explained. In all these experiments the peritoneum contained more bacteria than the blood.

Chvostek (12), in reviewing his own work and that of Wurtz and Herman, Beco, Achard and Phulpin, and others, concludes that bacterial invasion of the body during the death agony occurs frequently, that what has been considered post-mortem invasion is really the result of agonal invasion and post-mortem growth. At the end of life the vigorous germs, usually the pyogenic cocci which can overcome live cells, invade the body first, then the weaker ones which can overcome damaged cells,

and last the putrefactive germs. The more cachectic the individual the more easily agonal invasion occurs. The anatomically unaltered vessel walls have been shown to be permeable for bacteria, and Chvostek believes there may be a procession of bacteria into the blood, some being killed off while others are steadily invading the circulation. He believes that bacteriological findings at autopsy are not a safe ground for conclusion about the conditions which were present in life.

On the other hand, while admitting that intestinal germs may reach certain abdominal organs during the last hours of life, there is a good deal of evidence against the frequent occurrence of an agonal invasion and general distribution of bacteria over the body by means of the circulation. Sterile organs at autopsy are a very common occurrence in all sorts of non-infectious diseases, and even in infectious cases apart from the specific foci. Lesage and Macaigne (35) examining cadavers in winter found many of them sterile. Austerlitz and Landsteiner (2) and Beco remark upon the infrequency of finding the colon bacillus in fresh cadavers. On examining the results of Achard and Phulpin, we see that in the 8 chronic cases in which agonal invasion was believed to have occurred, the heart's blood was found sterile in all as late as 2 to 23 hours after death. In 24 other cases where the heart's blood was examined from 2 to 16 hours after death, only 2 positive results were obtained, both 10 hours and later after death.

Hauser, by injecting cultures of bacteria into the dead bodies of men and animals immediately after death, has shown that a rapid and widespread invasion of the body can occur in the period of time which intervenes ordinarily between death and autopsy. In his experiments the spread of bacteria was dependent partly on the position of the cadaver; if the animal was hung up by the hind legs, the liver, pleura and heart gave positive results, and if hung up by the fore legs, the bacteria were found in the liver, kidney and bladder. In experiments upon human cadavers, the pleura, liver, kidney and bladder were invaded after intraperitoneal injection of germs, and the pericardium and heart usually remained sterile. In a large number of autopsies performed 10 to 24 hours post mortem, he found the colon bacillus present in nearly half. Positive results were much more abundant in warm than in cold weather. He believes they are due largely to post-mortem invasion of the body.

With reference to the entrance of bacteria from the intestine into the blood, the statement of Nocard that the chyle acts as a vehicle for germs has been disproved by Neisser and Kühnau. They found the chyle and mesenteric glands of large animals uniformly sterile. Wyssokowitsch

found that in dogs and rabbits, when large numbers of *Staphylococcus pyogenes aureus* had been brought into the gut, either by the mouth or by direct injection, the mesenteric glands on later examination were found sterile in the great majority of cases; in a few cases in which contamination could not be excluded, a few bacteria were found. Heubner has shown that there are no bacteria in the wall of the gut in infants with intestinal disease. Ribbert (50) and Bizzozero (6) found bacteria in the intestinal wall only in the follicles of the cæcum of rabbits and in no other animals. Austerlitz and Landsteiner repeated Wurtz's and Chvostek's experiments with improved technique and different results. Fifty mice were killed by freezing and 250 cultures of the heart's blood were all sterile. Negative results were also obtained in animals slowly poisoned by arsenic. Max Neisser fed rabbits, mice and guinea-pigs freely with pyogenic cocci and typhoid bacilli, after damaging the intestine with a previous diet of broken glass and sodium fluoride: in 21 of the animals the organs were sterile at autopsy, in some others positive results were obtained which he thinks may be explained by unavoidable contaminations. In an investigation where so much depends on the technique of the removal of organs and culture-making, and the dangers of infection by manipulation are so great, negative results are more valuable than positive ones. It is evident that highly pathogenic bacteria may be present in the gut without producing general infection, and that even severe damage to the gut is not in itself sufficient to open a way for them into the circulation. Neisser concludes that there is hardly a greater danger of general infection from the bowel than from the skin or from other mucosæ.

Our own observations upon terminal and agonal infections cover 37 cases of severe chronic disease (11 cardiac disease, 9 cancer, 4 sarcoma, 3 phthisis, 3 chronic nephritis, 1 Pott's disease and nephritis, 1 arterio-sclerosis, 1 tubercular meningitis, 1 tubercular peritonitis, 1 gastric ulcer, 1 chronic rheumatism, 1 pernicious anæmia), of which 30 died in the hospital and 19 were autopsied; also 10 miscellaneous fatal cases, 5 of which were autopsied. We also include 7 cases of sepsis and 5 of cerebro-spinal meningitis, already referred to, which were negative in life, and in which post-mortem cultures were made. 79 blood cultures were made in all; 41 in the late stages of disease, and 38 one-half hour after death.

We give a brief description of the 9 cases in which blood cultures gave positive results:

Case VIII.—Chronic parenchymatous nephritis. Duration of symptoms one year, uræmia, death. Blood culture one day before death, 30 to 50 colonies of Streptoc. pyog. per cc.; one-half hour after death, 100 to 150 Streptoc. pyog. per cc. Autopsy, 17 hours after death, showed parenchymatous nephritis, anasarca, passive congestion of lungs, liver and spleen, bronchopneumonia. Cultures from heart, liver, spleen and kidney showed Streptoc. pyog.

Case IX.—Chronic parenchymatous nephritis. Duration 2 years. Temperature 96° to 97° for a week before death, abdominal pain one day. Blood cultures 2 days before death, 70 to 90 Streptoc. pyog. per cc.; one-half hour after death, 300 to 500 Streptoc. pyog. Autopsy, 15 hours after death, showed parenchymatous nephritis, anasarca, syphilitic hepatitis and orchitis, degeneration of spleen, liver and kidney, acute general peritonitis and acute pleuritis. Cultures from heart, spleen, liver, kidney, pleura and peritoneum showed Streptoc. pyog.

Case X.—Pott's disease, chronic nephritis. Duration of Pott's disease 5 years, of nephritis 1 year; exacerbation of nephritis, persistent vomiting, death. Temperature 101° for 2 days before death. Blood culture 4 days before death, 10 to 15 Streptococ. pyog. per cc.; one-half hour after death, 10 to 15 Streptococ. pyog. per cc. Autopsy, 6 hours after death, showed chronic diffuse nephritis, tuberculosis of lumbar vertebræ and lungs, tubercular salpingitis, amyloid liver, spleen and kidney. Cultures from heart, liver, spleen and kidney showed Streptococ. pyog.

Case XI.—Gastric ulcer. Gastric pain 2 months, hæmatemesis, bloody stools for 6 days, death. Temperature 102° last 12 hours. Blood culture $1\frac{1}{2}$ days before death, 6 to 10 Staphylococ. pyog. aureus per cc.; $\frac{1}{2}$ hour after death, 15 to 20 Staphylococ. pyog. aureus. No autopsy.

Case XII.—Myocarditis, pericarditis. Pericarditis with effusion 11 days, temperature 100° to 102° ; death. Blood cultures 4 days before death, 5 to 8 Staphylococ. pyog. aureus per cc. Autopsy, 27 hours after death, showed fatty myocarditis, fluid in cavities, passive congestion of organs, subacute fibrinopurulent pericarditis. Cultures from liver, kidney, spleen and pericardium showed Staphylococ. pyog. aureus.

Case XIII.—Mitral and aortic stenosis. Duration of symptoms 11 months, temperature 100° to 102° for 2 days before death. Blood culture 4 days before death, negative; $\frac{1}{2}$ hour after death, 5 to 6 Staphyloc. pyog. aureus per cc. Autopsy, 17 hours after death, showed mitral and aortic stenosis, chronic passive congestion of organs, acute bronchopneu-

monia. Cultures from liver and kidney showed Staph. pyog. aureus; from lung, Staph. pyog. aureus and pneumococcus; spleen sterile.

Case XIV.—Mitral regurgitation. Duration of symptoms 6 months, death sudden, no fever or complications. Blood cultures 3 days before death, negative; $\frac{1}{2}$ hour after death, 10 to 12 Staph. pyog. aureus per cc. No autopsy.

Case XV.—Cancer of epiglottis. Duration 1 year; laryngectomy, sudden death 10 hours later. Blood cultures 2 days before death, negative; $\frac{3}{4}$ of an hour after death, 10 to 20 Streptoc. pyog. per cc. No autopsy.

Case XVI.—Compound depressed fracture of skull. Operation, death after 6 hours. Blood culture $\frac{1}{2}$ hour after death, 20 Streptoc. pyog. per cc.

In the accompanying table we have classified the total number of cases examined, the number of positive results, the time the earliest positive cultures were obtained, and the number and kinds of bacteria found.

In 5 cases of chronic disease, bacteria were found in the blood one or more days before death, as follows:

2 cases of chronic nephritis,	Streptoc. pyog.,
1 case of Pott's disease and chronic nephritis,	Streptoc. pyog.,
1 case of gastric ulcer,	Staph. pyog. aureus,
1 case of myocarditis and pericarditis.	Staph. pyog. aureus.

These are considered cases of general terminal infection. In each of these 5 patients the invasion of the blood as shown by our cultures was followed in a few days by death. Degenerative changes were usually present in the organs at autopsy, but in no instance pyæmic foci. The sources of infection could not be absolutely determined. In one case a tubercular process in the lungs antedated general infection; in another a fibrino-purulent pericarditis. In one case a broncho-pneumonia was present, in another an acute peritonitis and pleuritis, but these are looked upon as part of the general infections. The clinical aspects of these cases were not remarkable; in three there was a moderate febrile reaction a few days before death, and in one for a period of eleven days; in another the temperature was subnormal for a week before death. There was grave constitutional disturbance

in each case, but any symptoms which may have occurred as a result of general infection were obscured by those which resulted from the chronic processes. In short, these cases of terminal septicæmia could hardly have been recognized clinically without blood cultures.

I.—POSITIVE BLOOD CULTURES DURING LIFE.

Disease.	Number of positive results.	Time of earliest positive culture.	Bacteria found.	Number of bacteria per cc. of blood.	Number of cases investigated
Septicæmia	4	(Days before death.)			18
Case 1		4 days.	Streptoc. pyog.	40 to 60	
" 2.....		3 "	Staph. pyog. aureus	11 to 15	
" 3.....		2 "	Streptoc. pyog.	50 to 1500	
" 4.....		2 "	" "	15 to 20,000	
Pneumonia	3				19
Case 5.....		1 day.	Pneumococcus.	40 to 60	
" 6.....		2 days.	" "	18 to 30	
" 7.....		2 "	" "	10 to 15	
C.-S. Meningitis	0				8
Chronic Nephritis ...	2				
Case 8.....		1 day.	Streptoc. pyog.	30 to 150	
" 9.....		2 days.	" "	70 to 500	
Chronic Nephritis } and Tuberculosis }	1				37
Case 10.....		4 days.	" "	10 to 15	(chronic cases).
Gastric Ulcer	1				
Case 11.....		1½ "	Staph. pyog. aureus	6 to 20	
Myocarditis and } Pericarditis }	1				
Case 12.....		4 "	" " "	5 to 8	
Miscellaneous cases..	0				10
	—				—
	12				92

II.—POSITIVE BLOOD CULTURES AFTER DEATH IN CASES WHERE THE BLOOD WAS NEGATIVE DURING LIFE.

Septicæmia	0	(Hours after death.)			7
C.-S. Meningitis.....	0				5
Mitral and Aortic } Disease }	1				
Case 13.....		½ hour.	Staph. pyog. aureus	5 to 6	16
Mitral Disease.....	1				(chronic cases).
Case 14.....		½ hour.	" " "	10 to 12	
Cancer of Epiglottis.	1				
Case 15.....		¾ hour.	Streptoc. pyog.	10 to 20	7
Comp. Fracture } of Skull }	1				(miscellaneous cases).
Case 16.....		½ hour.	" "	20	
	—				—
	4				35

In addition to the general infections in chronic cases, local infections have been frequently found at autopsy, such as broncho-pneumonia, pleuritis, nephritis, etc.; of these, broncho-pneumonia being far the most common.

With reference to the occurrence of general blood invasion during the death agony, cultures of the heart's blood were made in 35 cases where no general infection was found during life. The cultures were made as soon as possible after death, within half an hour in all but a few cases. These cases consist of 7 septicæmias, 5 cases of cerebro-spinal meningitis, 16 of chronic disease and 7 of miscellaneous acute diseases. We are struck by the fact that in these 35 cases, only 4 positive results were obtained; in 3 cases examination of the blood 2 to 4 days before death had given a negative result, and in the fourth case death occurred six hours after an accident in a healthy man.

1 case of mitral and aortic stenosis,	Staph. pyog. aureus,
1 case of mitral regurgitation,	Staph. pyog. aureus,
1 case of cancer of epiglottis,	Streptoc. pyog.
1 case of compound depressed fracture of the skull.	Streptoc. pyog.

These are considered cases of probable agonal infection. In chronic cases with grave cachexia, blood invasion seems a natural event; with reference to the case of fracture of the skull we quote Hauser, who says that severe disturbance of the nervous centres favors agonal invasion. We are satisfied that the large number of negative results represent the conditions which were actually present; that if any considerable number of bacteria have invaded the general circulation in the death agony, some would have been present in the heart's blood and have been found in the 5 cc. of blood aspirated and used for cultures.

Only two varieties of bacteria occurred, and these never in mixed infection. The colon bacillus was not present in a single culture. The number of bacteria was small—as a rule, 5 to 10 per cc. of the staphylococci, and 20 to 90 streptococci per cc. In 4 of the chronic cases positive cultures were obtained, both before and after death, and in 2 of these latter there was apparently a growth of bacteria in the blood, or an increased invasion of the blood; for the second cul-

ture showed the presence of a considerably larger number of bacteria than did the first. In case VIII, chronic nephritis, a blood culture a day before death showed 30 to 50 streptococci per cc.; a culture immediately after death, 100 to 150 per cc. In Case IX, chronic nephritis, a culture 2 days before death showed 70 to 90 streptococci, and a culture immediately after death, 300 to 500 per cc. In the two other cases the number of bacteria remained practically stationary. In a large majority of our chronic cases, the blood both before and immediately after death proved sterile.

In 5 of our nine positive cases an autopsy was performed and the same bacteria which were present in the blood cultures were found distributed through the organs, as would be expected.

In many of the cases where the blood was negative during life, bacteria, such as the colon bacillus, pneumococcus or pyogenic cocci, have been found in one or more organs at autopsy. Bearing in mind Hauser's proof of the rapidity of post-mortem extension of bacteria through the body, we believe that this is the explanation of their presence in most cases; on the other hand, some probably represent local infections in life, and some agonal infections. In a considerable number of the local infections the bacteria no doubt reached the infected organ by means of the blood stream, even in cases which gave negative blood cultures during life; probably a few bacteria gained entrance to the blood-vessels, were carried about and deposited in various organs, most of them being destroyed, while a few succeeded in gaining a footing and produced a local infectious process. In such cases we could hardly expect to obtain positive results in our blood cultures.

We have reached the conclusion that general agonal invasion by bacteria is a rather uncommon occurrence, from a consideration of the frequency of sterile organs at fresh autopsies, from the uniformly negative results obtained by Austerlitz and Landsteiner, and Neisser in animal experiment, and finally from the series of negative post-mortem cultures in our own cases. We cannot accept the theory that the normal or nearly normal bowel is easily and frequently penetrated by bacteria, or the application of this theory to post-mortem findings.

If autopsies are performed within a short time after death and the results of post-mortem growth of bacteria in the body thus avoided, we have every reason to believe that in the majority of cases the bacteriological findings at autopsy correspond to conditions present during life. We believe that the presence of the colon bacillus at autopsies is occasionally due to agonal invasion of the body and usually due to post-mortem outgrowth through the body from the intestine.

In addition to the use of blood cultures, certain evidence has been obtained by the author (60) from experiments with blood serum which I will briefly refer to here. It was thought that an explanation of general bacterial invasion of the body in chronic disease could be found in a loss or weakening of the germicidal properties of the blood, but the balance of evidence of previous work which was confirmed by a series of experiments by the author indicates that the blood serum, even in healthy individuals, is not appreciably germicidal for the pus organisms, which disposes of this theory so far as the pus organisms are concerned. On the other hand, it is well known that normal human serum is germicidal to the colon bacillus, and the author has found that the serum, as a rule, retained this property for this organism in cases of severe chronic disease up to the end of life, and in about half the cases examined, even for several hours after death. In only two cases in the series was there any evidence of loss of germicidal power before death. Now in this fact that the serum retained its germicidal properties in most cases until death and in many cases after it, we have a strong additional reason why agonal invasion of the blood by intestinal germs is not likely to occur in the majority of cases, even of severe chronic disease.

CONCLUSIONS.

Our conclusions from the literature and our own experiments may be summarized as follows:

- I. Blood for bacteriological examination during life should be taken directly from the veins and in considerable quantity.
- II. Resorption of toxines is the most important feature in cases

of sepsis; pyogenic bacteria invade the general circulation in a rather small proportion even of severe cases, and, as a rule, late in the course of the disease.

III. A general infection by the pneumococcus can be demonstrated occasionally in the late stages of acute lobar pneumonia.

IV. The value of blood cultures as a means of diagnosis in obscure cases of sepsis is limited by the fact that invasion of the blood by the specific organism cannot be demonstrated during life in the majority of cases. Positive cultures are very valuable; negative cultures do not exclude local septic infections.

V. The detection of specific bacteria in the blood of cases of sepsis and of pneumonia gives a very unfavorable prognosis in most cases.

VI. General terminal infections with pyogenic cocci occasionally occur as an immediate cause of death in chronic disease. Local infectious processes play this part more frequently.

VII. As far as our experiments have shown, invasion of the blood by bacteria during the death agony, with subsequent distribution of the germs to the organs by the circulation, is a rather uncommon occurrence.

VIII. Owing to the relative infrequency of agonal invasion, we believe that in the majority of cases where the autopsy is performed promptly after death, the bacteria which are found in the organs succeeded in reaching these organs previously to the death agony, and are associated with the course of the disease.

IX. The presence of bacteria in the organs of late autopsies is due in many cases to post-mortem extension from one organ to another, and in some cases to the post-mortem growth of small numbers of germs which were distributed to the organs by means of the circulation.

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