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BACTEREMIA: A CONSIDERATION OF SOME EXPERIMENTAL AND CLINICAL ASPECTS

INTRODUCTION

Invasion of the blood stream in the course of bacterial infection is a dramatic biological phenomenon, the clinical recognition of which has both diagnostic and prognostic significance. Despite the difficulties inherent in separating a single phase of the struggle between parasite and host from the complex process of the pathogenesis of infection, the peculiar clinical importance of bacteremia justifies its discussion as a general process, directing emphasis toward basic mechanisms rather than specific disease entities. It is the purpose of the present communication to review in detail some experimental studies of bacteremia as a basis for an understanding of its clinical significance.

THE ENTRY OF BACTERIA INTO THE BLOOD STREAM

A. *Intravascular Infection*

The simplest form of bacteremia is that which results from the multiplication of bacteria in an area of the body bathed by the circulating blood, an intravascular focus of infection. Obvious examples of this type of lesion are *bacterial endocarditis* and *infected patent ductus arteriosus* or *arteriovenous fistula.* In certain instances, a *mycotic aneurysm* may be an intravascular source of microörganisms. It should be recognized, of course, that these infections are actually not primary processes and that they are the results of previous bacterial invasion of the circulation.

One type of intravascular focus deserves further comment—a *septic* or *suppurative thrombophlebitis.* Infections due to certain types of bacteria or in certain anatomic locations may progress to actual infection of the walls of large veins with thrombosis, colonization of the clot by the invaders, and feeding of bacteria into the blood stream. Organisms likely to produce such infections are the beta-hemolytic streptococcus and members of the group of Gram negative, anaerobic, non-sporeforming bacilli referred to as *Bac-*

Received for publication January 20, 1954.

teroides. Bacteroides infections, which are being recognized with greater frequency,[20] are almost invariably characterized by invasion of veins,[60] especially in the regions of the throat and pelvis, the two commonest portals for this organism. Less frequently than in the days before chemotherapy and antibiotics became available, streptococcal endometritis is likely to produce pelvic thrombophlebitis; streptococcal infections of the throat are followed by septic thrombosis of the jugular vein and of the ear by lateral sinus thrombosis.[5, 77] Thrombosis of the angular vein is common in facial erysipelas. Complications of this type are by no means limited to infection by these two organisms; venous involvement may occur with staphylococcal infections also. The anatomic location of a lesion may be a determining factor, as in the case of cavernous sinus thrombosis complicating facial infection or the occurrence of pylephlebitis secondary to intra-abdominal suppuration in the area drained by the portal venous system. A danger in infections of this type is septic embolization. The small infarctions that result from emboli are a fertile breeding ground for bacteria and metastatic abscess formation is common.

Lastly, there are a few circumstances in which, experimentally at least, betahemolytic streptococci apparently enter the blood capillaries directly from the lung alveoli of dogs. Whether this occurs in human lung infections is not known and it was not found to follow instillation of other types of bacteria in dogs.[76]

B. *Extravascular Infection*

Although it is obvious that dissemination of bacteria into the blood stream may be accomplished easily from an intravascular focus of infection, the question of the entry of bacteria from an extravascular site is a more difficult one. The explanation usually offered by textbooks is a general statement to the effect that with severe infection and spread beyond local defenses there may be invasion of capillaries or lymphatics. There is, however, a body of evidence, much of it derived from the studies of investigators whose primary interest was not in the spread of infection, which permits a more precise statement of the probable route of entry of microörganisms into the circulating blood.

Rôle of the lymphatics. Certain characteristics of blood and lymph capillaries deserve emphasis. The typical blood capillary is a tube of endothelial cells connecting the arterial and venous circulations. Its continuous endothelial wall is permeable to crystalloids and smaller protein molecules. The capillary contains blood under pressure which, by appropriate means, can be raised to near arterial levels. The walls of lymphatic capillaries are

composed of very thin endothelial cells. The networks of lymphatic capillaries unite into larger trunks, acquire rudimentary muscle coats, and after interposition of one or more lymph nodes, unite with the venous circulation by way of the thoracic or right lymphatic ducts. In striking contrast to the pressure in blood capillaries, the normal lymph pressure is *zero;* it is well known to investigators who have cannulated the lymph trunks draining an extremity, for instance, that there is no detectable flow of lymph into the collecting vessel unless the extremity is manipulated by brief massage or muscle activity.[15] Lastly, and again differing from the blood capillaries, the endothelial walls of lymphatics are tightly bound to surrounding tissues by reticulum and collagen fibrils,[57] with the result that separation of tissue components by local edema and interstitial fluid accumulation actually holds them open and maintains their patency.

The movement of bacteria in the body has nothing to do with their intrinsic motility. Indeed, most pathogenic organisms are completely lacking in any power to propel themselves and are borne passively in the body fluids. Except for their power to multiply and certain special abilities, such as the elaboration of toxins, etc., they may be regarded as behaving in the body in much the same way as do inert particulate materials such as India ink or colloidal dyes. With caution, one may draw an analogy between certain experimental findings with particulate materials and the movement of bacteria.

There is no question that particulate matter passes through the uninjured walls of blood capillaries. The diapedesis of leukocytes and erythrocytes is familiar enough. Injected particles of India ink pass freely into the tissues from the blood stream.[15] Once a particle has passed out of a blood capillary, it rarely reënters. If one injects a suspension of dye particles into the skin, using a very fine needle and taking care to enter no blood capillary, the dye can be seen to diffuse rapidly into lymphatics.[39] Carbon particles injected intraperitoneally eventually appear in the circulating blood but they reach it by way of the diaphragmatic and mediastinal lymphatics.[9] In this instance, because of the constant rise and fall of the diaphragm, lymph flow is rapid and the particles are detectable in lymph channels within three minutes after injection.[9] Many different particulate materials have been observed to appear in lymph after intravenous injection[88] and such observations might seem to indicate an equal degree of permeability of blood capillaries and lymphatics. In a sense, this is the case, but from the point of view of clearing the tissues of extravascular foreign material, one faces a different set of circumstances. The large size of the lymphatics and the lack of a pressure difference between their contents and the tissues in which they

are found makes them open to the influence of motion or massage and causes them to be the pathways for removal of foreign materials.[15]

Thus far, we have discussed the situation as it obtains with uninjured capillaries and lymphatics. One might reasonably raise the objection that there might be injured or even ruptured blood and lymph channels at the site of a local bacterial lesion. McMaster and Hudack[40] have made observations which bear out the importance of lymphatic channels in removal of particulate materials from a site of injury. These investigators observed under the microscope the course of events after making small incisions or burns in the ear of the mouse. With such injuries, blood capillaries promptly contract, whereas the lymphatic channels remain widely patent for as long as 48 hours. Particulate dyes introduced into wounds were seen to be rapidly taken up through the "gaping ends" of the lymphatics; none entered the closed and sealed capillaries.

There is one other effect of inflammation upon lymphatic function which is noteworthy. With the development of edema, one of the fundamental events in the inflammatory response, there is striking rise in both tissue pressure and lymphatic pressure with consequent increase in lymph flow from the involved area. The classic experiment of Field, Drinker, and White[17] demonstrated that within 2½ hours after immersion of a dog's foot in boiling water, pressure in lymphatics draining the extremity rose from zero to more than twice the venous pressure.

So much for the way in which inanimate particles are cleared from the tissues and for the effects of edema and inflammation upon lymphatic function. What evidence is available from experimental investigations employing bacteria, the specific type of particle with which we are concerned? It will suffice to cite only three of numerous studies[88] which indicate the importance of the lymphatics as a portal of entry of bacteria into the blood stream from extravascular foci.

In 1937, Field and her associates[18] found that rabbits injected intravenously with virulent Type III pneumococci showed these organisms less than one hour later in leg, neck, and thoracic duct lymph. Pneumococci possess no motility of their own; to have reached the lymph, they must have crossed both vascular and lymphatic endothelium.

In 1938, Schulz, Warren, and Drinker[66] cannulated the thoracic duct in rabbits and instilled small amounts of cultures of Type III pneumococci into the trachea, inclining the animal so as to allow the fluid to run down into the alveoli. Organisms were frequently cultured from the lymph within an hour and *while eventually blood cultures often became positive, the lymph cultures were always positive first.*

The interesting researches of Barnes and Trueta[1] must be mentioned. These investigators pointed out that there was doubt in the minds of many workers that bacteria ever enter the blood capillaries directly. It might, however, be imagined that bacteria placed in freshly made wounds could enter the blood stream directly through the open ends of the divided blood vessels, although theoretically this is unlikely because blood is either flowing from them or they are occluded by clot. Using rabbits, Barnes and Trueta exposed the femoral blood vessels and dissected and ligated the lymphatics under a microscope. The muscle, skin and bone were then tied by mass ligation on either side of the femoral artery and vein, leaving the circulation intact as evidenced by active bleeding from freshly made wounds in the calf and by the fact that injection of strychnine into the front of the leg caused death in the afflicted animals as rapidly as in normal controls (strychnine is a drug known to be absorbed directly into the blood stream). Six such experimental animals and 6 controls were then given 0.3 cc. of a saline suspension of *Pseudomonas* bacilli into the skin of the ankle, into the knee-joint or into a deep, fresh wound in the calf muscles. The limb was passively flexed and extended for 30 seconds, and at 10 minutes and 1 hour, blood cultures were taken. With the exception of one experimental animal in which the ligatures slipped, no positive cultures were obtained in the operated group; all controls showed bacteremia. From this and similar experiments, it is clear that even from a recent wound into which an overwhelming number of bacteria has been poured, none are taken up by the freshly injured blood vessels; they appear in the circulation only when lymph drainage from the area is uninterrupted.

Before concluding that bacteria, like inert particles, travel from the tissues to the blood predominantly by the lymphatics, there are at least two possible objections to be met. The first of these is related to the rôle of what Menkin has called "lymphatic blockade" in the localization of bacteria at a site of inflammation.[47] There is no question about the fact that the inflammatory response exerts an influence in preventing the spread of invading pathogenic organisms. All the factors involved in this localization are still not fully understood. Menkin contends that the most important element in local defense is the formation of thrombi in the lymphatics; these thrombi can be demonstrated histologically at inflammatory sites although they are infrequent at the spreading edge of an infection. However, certain other findings and considerations effectively invalidate this as an argument against the spread of bacteria by lymph. First, instead of reduction, there is an increase in the flow of lymph from an inflamed area.[15] Second, Menkin himself has demonstrated that the lymph draining an area of inflammation

contains large numbers of polymorphonuclear leukocytes and, as Rich has pointed out,[61] this finding necessitates that those who uphold lymphatic thrombosis as being significant must argue that there is blockade in the region containing bacteria but none in the region where the leukocytes are located. Miles and Miles[48] believe that much of the "fixation" of various substances, such as dyes, at inflammatory sites is due to dilution by the accumulated exudate such that, despite increased lymphatic drainage, there appears to be retention of the foreign material. Lastly, the simple clinical observation of the frequent swelling and tenderness of regional lymph nodes with local infection argues against any complete lymphatic blockade.

A second possible objection is that lymph nodes filter bacteria and other noxious materials from the lymph stream. There has never been demonstrated a pathway for lymph from the peripheral tissues to the blood stream which avoids passage through at least one lymph node.[15] These nodes are extremely effective, although by no means perfect bacterial filters. Drinker *et al.*[14] observed the filtration efficiency of lymph nodes to be 99 per cent for streptococci but concluded that the protective action of a node may break down when the number of bacteria reaching a node is excessive, when the perfusion pressure of the lymph becomes too high, when the organism is unusually virulent, or when the node is subjected to massage. The protective rôle of the lymph nodes, therefore, does not offer an insuperable objection to a lymphatic route of spread, particularly if one considers recent studies by Smith and Wood[70, 71] who have shown that the filtering action of *normal* lymph nodes is inefficient in that the nodal sinuses possess relatively few cells capable of phagocytosis. However, during active infection, there is also infection of the node and, within a few hours, there occurs an explosive inflammatory response with outpouring of polymorphonuclear leukocytes into the sinuses. The node is thus transformed into a highly efficient filter. In the early stages of infection, there is good opportunity for the infected lymph stream to reach the blood.

It seems clear then, that the lymphatics play a primary rôle in the entry of bacteria from extravascular foci of infection into the blood stream and the production of bacteremia. Later, in discussing clinical aspects of bacteremia, there will be occasion to refer to some of the characteristics of lymphatic function.

Transport by polymorphonuclear leukocytes. The facts that many bacteria are engulfed by polymorphonuclear leukocytes at a local inflammatory site and that the filtering action of lymph nodes is in such large measure dependent upon phagocytosis by polymorphonuclear leukocytes led to consideration of another mechanism for entry of bacteria into the blood stream,

namely the reëntry directly into blood capillaries of leukocytes which have ingested organisms. Drinker has demonstrated the occurrence of this in the capillary circulation of lymph nodes.[15] Although most bacteria taken up by phagocytes are destroyed by intracellular digestion, as Topley and Wilson[88] put it, "the tacit assumption that a bacterium phagocytosed is, of necessity, a bacterium finally disposed of is certainly unwarranted." There is excellent evidence that phagocytosis protects some bacteria,[22, 65] and recent studies by Rogers and Tompsett[68] indicate that pathogenic staphylococci can survive ingestion by human leukocytes. Wilson[92] has shown that streptococci are often ingested and then egested by leukocytes, retaining ability to multiply.

FATE OF BACTERIA IN THE BLOOD STREAM

A. *Factors Influencing the Removal of Injected Bacteria*

The simplest method for experimental study of the fate of microörganisms which enter the circulation is the injection of bacteria directly into the blood stream of an experimental animal. Shortly after a single intravenous injection of viable bacteria, the blood culture of an animal contains many colonies of the organism. When serial cultures are taken, the colony count is found to decrease precipitously and, with many bacterial species, the blood stream becomes sterile within a period of one to several hours. Numerous investigators, beginning with Wyssokowitsch in 1886,[88] have demonstrated this rapid removal of injected bacteria from the blood.[88] The factors which influence disappearance rate and completeness of removal have been studied extensively. Although there have been minor variations in the results obtained with different animals and bacteria, the operation of an efficient mechanism for clearing bacteria from the circulation is easily and consistently demonstrable.

The *virulence* of the injected bacteria is important. The extensive studies of pneumococcal infection by Wright[97] included observations of the number of pneumococci in blood cultures of rabbits at intervals after intravenous injection of an avirulent, a moderately virulent, or a highly virulent strain of this organism. The avirulent strain was rapidly and completely removed from the blood, all cultures being sterile after five hours. Injection of moderately virulent pneumococci was followed by a tremendous fall (99%) in colony count during the first five hours. This initial decrease in the number of organisms which could be cultured from the circulating blood was followed by a transient rise at 24 hours, presumably due to the ability of this strain to multiply in the host's tissues and to reinvade the blood. The circu-

lation, however, finally became bacteria-free and remained so. Virulent pneumococci were also cleared rapidly from the blood stream during the first five hours after injection, but the bacterial count promptly returned to high levels as this strain began to multiply and to invade, and all animals died with sustained bacteremia. These examples from the experiments of Wright are representative of the pattern of events observed by many other investigators.[88] The number of microörganisms in the circulation at a given time is a balance between multiplication, invasion, and the clearing mechanism. Evidence that the ability to remove bacteria is retained even in fatal infections is the fact that injection of an excess of organisms into the blood stream of an animal dying with an infection due to the same bacteria is followed by removal of the injected microbes at a normal rate. This has been demonstrated by several investigators with different bacteria.[6, 27, 59]

Before specific mechanisms of bacterial clearing are described, certain factors which modify the disappearance rate after a single injection of a suspension of organisms may be mentioned. The disappearance of injected bacteria, pathogenic or non-pathogenic, is accelerated in the presence of *specific antibody,* whether present by active or by passive immunization.[11, 73, 74, 87] The injection of virulent bacteria into the immune animal results in a disappearance curve resembling that for avirulent bacteria in the normal animal. Furthermore, Wright found that prior contact with the organism resulted in enhanced clearing of the blood stream in animals before specific antibody became demonstrable.[87]

The production of *severe leukopenia* (by benzol injection) does not influence the rabbit's ability to remove injected pneumococci from the blood.[87] Injection of India ink or lithium carmine particles in attempts to *blockade the "reticulo-endothelial" cells* did not influence removal rate of pneumococci in Wright's experiments. These experiments have never been repeated using Thorotrast, a potent blocking agent for the fixed macrophages.

One of the striking effects of cortisone and ACTH upon experimental bacterial infections has been the tremendous increase in mortality in animals given these hormones and the presence of high levels of bacteremia in these animals.[29] Germuth, Ottinger, and Oyama[24] have demonstrated, however, that the increased bacteremia in cortisone-treated rabbits infected with pneumococci is probably not the result of any interference with the clearing mechanism but rather represents some enhancement of multiplication of organisms or their entry into the circulation. The reasons for the increased mortality from infection in animals pretreated with adrenal steroids are far from clear.[29]

Recent studies by Stavitsky[72] have shown that the production of an anaphylactic reaction impairs the ability of rabbits to clear the blood of injected dysentery bacilli.

Where do bacteria go when they leave the circulation? Briefly, on the basis of numerous cultural and histological studies, it can be said that the majority of bacteria cleared from the blood after a single intravenous injection can be found in the liver, the spleen, and, in certain instances, the lung.[11, 53, 73, 74]

B. *Rôle of the "Reticulo-endothelial System" (RES) in Removal of Bacteria from the Blood*

It is well known that particles of India ink, various dyes, and colloidal metals are not excreted after injection but are deposited in various organs where they are stored in macrophages which have a characteristic distribution throughout the body. These fixed phagocytes, the Kupffer cells of the liver, the lining cells of the splenic sinusoids and sinuses of lymph-nodes, and the histiocytes of the bone-marrow, possess the common characteristic of storing dyes and particulate matter and probably constitute an integrated, functional system. It is in the macrophages of the RES in the liver and spleen that most bacteria removed from the blood after a single injection are found.[11, 41, 53, 73, 74] Organisms occasionally cultured from the lung are apparently trapped and ingested by polymorphonuclear cells in the alveolar capillaries.[73, 97] The rôle of the lung in clearing the blood stream as well as the part played by polymorphonuclear leukocytes will be discussed in a later section.

The importance of certain tissues in maintaining the balance between multiplication of bacteria in the tissues, invasion of the blood stream, and the operation of a clearing mechanism in human bacteremia was demonstrated by the investigations of Beeson, Warren, and Brannon[4] in patients with bacterial endocarditis. The experiments involved multiple simultaneous cultures of arterial and venous blood. Arterial samples were collected from the femoral artery and venous samples were collected from several sites by means of an intravenous catheter, including right atrium, renal vein, and hepatic vein. It was noted first that the bacterial count in arterial blood in this disease remained remarkably stable over periods of a few hours. (This is in accord with findings of previous workers who obtained cultures every few hours for several days.[80]) A significant reduction in the number of organisms in pooled central venous blood from the right atrium as compared with arterial counts was consistently demonstrable. No evidence was found of removal of bacteria from blood circulating through the extremities

or kidney, but as blood passed through the liver, a dramatic reduction in bacterial count occurred. Hepatic venous blood always contained many fewer colonies than arterial or other venous samples. Two conclusions can be drawn from these experiments. First, in bacterial endocarditis, the bacteremia was shown to be maintained at a relatively constant level, eliminating the idea that bacterial invasion of the blood stream in this disease consists only of irregular spurts and showers of organisms as tiny bits of valvular vegetations break off—there is a *steady* feeding of organisms into the blood. Second, the operation of a clearing mechanism through the liver in human bacteremia was demonstrated, furnishing a firm basis for drawing conclusions from animal experiments pointing to a rôle of the RES.

Using a modification in animals of the catheterization technique, Martin, Kerby, and Holland have conducted an extensive series of studies of the removal mechanism in rabbits and dogs. Because the hepatic veins drain not only the liver, but also the spleen and a portion of the gut, these workers prefer the term "splanchnic" removal of organisms. Essentially, their technique has been to obtain simultaneous arterial and hepatic venous cultures for comparison of colony counts.[45] Bacteremia is maintained by a constant intravenous infusion of organisms, thus more nearly duplicating the situation in most clinical infections than does a single injection of a bacterial suspension. The findings of these investigators may be summarized as follows:

(a) For a given organism there is a remarkably constant per cent removal rate.[33] This allows accurate comparison of results in normal animals with those in animals subjected to various types of treatment or manipulation.

(b) Removal rate varies with the species of organism studied. Staphylococci are rapidly removed, encapsulated Friedlander's bacilli less rapidly, and virulent pneumococci slowly.[33] Non-mucoid Friedlander's bacilli are removed more rapidly than the encapsulated variant of the same species.[32]

(c) Specific antibody enhances splanchnic removal of bacteria.[33]

(d) Whole body x-ray irradiation or radiation localized to the liver and spleen exerts no effect upon the clearance rate in the splanchnic area.[10]

(e) Animals made granulocytopenic by nitrogen mustard show normal splanchnic clearance of infused bacteria.[34]

(f) The prior injection of Thorotrast, a colloid which localizes in the cells of the RES (so-called "blockade"), depresses the rate of splanchnic clearance.[46]

(g) The splanchnic clearance rate is uninfluenced by large doses of ACTH or cortisone.[44] This finding, with those of Germuth, Ottinger, and

Oyama[24] mentioned earlier, indicates that the enhancement of infection by adrenal steroids is due to some effect upon the infection in the extravascular tissues.

(h) In the course of fatal pneumococcal bacteremia in rabbits, the increased number of bacteria which appear in the circulating blood is not due to any overwhelming of the splanchnic clearing mechanism but is a result of increased multiplication and invasion by the organisms. If staphylococci are infused intravenously into an animal dying with pneumococcal bacteremia, the staphylococci are removed in the splanchnic area at a normal rate.[43]

These studies confirm the ability of the RES to remove bacteria from the blood and demonstrate that its function is extremely stable. However, all of the observations were limited to the splanchnic clearing mechanism and the effect of such procedures as injection of Thorotrast, etc. upon the total ability of the blood to remove bacteria after a single intravenous injection is not known. It is conceivable that other mechanisms of bacterial removal might enable clearance to continue at a normal pace despite depression of the splanchnic removal by a "blocking" agent.[86, 87] Indeed, the studies of Narita[51] suggested that this may be the case although he used India ink rather than the more effective Thorotrast to produce blockade of the fixed macrophages.

The removal of bacteria by the RES is easily demonstrated and has been studied extensively. That it is of importance in infection can hardly be questioned. Other factors, however, may be of equal importance in bacterial removal although our knowledge of these other mechanisms is still incomplete.

C. *Rôle of the Polymorphonuclear Leukocyte in Clearing the Blood Stream*

Although most of the bacteria removed from the circulation after intravenous injection are found in the liver or spleen, the lung is regularly found to contain an appreciable number of organisms. Histologically,[33, 87] many of these are found to be ingested by polymorphonuclear leukocytes within the alveolar capillaries. Several workers have described phagocytosis of bacteria by granulocytes in the capillaries of other organs also.[75] Subsequently, many of these cells are probably transported to the phagocytes of the RES where final disposition takes place. Wood, on the basis of further studies of intravascular phagocytosis, has suggested that the ingestion of bacteria in the circulating blood serves as an important defense of the host in acute bacteremia.[86] Observations were made on the intravascular reaction to injection of pneumococci or Friedlander's bacilli by employing the rabbit ear-

chamber. Following injection of the bacterial suspension, the polymorphonuclear leukocytes were seen to stick to the endothelium of capillaries and to become motile, migrating freely about the endothelial surfaces. Within 15 minutes, ingestion of bacteria by these cells began to occur by the mechanism which Wood has called "surface phagocytosis," a process which is possible in the absense of specific antibody or "opsonin."[85] The relative importance of the RES and the polymorphonuclear leukocyte in removing bacteria from the blood cannot be evaluated on the basis of the evidence now available. Although destruction of leukocytes by benzol[87] or nitrogen mustard[84] does not alter clearance rates, the effect of RE blockade upon total clearance is not known. Wood has suggested that the peripheral leukocytes and the macrophages of the RES supplement one another in clearing the blood of bacteria and that impaired function of one system is quickly compensated by the other mechanism.[86] Further experimental observations will be needed to clarify this relationship. The observations of Gregg and Robertson[25] on dogs with bacteremia due to the pneumococcus suggest strongly that intravascular phagocytosis by polymorphonuclear leukocytes is of great importance in clearing pneumococci from the blood stream in this animal.

The finding of Stavitsky,[72] mentioned earlier, that mild anaphylaxis results in prolongation of the time required for clearing of injected dysentery bacilli from the blood of rabbits is of interest in connection with the possible rôle of polymorphonuclear cells in bacterial removal. Among other changes which accompany anaphylactic shock, severe neutropenia is regularly present.

Despite the gaps in our knowledge concerning the exact mechanisms and the relative importance of clearing of bacteria from the blood by the cells of the RES and peripheral polymorphonuclear leukocytes, it is clear that in most instances the blood stream is endowed with powerful antibacterial defenses. The poor prognostic significance of bacteremia in the course of infections is not due to multiplication of bacteria in the blood stream, but is important because it reflects the failure of localization of infection at the extravascular site with subsequent spread and invasion of the blood. Illustrative of the great ability of the blood to resist infection as compared to other tissues of the body are many experiments such as those of Lange and Gutdeutsch who showed that it is far more difficult to establish fatal infections in mice by injecting pneumococci or streptococci intravenously than when the intraperitoneal or subcutaneous route is used.[88]

In summary then, we may conclude that there is a normal, efficient clearing mechanism for bacteria which enter the blood stream, and that this mechanism is in part a function of the fixed macrophages of the RES

and also of the circulating leukocytes. Specific antibody enhances bacterial removal and other agents may depress it. The level of bacteremia in any given infection represents a balance between bacterial multiplication, invasion of the blood stream, and the activity of the clearing mechanism.

SOME CLINICAL CONSIDERATIONS

A. *Types of Bacteremia*

Clinically, bacteremias are of two types, *continuous* and *intermittent.* Continuous bacteremia is always a sign of serious infection.[31, 54] Bacterial endocarditis has been mentioned already. Bacteria are constantly present in the blood during the first week of typhoid fever, and brucellosis may be accompanied by bacteremia which persists for several weeks.

In contrast to these severe, continuous bacteremias are those of the intermittent variety. Transient bacteremia probably occurs in nearly all patients with pneumococcal pneumonia at the beginning of the disease, hence the typical onset with shaking chill. In most cases, this spill-over of organisms from the lung is promptly dealt with by the clearing mechanism as the infection in the lung localizes. However, 20 to 30 per cent of patients with pneumonia are bacteremic when hospitalized.[18] As is well known, the later in the course of pneumonia that organisms can be grown from the patient's blood, the more guarded is prognosis.[18] The presence of organisms in the blood is simply an excellent indication that there is spreading infection in the lung.

There are many types of transient bacteremia which are of little consequence. Most of these are the result of a sudden shower of organisms into the blood stream. Clearing is usually rapid and the episode is often unaccompanied by characteristic chill and fever. In the majority of instances, these transient bacteremias follow manipulation of infected or contaminated tissues.

Instrumentation of the genito-urinary tract, even so simple as the insertion of a urethral sound, may be followed by chill and transient fever.[2, 55] Failure to obtain positive blood cultures at the time of the chill led for many years to the belief that some peculiar property of the urinary tract was responsible for so-called "catheter fever." However, when the lag-period between bacteremia and chill is allowed for, and blood is drawn immediately after instrumentation, in a large number of cases organisms can be cultured.[2]

Schottmüller[67] observed large numbers of bacteria, as many as 1,000 per cc., in the circulation immediately after *uterine curettage* for septic abortion. The blood was invariably sterile 15 minutes later. Büngeler[7] described

hematogenous dissemination of tuberculosis after curettage for tuberculous endometritis. Bacteremia has been observed to accompany the pelvic turmoil of normal labor; and Kulka, who took blood cultures at regular intervals in a number of normal women, found frequent, asymptomatic bacteremias during their menstrual periods.[86]

Several types of operative procedure may be accompanied by bacteremia. As examples from numerous studies, Elliott[16] found 38 positive cultures among 100 patients bled within five minutes after *tonsillectomy.* All were negative at 15 minutes. Similarly, Fischer and Gottdenker[19] found 21 positive blood cultures among 64 patients immediately after tonsillectomy. Likewise, *dental manipulations* often lead to spill-over of organisms into the circulation.[8, 52, 64] Positive blood cultures have been obtained after extraction of teeth and even after such a procedure as simply chewing paraffin for 30 minutes.[50] Careful studies indicate that the incidence of bacteremia following intraoral procedures is more closely related to the degree of trauma than to actual intensity of oral sepsis.[88] Seifert[80] cultured bacteria from the blood 10 minutes *after incision of an abscess* in 45% of his patients. Richards[62] obtained positive blood cultures in 15% of 376 patients after simple massage of infected foci such as furuncles. Lastly, the study of Reith and Squires[58] should be mentioned. These workers took blood for culture at random intervals over a period of months from 293 subjects of whom 278 were males. They obtained one or more positive cultures in 65 of these normal individuals and observed that positive cultures were far more frequent during months of the year when upper respiratory infections were common.

The relationship of many of these transient bacteremias to massage or manipulation is strongly reminiscent of the procedures used experimentally to stimulate the flow of lymph. Their significance, of course, lies in the important relationship they are now known to bear to the pathogenesis of bacterial endocarditis in patients with residual valvular damage. Tonsillectomy, dental procedures, normal labor, and genito-urinary instrumentation are now widely recognized predisposing causes for endocarditis. Fortunately, premedication with penicillin will largely (although not entirely) prevent these bacteremias[26] and in patients with known valvular heart disease it should certainly be used. Because of the type of organism likely to be encountered in the genito-urinary tract, aureomycin or some similar drug is probably preferable.

B. *Blood Cultures*

Can we draw any conclusions about taking blood cultures for diagnosis? In the patient with intermittent chills blood for culture should be obtained

during the hour preceding the expected chill or spike in temperature.[23, 35, 80] This is important because there is a lag period of about one hour between the time of the sudden influx of bacteria and the onset of the rigor, and the blood is often sterile by the time fever begins. In patients with suspected endocarditis, rather than many cultures in one day, a few cultures daily for several days is the proper schedule. It is striking to note that blood cultures in this disease are usually *all* positive or *all* negative—rarely does one see an isolated positive culture in this disease. It is not meant to imply that the taking of many cultures at frequent intervals is not indicated in febrile patients in whom the diagnosis is obscure. In many cases of chronic meningococcemia, for example, the organism can be obtained only after many cultures have been made.

The question occasionally arises of obtaining *arterial blood* for culture when ordinary venous blood cultures are negative. Although it has been stated, without adequate demonstration, that this procedure may offer diagnostic advantages,[49] the balance of experimental and clinical evidence indicates that there is no removal of bacteria in the circulation of the extremities. Consequently, blood from the antecubital vein is as likely to contain organisms as blood from the brachial or femoral arteries.[4, 80]

In certain infections, culture of the bone marrow may give superior results.[5] This is particularly true in typhoid after the first week of the disease and in histoplasmosis; occasionally it is helpful in brucellosis. The superiority of marrow culture in these diseases probably lies in the fact that these organisms survive for long periods of time in macrophages, and in the marrow one taps a richer source of these cells than in the peripheral blood.

In rare instances, direct observation of a stained smear of peripheral blood or the buffy coat[28] may reveal organisms. Meningococcemia, in which enormous numbers of bacteria may be present, is the commonest disease in which this procedure is helpful. It is estimated that when organisms can be seen on direct smear, the colony count is at least 100,000 per cc. The tremendous number of meningococci which may be present in the peripheral blood raises the possibility that in this infection, actual multiplication of organisms in the blood stream may occur, although this has not been established. Of course, in histoplasmosis or relapsing fever, the causative organism may be first found in the peripheral blood smear.

What is the significance of colony counts in clinical blood cultures? It is obvious that invasion of the blood stream by bacteria is per se a benign event as compared to invasion of other tissues such as the peritoneum. Unless the colony count rises to several thousand per cc., few conclusions

can be drawn other than the general conclusions already discussed—10 or 200 pneumococci per cc. of blood have the same meaning. It is of interest that the actual number of typhoid bacilli present in the blood, for instance, is rarely more than 30 per cc. and is usually less than 10.

C. *"Treatment" of Bacteremia*

Contrary to statements advocating the immediate administration of penicillin or some other antibiotic *intravenously* if bacteremia is present, therapy should be directed at the primary focus of disease.[81] As we have seen, of all tissues which display defensive powers, the blood stands at the top. Suppose we are told that there are 500 colonies of pneumococci per cc. of blood? Consider the millions of organisms present in a single cubic centimeter of the infected lung and direct therapy to the real source of trouble.

D. *Bacteremia and Hemolysis*

It is often stated that hemolytic streptococcal infection accompanied by bacteremia results in severe anemia due to hemolysis. This is not the case as should be obvious from the lack of signs of rapid blood destruction such as jaundice or hemoglobinuria. Although some severe staphylococcal or salmonella infections are accompanied by icterus, the bilirubinemia is a result of toxic hepatitis rather than hemolytic action. Bacteremias due to *Clostridium welchii,* however, are characterized by rapidly developing icterus, hemoglobinuria, and severe anemia; the development of such a picture should raise the possibility of this infection.

E. *Bacteremia and Lumbar Puncture*

A question which commonly arises relates to the possibility of producing meningitis by performing lumbar puncture upon a patient with bacteremia. Although under very special experimental conditions in animals this is possible,[78,79] there is no evidence that it is of clinical importance[56] and it should not deter us from spinal fluid examination when this is indicated.

F. *Bacteremia and Specific Antibodies*

With the exception of brucellosis, the demonstration of specific antibody against an organism at a time when that bacterium is cultured from the blood is pathognomonic of endocarditis (or some more unusual intravascular forms). As an example, the demonstration of the Quellung reaction with a patient's serum against pneumococci cultured from his blood means

endocarditis. However, the antibodies must be shown to be present when the culture is *drawn,* not when it is reported positive a few days later.

G. *Negative Blood Cultures*

Negative blood cultures are often as much of a problem to the clinician as positive findings. In many patients with bacterial endocarditis, there is little doubt that the number of bacteria entering the blood stream may be so small and so easily dealt with by the clearing mechanisms that positive cultures are not obtained.[80] Such patients may die, ample evidence of the relative unimportance of bacteremia itself as compared to the original focus of infection in the heart valve. In 1908, Dr. Emanuel Libman[87] pointed out that there are a number of bacterial infections in which it is unusual to find positive blood cultures. Among those listed were liver abscess, cholecystitis, appendicitis, peritonitis, and pylephlebitis. The striking thing in common among these is the fact that all are located within an area drained by the portal venous system. It seems possible that any overflow is promptly cleared by the RES of the liver before reaching the systemic circulation. In the case of pylephlebitis, organisms enter the portal blood directly. However, the probability is that any entry of organisms into the blood from the others is via the lymphatics and other factors are responsible for the infrequency of positive blood cultures.

H. *Bacteremia in Cirrhosis*

In some patients with Laennec's cirrhosis, there occur spontaneous bouts of bacteremia due to organisms which normally inhabit the intestine, usually the colon bacillus.[81] One possibility offered to explain this occurrence is that there is normally some passage of intestinal organisms into the portal circulation and that the normal liver promptly removes these bacteria from the blood. In the cirrhotic, however, if this be the case, there are two possible explanations for failure of a normal clearing mechanism. The first is that there is some impairment of function of the RES as well as the parenchymal cells in cirrhosis. A second alternative is that with the occurrence of portal hypertension and the development of shunts (such as esophageal varices) around the liver, blood containing bacteria simply fails to pass through this organ and bacteremia occurs. The comprehensive study of Sborov *et al.*[66] may help with the question of possible escape of intestinal bacteria to the liver in man. Although it is well known that this occurs in dogs,[12, 42, 84] Sborov, who cultured portal venous blood and biopsy specimens from more than 60 patients, found only one positive culture; interestingly, this patient

had cirrhosis of the liver. Therefore, while it seems unlikely that the normal liver is called on to filter out intestinal flora in human subjects, it is within the realm of possibility that there is some leakage of organisms into the portal vein from the gut in patients with cirrhosis and that these bacteria escape the normal clearing mechanism in some way. The failure of Sborov to find bacteria in portal venous blood is in accord with the probability that the entry of most organisms into the blood stream is indirect by way of the lymphatics rather than directly into the circulation.

I. *Bacteremia and Diphtheroids*

Lastly, there may be mentioned the possible significance of finding organisms usually regarded as contaminants in blood cultures, the so-called diphtheroids. It has been reported by Fleisher[21] that a very high percentage of blood cultures containing diphtheroids are found to come from patients with malignant lymphoma and other chronic febrile disorders. Fleisher does not postulate a causal relationship, rather he simply suggests that diphtheroids in a blood culture should bring to mind these diagnostic possibilities. We have studied a case in which diphtheroids were cultured repeatedly from blood and bone marrow of a patient found at autopsy to have periarteritis nodosa. Further observations are needed regarding the significance of this kind of bacteremia.

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