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Recovery of Uncommon Bacteria from Blood: Association with Neoplastic Disease

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INTRODUCTION

The recovery of an unusual organism from blood typically captures the interest of microbiologist and clinician alike. A positive blood culture may indicate contamination of skin flora from the venipuncture site at the time the blood culture was obtained, a transient bacteremia due to entrance of microorganisms through superficial abrasions of the mucous membrane as may occur during brushing of the teeth or during a hard bowel movement, or a serious disseminated infection with risk of morbidity and mortality. Recovery of any microorganism from blood requires that a careful clinical correlation of signs and symptoms suggestive of bacteremia be made to properly assess the significance of the finding. When an uncommon isolate is obtained in this setting, the presence of underlying disease, with special attention toward possible neoplastic disease, should be considered as well.

Laboratory isolations of rare bacteria have catalyzed the initiation of studies to determine the pathogenetic significance of the event and the possible associations of these microorganisms with underlying disease, especially cancer. The purpose of this paper is to review the evidence that the recovery of certain bacterial species from blood cultures indicates the presence of an underlying, occult, or undiagnosed neoplasm (20) or is associated with certain types of neoplastic disease.

Numerous studies have shown that individuals afflicted with neoplastic disease have higher rates of infection, especially bacteremias (20, 172–174, 275, 276, 321). Among the microorganisms commonly recovered from the blood of cancer patients are the following: *Escherichia coli* (27, 28), *Klebsiella pneumoniae* (28), *Pseudomonas aeruginosa* (29, 82), *Staphylococcus aureus*, *Streptococcus pneumoniae* (104), *Streptococcus pyogenes* (141), *Bacteroides* spp. (101, 277), and *Candida albicans*. On balance, we recognize that these microorganisms are often recovered from blood of patients with other diseases and underlying conditions. The increased incidence of polymicrobic bacteremias among cancer patients is also well documented (30, 142, 255). Proven bacteremia in cancer patients generally indicates impairment of one or more host defenses: breaks in integumentary and mucosal barriers, compromised phagocytic defenses, and defects in cellular and humoral immunity related to an affected mononuclear phagocyte system (MPS) (234). In certain cases, the recovery of a rare microorganism has been linked to a singular pathogenetic mechanism, while for some of the many other organisms considered in this review, their means of agency will necessarily be speculative.

As suggested by Keusch (169), there are two ways to assess the possible association between neoplasia and bacteremia caused by a particular microorganism: study a series of bacteremias and determine the nature of underlying disease or study a series of cancer patients and measure the frequency of bac-

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teremia caused by the organism of interest. Both of these approaches can provide support for an association.

In addition, some studies have compared the frequency of bacteremias due to various bacterial species in general hospitals with that in a cancer hospital. Various reports have shown that the rate of recovery of unusual bacteria from cancer patients, while apparently greater than in individuals free of neoplastic disease, is much lower than the rate of recovery of common bacteria, such as *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *S. aureus*. The value of comparison of rates of recovery of bacteria from blood from different types of hospitals is also confounded by the lack of longitudinal information on patients from general hospitals, that is, the number of general hospital patients who are eventually diagnosed as cancer patients.

Many authors have described isolation of unusual bacteria from blood which resulted in diagnostic investigations revealing the presence of an undetected neoplasm. Often the report of a single case history has stimulated the reports of similar observations such that a picture of association emerges.

POSSIBLE MECHANISMS FOR THE ASSOCIATION BETWEEN BACTEREMIA AND CANCER

The recovery of bacteria from blood cultures may reflect compromises in host defenses at several levels. Therefore, bacteremia in patients with cancer may have as much to do with alterations in underlying conditions of the host as with the neoplasm itself. Bacteremia in patients with cancer may reflect alterations in local conditions at the site of the neoplasm, allowing bacteria to proliferate and gain entry into the bloodstream. The bactericidal action of plasma and the phagocytic and intracellular killing properties of circulating neutrophils and monocytes, and/or of the macrophages within the MPS, may be compromised. Maderazo et al. (195) describe a circulating inhibitor to chemotaxis and phagocytosis of polymorphonuclear leukocytes in patients with solid tumors. The phagocytic dysfunction was related to the finding that organisms did not attach to the membranes of the polymorphonuclear leukocytes due to a compromise in the activities of the Fc fragment of opsonin and the complement component C3b. These authors also found diminished oxidative metabolism and defective killing of bacteria by phagocytes two times more commonly in patients with solid tumors. Advanced age, malnutrition, and weight loss were other factors predisposing patients with solid tumors to bacteremia. Similarly, Phair et al. (231) found that polymorphonuclear leukocyte dysfunction was more common in older bacteremic patients with and without cancer. In in vitro experiments, they found that the polymorphonuclear leukocyte abnormality in these patients appeared to be cellular and manifested by poor uptake of *S. aureus* cells used as challenge organisms in this assay. Pizzo and Young (234) also cite impaired phagocytic defenses and MPS functions along with integumentary and mucosal barrier breaks and compromised humoral immunity as major factors predisposing cancer patients to bacteremia. It is these and other factors that will be discussed here in an attempt to better explain the association between bacteremia and neoplasia.

Local Conditions at the Site of Neoplasm Predisposing to Bacteremia

Several factors by which microorganisms may find entry into the circulation may be at play at the site of a neoplasm. A cancer that extends into the surrounding tissues causes a barrier break through mucosal and epithelial surfaces. Inflammation and focal necrosis in the alimentary tract are documented features of a variety of cancers. Intestinal lesions, including those of the colonic mucosa, are frequently observed in surveys of pathology of patients with leukemias (84, 184, 306). Prolla and Kirsner showed that lesions can be demonstrated in the esophagus, stomach, small intestine, and colon (237). There is ample evidence for barrier breaks in cancer patients and especially in those undergoing cancer chemotherapy.

Bretzke et al. (42) and Schaaf et al. (262) found a high correlation between *Clostridium septicum* bacteremia and carcinoma of the colon, with the majority of the patients in the latter study having breaks in the bowel mucosa. They cite an autopsy study of 21 patients with *C. septicum* bacteremia, 17 of whom had bowel lesions with associated ulcerations. At the microfocal level, disruption of capillary channels by either tumor or other ulcerative processes causes microfoci of bleeding where bacteria gain access to the bloodstream. Bacterial entry at the tumor site is further assisted by the local action of cytokines and other chemical mediators that promote vasodilatation and increased capillary permeability. This disruption of the microcirculation may also result in eddies and turbulence in blood flow, leading to the deposition of fibrin and platelets, providing shelter for bacterial growth (90).

Even if a barrier break occurs, factors promoting local bacterial proliferation in numbers sufficient to cause bacteremia must also be in effect. The obstruction of conduits and ducts, such as bronchioles, the ureter, the gastrointestinal tract, branches of the biliary tree, and secretory ductules of exocrine glands, lying adjacent to expanding tumors may result in pooling of fluids and secretions, providing a favorable environment for proliferation of endogenous flora (174). Potentially, local cellulitis and/or suppurative abscesses may develop, providing an additional source for microorganisms to enter the circulation. The relief from the inhibitory effects of the normal flora may indirectly promote the growth of certain bacterial species at the sites of infection. For example, prolonged antibiotic therapy may diminish the normal flora to such an extent that antibiotic-resistant strains may be selected out and proliferate sufficiently at local sites to cause infection, including the possibility of bacteremia if access to the circulation is also provided. Such is the case with bacteremias caused by both community- and hospital-acquired antibiotic-resistant strains of *Corynebacterium jeikeium* (group JK corynebacterium) (73) and *Enterococcus* species (133), to mention only two.

Tumor necrosis also provides a microenvironment conducive to the proliferation of bacteria, particularly anaerobes. Specifically, Bretzke et al. (42) cite tumor necrosis as producing zones of low oxygen tension and acid accumulation that are conducive to the germination of *C. septicum* spores. In two previous studies, one by Malmgren and Flanigan (196) and the other by Thiele et al. (296), the spores of nonpathogenic strains of *Clostridium* species were found to preferentially germinate in the micro- and macronecrotic areas of tumors. This phenomenon was explored experimentally as a therapeutic measure for cancer treatment (95).

In the study by Malmgren and Flanigan, *Clostridium tetani* spores, known to be nonpathogenic for normal tissues, were administered systemically and found to preferentially localize in the necrotic areas of tumors. They cite the previous finding of Warburg (313) that anaerobic glycolysis in tumor tissues leads to the accumulation of lactic acid and the work of Younger and Algire (329) demonstrating alterations in the vascular system as showing prime factors leading to colonization in tumors. Thiele and colleagues (296) reasoned that it is probably not any special property of the tumor tissue per se that leads to localization and germination of the clostridial spores used in these experimental models but rather the poor

vascularization and the presence of necrotic areas in the tumor. Other mechanisms may also allow bacteria to proliferate at the tumor site and reach numbers sufficient to cause bacteremia. For example, Friedrich et al. (108) discussed the increase in fecal carriage of *Streptococcus bovis* in patients with colorectal cancer by physical or biochemical factors that remain largely unidentified. Similarly, Bretzke et al. (42) found the tumor milieu to be an excellent environment for the vegetative growth of *C. septicum*. They cite their experience that spores of nonpathogenic *Clostridium* species, which have no effect on normal tissue, will localize and grow well in malignant tissue, resulting in extensive lysis. Kudsk (181) also found that *C. septicum* organisms seem to cluster within the substance of the tumor itself, citing the aerotolerant nature of the organism and undetermined elements of the tumor environment that seem to make this site conducive to bacterial colonization and proliferation.

Friedrich et al. (108) also mention that the accumulation of hemoglobin and iron at the site of the tumor, either from local hemorrhage or from the production of iron chelators by the tumor, may promote the growth of several species of hemophilic bacteria. For example, *Vibrio vulnificus*, *Listeria monocytogenes*, and *Yersinia enterocolitica*, in particular, proliferate rapidly in the presence of iron (32). However, Maskell and Miles (199) point out that iron accumulation in the tissues may promote the growth of only a small proportion of bacterial species, and they question the extent to which this mechanism affects those microorganisms commonly associated with infections in hospitals.

The role of iron overload secondary to other causes in promoting the overgrowth of microorganisms in the bowel remains in question. *Y. enterocolitica* and *Yersinia pseudotuberculosis* bacteremia have been found in patients with iron overload undergoing hemodialysis (32), particularly in those patients being treated with the iron-chelating agent desferroxime (39, 167). Enhanced growth of these and other bacterial species has also been observed in patients with iron overload secondary to hemochromatosis (46, 214). Also, patients incurring accidental overdosages of supplemental iron therapy may accumulate iron in the bowel (208). Fakir (97) attributed the enhanced proliferation of *Y. enterocolitica* and other bacterial species in the bowel directly to the rise in intraintestinal pH and the increase in intraluminal iron load in these patients. Thus, rapidly proliferating bacteria at these focal sites of tumor-induced hemorrhage or focal iron overload induced by other means may enter the bloodstream in large numbers if the invading tumor has also caused a mucosal break or ulceration, potentially leading to bacteremia.

Zarkin et al. (331) propose that liver disease may be yet another factor leading to the overgrowth of bacteria in the bowel, particularly of *S. bovis*. They found that 50% of patients with *S. bovis* bacteremia and carcinoma of the colon also had underlying liver disease, including cirrhosis, extrahepatic obstruction, fatty infiltration, and congestion. These authors further suggest that portal hypertension may also be responsible for the portal-systemic shunting of blood, providing a direct route of entry for microorganisms. In addition to portal hypertension, they further postulate that an increase in hepatic secretion of bile salts may promote the translocation of bacteria from the bowel to the portal system.

Intravascular Factors Affecting Bacteremia

If bacterial cells should enter the bloodstream from passage through a defective integument or mucous membrane, several mechanisms are in place in the normal host to quickly eliminate these intruders. In a textbook chapter covering this subject, Durack (90) cites circulating blood itself as inhospitable to the survival of bacteria. Described are various factors circulating in the plasma that have antibacterial activities: opsonins, substances that enhance the ability of phagocytes to ingest microorganisms; lysozyme, an enzyme that specifically cleaves bacterial cell murein at its sugar backbone, killing mostly gram-positive bacteria; and bactericidins and certain cleavage products of serum complement, particularly C3b, which covalently bond to the surface of bacteria, provide anchor sites for phagocytes, and are immediately active to thwart any intruding microorganism.

However, defects in the numbers and activity of circulating phagocytes may permit microorganisms to proliferate in the circulation (238). For example, it is known that patients with low peripheral leukocyte counts are prone to infection (275); however, compromised cellular immunity may play a more subtle role than that stemming from a reduced leukocyte count (122). Goldblum and Reed (122) describe a scenario in which microorganisms that enter the bloodstream may encounter phagocytes that not only are reduced in number but are present with subnormal locomotion, diminished phagocytic activity, and defective intracellular killing. These deficiencies may be subtle, particularly during stages of marrow myeloid dysplasia, when unsuspected bacteremia may serve as an initial marker for incipient acute leukemia. As previously mentioned, Maderazo et al. (195) have demonstrated circulating inhibitors of chemotaxis and phagocytosis of polymorphonuclear leukocytes that show low activity in normal patients but are markedly increased in patients with solid tumors. Additionally, Virelizer (307) suggests that defective leukocytes may be unable to produce normal levels of interferon after stimulation with soluble antigens or allogeneic lymphoblastoid cells, resulting in a special type of immunodeficiency. Shurin et al. (271) demonstrated defects in the neutrophils obtained from two patients with a history of dental infections. The defects were caused by the production of a potent factor produced by *Capnocytophaga* species recovered from the mouths of these patients. They demonstrated that this *Capnocytophaga* factor disrupted neutrophil chemotaxis in experimental glass slide models by affecting the locomotion mechanism. The affected neutrophils failed to adhere to the coverslips but assumed a flattened state and extended multiple pseudopods in all directions, simulating the activity of macrophages. These authors did not observe this phenomenon with any other bacterial species tested and thought that the factor was specific to *Capnocytophaga* species.

Kilian reported that some strains of *Capnocytophaga ochraceus* are capable of hydrolytically degrading immunoglobulin A subclass 1. This property may enhance colonization and invasion of oral lesions which characterize many bacteremias due to *Capnocytophaga* spp. (171).

Role of Humoral Immunity in Bacteremia

Patients with early cancer may manifest deficiencies of the lymphoid cells as well, leading to depressed cell-mediated immunity. Lymphopenia, shortened lymphocyte survival, inhibition of lymphocyte transformation, and suppressor T-cell activity may also be seen early in cases of hematologic and mononuclear phagocyte malignancies (90, 103, 122). Impaired antibody production may be seen early in cases of multiple myeloma, in which the presence of encapsulated organisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *K. pneumoniae* may serve as a marker for that disease. Recently, Neuzil et al. (217) reported a patient with erythrocyte aplasia and malignant thymoma who suffered a relapse of

Campylobacter fetus subsp. *fetus* bacteremia after 7 years. They showed that this patient lacked opsonizing antibody necessary to clear the organism from the bloodstream.

Decline in lymphoid function is part of aging, leading to immune senescence and predisposing elderly individuals not only to the development of neoplasms but also to an increased risk of infections, including bacteremia (103, 222). Failure of the hepatic MPS to clear the portal circulation of circulating microorganisms may play a causative role in the triad of *S. bovis* bacteremia, colorectal cancer, and liver disease discussed before (331). Kaye et al. (166) suggest that disturbances in the MPS caused by hemolysis and erythrophagocytosis may be responsible for the specific inability to clear bacteria in cases of *Salmonella* bacteremia. Wolfe et al. (323) also indicate that the defects in cellular immunity described by Kaye et al. (166) leading to bacteremia with certain strains of *Salmonella* species may also pertain to bacteremias caused by other intracellular parasites, including *L. monocytogenes*, *Brucella* species, *Mycobacterium* species, and *Histoplasma capsulatum*. In the case of *Salmonella* bacteremias, a predisposing event is hemolysis, which is postulated to result in the blockade of the entire MPS (323). Cherubin et al. (59) also indicate that *Salmonella* bacteremia in patients with Hodgkin's disease may be caused by a defect in the delayed hypersensitivity response.

Role of Complementary Surface Receptors in Bacteremia

The notion that receptors on the surface of proliferating tumor cells may react with complementary receptors on bacteria, providing yet another nidus for proliferation, is another possibility. The avid relationship between *S. bovis* bacteremia and carcinoma of the colon suggests that such receptors may be involved. The most convincing evidence has been provided by Kaplan et al. (165), who have demonstrated a serum antibody against a common *S. bovis* antigen in patients with endocarditis. In fact, common antibody was found in all patients with *S. bovis* bacteremia but not in patients with other forms of gram-positive bacteremia or endocarditis. This finding suggests that detection of this antibody may provide a marker for *S. bovis* endocarditis. These authors further suggest that common (c) antigen may be an important antigen of *S. bovis* and may in fact define this organism serologically. The authors conclude, "Perhaps some of these antigens are factors in attachment of the infective organism to both valvular and colonic tissue."

In experimental animal models, *S. bovis* cells have also shown avid adherence to buccal epithelial cells (309). The mechanism of adherence was found by these workers to involve lipoteichoic acid and other protein-mediated substances. However, there is no evidence that such a mechanism is involved in the association of *S. bovis* and malignant cells in human cases of carcinoma of the colon. Tangentially, Dubrow et al. (87) have made the observation that there is little if any association between fecal carriage of *S. bovis* and colon adenomas; however, Moshkowitz et al. (212) have reported a case in which the diagnosis of *S. bovis* endocarditis was the presenting manifestation of idiopathic ulcerative colitis.

Malnutrition as a Predisposing Factor for Bacteremia

One other factor underlying the increased susceptibility of patients with hidden cancer to infection and bacteremia is the overall nutritional status of the patients. The common symptom of weight loss as an early indicator of malignancy reflects negative nitrogen balance and protein depletion. Phair et al. (231) found bacteremia to be three times more frequent in patients who had experienced weight loss than in those who had not. Malnutrition is associated with an increased susceptibility to infection by altering host defense mechanisms. For example, in an experimental animal study, normal rats challenged with *E. coli* in a hemoglobin adjuvant developed peritonitis and had a 66% survival rate as opposed to a 15% survival rate in protein-depleted rats (230). Death was typically due to *E. coli* sepsis. In the same study, protein-depleted rats fed regular diets had a 60% survival, comparable to normal controls. Thus, the authors conclude that protein depletion is associated with loss of host defense mechanisms, which may first be detected by increased incidence of sepsis. Deitch et al. (79), working with protein-malnourished mice, cite the combination of protein malnutrition and endotoxin production, along with the mechanical damage to the gut mucosal barrier, as being responsible for what they call the translocation of bacteria from the gut into mesenteric lymph nodes. They conclude from their experiments that the gut serves as an important portal of entry of bacteria.

As part of overall nutritional deficiency, the potential role that certain heavy metals may have on the incidence of infections in patients who are heavy-metal deficient is intriguing. Several trace elements have been shown to regulate immune responses, particularly cell-mediated immunity (57). Chandra (57) cited evidence that zinc deficiency is associated with lymphoid atrophy and reduced capacity to respond to many T-cell-dependent antigens. In animal experiments it was found that the generation of cytotoxic lymphocytes in the spleen is reduced in zinc-deficient rodents. Chandra also describes a slight decrease in the number of rosette-forming T cells and significant impairment of lymphocyte response to mitogens and antigens in patients with iron deficiency. Effective killing of ingested bacteria may also be compromised in iron-deficient patients.

Copper deficiency also leads to impaired cell-mediated immunity. Heese et al. (139) found that copper levels were significantly lower in patients with bacteremia. These patients, in turn, tended to have more severe disease, a higher incidence of shock and manifestations of disseminated intravascular coagulation, and fatal outcomes. Selenium deficiency also is associated with impaired cell-mediated immunity, particularly when paired with low levels of vitamin E (57).

Organism Factors in Bacteremia

Microorganisms have developed mechanisms for further evading host resistance. Examples include elaboration of capsules that prevent phagocytosis, production of compounds that consume complement, synthesis of proteases that split and inactivate surface-bound antibodies, and development of resistance to the action of other intracellular host-protective events such as the oxidative burst, the release of lysosomal enzymes that occurs with phagosome formation (90). Although in the normal host these defense mechanisms may be sufficiently intact to prevent bacterial proliferation, any slight impairment in patients with known or hidden neoplasms may tip the scales in favor of the bacteria.

In summary, to what extent any of the above factors may predispose a patient with hidden or occult malignancy to develop bacteremia must be evaluated on an individual basis. In a study of 271 febrile cancer patients who experienced 652 episodes of bacteremia, Kramer et al. (180) found that the results derived from daily surveillance blood cultures often were helpful in influencing therapy and outcome. However, the issue of how to interpret positive blood cultures in patients with fever of unknown origin, and the clues one might use to consider when bacteremia may serve as a marker for a hidden malignancy, is not adequately addressed in the medical litera-

ture. Following are descriptions of the association of unusual microorganisms which, when recovered from the blood of patients experiencing febrile episodes in the absence of predisposing causes and lack of obvious underlying disease, may suggest the possibility of hidden malignancy. Whether or not to draw blood cultures when one or more of the other associated conditions of barrier breaks, defective cell-mediated and humoral immunity, and/or nutritional deficiency are discovered remains open to conjecture.

Many authors have described the isolation of unusual bacteria from blood which resulted in diagnostic investigations revealing the presence of an undetected neoplasm. Often the report of a single case history has stimulated the reports of similar observations such that a picture of association emerges. Although the increased incidence of fungal, especially yeast, infection is an acknowledged phenomenon among hospitalized cancer patients, we will consider only bacteria and mycobacteria in this review.

AEROMONAS AND *PLESIOMONAS* SPP.

In 1966, Bulger and Sherris (45) reported the isolation of *Aeromonas hydrophila* from the blood of a patient with lymphoblastic leukemia. The following year, Dean and Post (78) reported a fatal *A. hydrophila* infection in a patient with acute myelogenous leukemia. Until this time, *Aeromonas* spp. were generally regarded as aquatic microorganisms that parasitized fish, amphibians, and reptiles. Human infections caused by this genus were reviewed by von Graevenitz and Mensch (308) in 1968. They described the findings for 30 cases of human infection and a review of the literature, demonstrating an association of *Aeromonas* spp. and *Plesiomonas shigelloides* with diarrheal disease, cellulitis, and bacteremia. Their study and the review of the literature identified seven patients with blood cultures positive for *A. hydrophila*. Of the seven, two were the leukemia patients previously cited (45, 78) and three had Laennec's cirrhosis (66, 175). One of the cirrhosis patients also had esophageal carcinoma (66). Evidence that showed the association of *A. hydrophila* with gastroenteritis (160, 183, 258) continued to be reported. It was also shown that the organism can cause a wide variety of infections, including superficial wounds, ocular infections, pneumonia, osteomyelitis, peritonitis, meningitis, endocarditis, cholecystitis, and gynecologic infections (162, 317). Most cases reported indicated the presence of underlying diseases or other immunocompromising factors, but the organism also was reported to cause infections, sometimes fatal, in immunocompetent individuals (145, 268, 278, 293). A series of case reports of *A. hydrophila* sepsis in patients with leukemia were reported subsequently (1, 116, 192, 281, 294, 317, 324, 330).

In 1973, a group at Memorial-Sloan Kettering Hospital reported on a series of nine patients with *A. hydrophila* sepsis (168). Of the nine patients, five had leukemia, three had carcinomas, and one had sarcoma. Intestinal lesions were documented for three patients, prompting these authors to suggest that the origin of the bacteremias was the gut.

In 1978, Davis et al. reviewed the literature and provided the accumulating testimony for the role of aeromonads as primary pathogens as well as opportunists (77). Summarizing the findings for 42 hospitalized cancer patients, they noted that of patients with aeromonas bacteremias, 40% had hematologic malignancies, 14% had solid tumors, and 17% had cirrhosis. Harris et al. (136) conducted a retrospective study of *Aeromonas* bacteremias that occurred in hospitalized patients at a cancer institute over a 13-year period. They identified 24 patients with *Aeromonas* bacteremia, of whom 6 (25%) had polymicrobial bacteremia in which *Aeromonas* species as well as other organisms were recovered. All but one of these patients had a malignancy, and strikingly, 88% had leukemia, including acute myelocytic, acute lymphocytic, and chronic myelocytic forms.

Although aeromonads are not commonly recovered from stool, many authors have postulated that the gastrointestinal tract is the source of *A. hydrophila* for bacteremia (308) and that access to the bloodstream stems from gut mucosal lesions that provide a portal of entry (168). Compromised phagocytic function in cirrhotics has been cited as a predisposing factor for cases of aeromonas bacteremia in which circulating organisms may not be effectively cleared from the bloodstream. In addition, it has been demonstrated that *A. hydrophila* resists the bactericidal activity of normal serum, much as does *P. aeruginosa* (168).

In a more recent review, Janda and Duffey (162) summarized recent studies (136, 161, 185, 232, 278) that showed that *Aeromonas* bacteremia is seen in males more often than in females (male/female ratio = 2.2) and is more often acquired in the community (61%) than in a hospital (39%). Overall mortality was 41%, and for the great majority of cases no event which triggered the bacteremic episode could be discerned. Nearly half of all patients (48%) exhibited an underlying hematologic disorder, usually leukemia.

One study (185) indicated the frequency of *Aeromonas* bacteremias to be 2.3% of all gram-negative bacteremias at a Taiwan hospital. This rate is probably considerably higher than observations made in U.S. hospitals. For example, *Aeromonas* organisms accounted for only 3 (0.4%) of the 675 gram-negative bacilli isolated from over 18,000 blood cultures performed on patients at the Columbia-Presbyterian Medical Center in 1972 to 1976 (91) and 3 (0.8%) of 364 gram-negative bacilli in a study of bacteremias by Singer et al. (276).

In most studies of *Aeromonas* bacteremias, the methods employed for the identification of the isolates recovered were not described in detail or the extent of identification was relegated to genus level. In the review by von Graevenitz and Mensch (308), 2 of 30 isolates are described as *Plesiomonas shigelloides*, neither of which was in involved in cases of underlying neoplastic disease. The report by Harris et al. (136) describes the use of the API 20E (Analytab Products, Plainview, N.Y.) for identification of blood culture isolates to the genus level only. Janda and Duffey (162) have delineated the evolution of *Aeromonas* taxonomy, which now includes *A. hydrophila*, *A. sobria*, and *A. caviae*, known to cause infections in humans; *A. salmonicida*, a fish pathogen; and *A. media*, a river water species. It is not possible to determine if some of the human cases reported in the bacteremia studies may have been caused by species other than the one most commonly recovered, *A. hydrophila.*

Isolated reports demonstrate that *P. shigelloides* bacteremias also occur in cancer patients. McCracken and Barkley (201) reported on 13 patients with *P. shigelloides* infections in a general hospital, 4 of whom had bacteremias. Of these four patients, two had cancer: one had a urinary tract carcinoma, and one had a blast cell leukemia. Curti et al. (72) reported a cause of fulminant sepsis due to *P. shigelloides* in a patient who, 5 years previously, had been cured of Hodgkin's disease. It is worthy of note that there have been many more reports of *P. shigelloides* bacteremias in normal adults (61, 62, 157, 201), infants (61, 62, 157, 201), sickle-cell disease patients (92, 204), and individuals with diagnosed alcoholic liver disease (77, 124, 155) than in cancer patients.

TABLE 1. Association of *Bacillus* bacteremia with neoplastic disease

Total no. of patients	Total no. of cancer patients	No. of cancer patients with associated neoplastic disease					Reference
		Leukemia	Lymphoma	Multiple myeloma	Carcinoma	Other	
38	7					7[a]	280
34	5		1	2	2		226
18	18	11	4		3		12
17	16	4	5			7	68
12	2	2					156
7	1	1					298
2	2	1				1	229
1	1		1				129
1	1	1					261
1	1	1					100
1	1				1		54
1	1				1		13
1	1	1					67
1	1	1					65
1	1		1				111
1	1				1		121
1	1	1					297
1	1	1					132
1	1	1					186
Total 140	63	26	12	2	8	15	

[a] Type of malignancy not specified.

BACILLUS SPP.

Bacillus species are among the most common contaminants of blood cultures. In the absence of mitigating clinical circumstances, the recovery of *Bacillus* species is typically regarded as lacking clinical significance. In 1958, Sathmary reported a case of *Bacillus subtilis* sepsis coupled with generalized aspergillosis in a patient with acute myeloblastic leukemia (261). Subsequent reviews by Farrar (98) and Pearson (226) showed that *Bacillus* species other than *B. anthracis* caused serious infections, often in trauma, postsurgical, and burn cases and with predisposing conditions that included alcoholism, diabetes, sickle-cell trait, and cancer. In a number of studies, evidence for the infections in cancer patients by previously regarded nonpathogenic *Bacillus* species accumulated. Pennington et al. (229) cited the association of severe neutropenia in two leukemia cases with *B. subtilis* bacteremia. Idhe and Armstrong (156) described a group of 12 cancer hospital patients with *Bacillus* infection. Ten of the patients were diagnosed with a variety of neoplasms, and in two of these patients with leukemia, blood cultures yielded isolates of *B. cereus* and *B. subtilis*. Banerjee et al. (12) described a series of 18 patients with 24 episodes of *Bacillus* bacteremia. Fifteen of the patients had either leukemia or lymphoma and three had breast cancer. Again, the occurrence of neutropenia (nine patients) was remarkable. Seven patients had a Hickman catheter in place, providing evidence for a barrier break as a portal of entry for the organism.

In a recent review, Drobniewski (86) summarized the spectrum of infections caused by *B. cereus* and related species. Neoplasia as well as intravenous drug use, hemodialysis, intravenous catheterization, and diabetes stand as significant risk factors for the patients considered. Mortality associated with disseminated *Bacillus* infections is high (68, 132, 156, 280). Table 1 summarizes *Bacillus* infections in cancer patients. There is a high association with leukemia and lymphoma. The most common species are *B. cereus* and *B. subtilis*. The majority of patients are previously diagnosed cancer patients in whom neutropenia is the most significant predisposing condition. The portal of entry frequently stems from the use of intravenous catheters (12, 68, 280). Pneumonia commonly occurs as a result of hematogenous dissemination of the organism (67, 86, 100, 156, 186, 297).

Table 1 summarizes the studies described and other case reports (12, 13, 54, 65, 67, 68, 86, 98, 100, 111, 121, 129, 132, 156, 186, 226, 229, 261, 280, 297, 298). Fully 45% of the infections reported were accompanied by underlying neoplastic disease. However, the majority of these patients had been hospitalized for treatment of diagnosed neoplasms and were frequently subjected to invasive procedures and the debilitating effects of cancer as well as therapeutic measures. These factors are probably responsible for the frequency of bacteremia due to *Bacillus* spp. among these patients. *Bacillus* species other than *B. anthracis* are weakly pathogenic and appear to require both a portal of entry and a compromised immune system for disease production. Table 2 shows that the predominant type of infection, other than bacteremia with septic complications, is pneumonia. This supports the thesis that inhalation of spores is a mode of transmission of this group to susceptible hosts. Table 2 also shows that *B. cereus* is the most commonly recovered organism in these infections, followed by *B. subtilis*. A wide variety of other species have also been identified in these cases.

CAMPYLOBACTER SPP.

The first human case of bacteremia due to an organism called "*Vibrio fetus*" was reported in 1947 (305). Although the organism had been demonstrated as a pathogen for animals, including cattle, sheep, goats, and swine (211, 228), a succession of human case reports appeared in the literature in the 1950s and 1960s (63, 153).

In 1964, Collins et al. (63) reported a case of protracted *V. fetus* bacteremia and meningitis in a 55-year-old man with chronic lymphatic leukemia. In 1970, Bokkenheuser (34) reported the clinical findings for 10 patients with *V. fetus* bacteremia, four of whom had cancer: two cases of chronic myelogenous leukemia, and one case each of hepatoma and lymphosarcoma. Bokken-

TABLE 2. Type of infection and species of *Bacillus*

Type of infection (no. of episodes)[a]			No. of isolates of:			Reference
Septicemia or bacteremia	Pneumonia	Other infections	*B. subtilis*	*B. cereus*	Other *Bacillus* spp.	
7					7	280
5					5	226
24	2	1	2	8	14[b,c]	12
17				6	11[d]	68
2	2		1	1		156
1					1	298
1	2		2			229
		1		1		129
1			1			261
1	1	1		1		100
1				1		54
1		1		1		13
1	1			1		67
		1		1		65
1		1		1		111
				1		121
	1			1		297
1				1		132
	1			1		186
Total 64	10	6	6	26	33	

[a] Multiple episodes and more than one type of infection occurred in some patients.
[b] Isolates represent 24 episodes of bacteremia.
[c] Includes *B. circulans* (three isolates), *B. pumilis* (two isolates), *B. licheniformis* (one isolate), *B. coagulans* (one isolate), *B. sphaericus* (one isolate), and unidentified *Bacillus* spp. (six isolates).
[d] Includes *B. pumilis* (two isolates), *B. licheniformis* (three isolates), *B. sphaericus* (one isolate), and unidentified *Bacillus* spp. (five isolates).

heuser also reviewed all published reports regarding infections due to this organism and showed that, besides cancer, infections occurred in the setting of underlying disease such as diabetes, alcoholism, and cardiovascular, renal, and gastrointestinal disorders and in pregnancy and infancy. Later taxonomic studies resulted in the reclassification of *V. fetus* as *Campylobacter fetus* subsp. *jejuni* and *C. fetus* subsp. *intestinalis*. Subsequently, these species were renamed *C. jejuni* and *C. fetus* subsp. *fetus*, respectively (282). *C. jejuni* is recognized as a common cause of gastroenteritis (24, 211, 248), while *C. fetus* subsp. *fetus* has demonstrated a predilection for disseminated disease with bacteremia (64, 106, 131). This distinction was pointed out by Guerrant et al., who described 5 cases and reviewed 91 cases in the literature (131). Patients with *C. fetus* subsp. *fetus* bacteremia tended to be male and have an underlying disease. One of the five cases described was a 65-year-old male with a poorly differentiated malignant tumor in the right flank. In 1980, Schmidt and coworkers (264) reported an additional five cases of extraintestinal *Campylobacter* infections and reviewed the burgeoning number of 247 reports of infections. Although their summary indicated that a predominance of patients had either sepsis or septicemic enteritis (54.7%) and underlying disease (52.6%), including cancer (11.7%), the subspecies were not identified. The information in these reviews does not allow determination of the epidemiologic profile for the various subspecies of *Campylobacter*. These distinguishing features began to be elucidated when studies that definitively identified the recovered subspecies were reported.

Francioli et al. (106) reported eight cases of *C. fetus* subsp. *fetus* bacteremia in 1985. Their patients included three with cancer: lymphoma with acquired agammaglobulinemia, adenocarcinoma with hepatic metastasis, and a preleukemia case. On balance, underlying disease was documented in four of the other five noncancer patients: alcoholism with (two cases) and without (one case) cirrhosis and one case of diffuse arteriosclerosis.

From these aforementioned reports and additional case reports (64, 248, 299, 326), a picture of *C. fetus* subsp. *fetus* as an invasive opportunist has emerged. A substantial proportion of patients with *C. fetus* subsp. *fetus* bacteremia have a cancer, either a solid tumor or a leukemia, and often a second condition that affects the liver. A diminished ability of the MPS cells of the liver to clear circulating *Campylobacter* cells once they have gained access to the blood may provide an explanation for the frequency of these bacteremias.

The portal of entry remains to be established, although the tendency for gastrointestinal infections by species of the genus *Campylobacter* is well documented (24, 228, 251).

CAPNOCYTOPHAGA SPP.

In a fashion similar to development of our understanding of disseminated disease due to *Campylobacter* spp., the taxonomy and the spectrum of infections caused by *Capnocytophaga* species have evolved over the past decade. Essential to understanding the characteristics of infection has been the gradual establishment of defined taxons. The group of organisms associated with periodontal disease and referred to as dysgonic fermenters, or the "gliding" bacteria, were and are very infrequent isolates in the clinical laboratory (288). An isolation from a blood culture is similarly rare. Throughout the 1980s, various investigators reported the isolation of *Capnocytophaga* species from the blood of patients with previously diagnosed neoplasia (6, 9, 102, 110, 119, 138, 146, 197, 216, 224, 235, 243, 316, 325).

The recovery of *Capnocytophaga* sp. known as dysgonic fermenter-1, or DF-1, was strongly associated with ulcerations of the oral mucosa (218). Entrance of the microorganisms into the circulation is believed to proceed from this site. In some reports, the organism is identified as *C. ochraceus* (119, 269), while in other reports it is merely identified to the genus level (137, 138, 243, 316).

Warren and Allen (315) reported on 13 patients with *Capnocytophaga* infections, seven of whom had bacteremia. All seven bacteremic patients had an underlying neoplastic disease: six with leukemia and one with rhabdomyosarcoma of the paranasal sinus. Six of the seven were granulocytopenic at the time of the *Capnocytophaga* bacteremia, and all seven patients exhibited a potential oral barrier break including oral mucosal lesions, gingivitis, stomatitis, esophagitis, or in the case of the rhabdomyosarcoma patient, surgery on the paranasal sinus and irradiation. These authors also pointed to the preponderance of patients less than 20 years of age in this series as well as others.

Parenti and Snydman (224) reported the largest study to date, 31 patients with *Capnocytophaga* infection. They found that bacteremia (three episodes) was a relatively uncommon event in the 16 nonimmunocompromised patients. However, of the 15 patients categorized as immunocompromised, all had at least one episode of bacteremia and some had as many as six. This group included six cases of acute nonlymphocytic leukemia, four cases of acute lymphocytic leukemia, and one case each of neuroblastoma, pancreatic carcinoma, and squamous cell carcinoma of the oronasopharynx and larynx. The remaining case was a renal transplant patient with disseminated cytomegalovirus infection. An oral lesion was present at the time

TABLE 3. *Capnocytophaga* bacteremias and neoplastic disease

Total no. of patients	No. of cancer patients	No. of cancer patients with associated neoplastic disease			Species	Reference
		Leukemia[a]	Lymphoma[b]	Other		
19	14	11 (AL)[c]		3[d]	*Capnocytophaga* sp.	224
7	5	4 (AML, 2;ALL,2)		1 (rhabdosarcoma)	*Capnocytophaga* sp.	315
6	5	5 (AML, 2;ALL,3)			*Capnocytophaga* spp.	105
2	2	1 (AML)	1 (LL)		*C. ochracea* and *Capnocytophaga* sp.	269
2	1	1 (ALL)			*C. ochracea*	138
1	1			1 (myeloid metaplasia)	*Capnocytophaga* sp.	137
1	1	1 (AML)			*Capnocytophaga* sp.	316
1	1			1 (multiple myeloma)	*Capnocytophaga* sp.	110
1	1	1 (ALL)			*C. ochracea*	119
1	1	1 (CML)			*Capnocytophaga* sp.	243
1	1		1 (HD)		*C. ochracea*	6
41	5	2 (CLL)	3 (HD)		DF-2	144
2	2	1 (CLL)		1 (heart valve myxoma)	DF-2	325
1	1	1 (CLL)			DF-2	102
1	1		1 (HD)		DF-2	146
1	1		1 (HD)		DF-2	197
1	1	1 (HCL)			*C. canimorsus*	216
1	1			1 (T-gamma lymphoproliferative disorder)	*C. canimorsus*	235
1	1	1 (ALL)			DF-3	9
1	1			1 (unspecified)	DF-3	118
Total 92	47	31	7	9		

[a] AML, acute myelogenous leukemia; ALL, acute lymphocytic leukemia; CML, chronic myelogenous leukemia; CLL, chronic lymphocytic leukemia; HCL, hairy-cell leukemia.
[b] LL, lymphocytic lymphoma; HD, Hodgkin's disease.
[c] AL, acute leukemia; includes acute nonlymphocytic leukemia (six patients), acute lymphocytic leukemia (four patients), and chronic lymphocytic leukemia (one patient).
[d] Includes neuroblastoma (one patient), pancreatic carcinoma (one patient), and oropharyngeal carcinoma (one patient).

of 75% of the bacteremic episodes. Predisposing factors included chemotherapy and whole-body irradiation. As with other studies, these therapeutic measures resulted in many episodes of profound granulocytopenia; and in this series, *Capnocytophaga* bacteremia occurred in 14 of 16 episodes involving severe depression of granulocyte counts.

Unfortunately, species identification was not available or not attempted in either of these large studies. While the majority of isolates in these studies were likely to be *C. ochraceus*, the necessary identification studies were not performed.

Shurin et al. (271) obtained evidence for the inhibition of polymorphonuclear leukocyte migration by *Capnocytophaga* spp. This phenomenon may constitute a means by which *Capnocytophaga* spp. may evade phagocytosis after gaining access to the circulation. Similar to accounts of bacteremia due to *Bacillus* spp. in cancer patients, *Capnocytophaga* bacteremia commonly occurs in the clinical setting of cancer chemotherapy with attendant neutropenia. It is clear that *C. ochraceus* is an opportunist capable of causing bacteremias in cancer patients, especially those with hematologic malignancies (105).

In 1976, Bobo and Newton (26) described a case of meningitis with bacteremia due to a previously unrecognized organism in a 42-year-old man with a history of alcoholism and dog bite. The following year, Butler et al. (49) reviewed the findings for 17 patients with infections caused by this organism, then designated dysgonic fermenter-2, or DF-2. These authors showed a high association of DF-2 infections with underlying disease and other compromising conditions including splenectomy, alcoholism, and pulmonary disease. Most of this series of patients had either a history of recent dog bite or exposure to dogs. *Capnocytophaga canimorsus*, as DF-2 is now designated (41), is a normal resident of the canine oropharynx (11). The laceration of the dog bite provides the barrier break necessary to introduce the organism into the bloodstream.

While cases of *C. canimorsus* bacteremia in patients with the predisposing factors of alcoholism, splenectomy, and chronic lung disorders (26, 49, 144, 197, 263, 266, 283) and in otherwise healthy individuals (41, 49, 109, 144, 283, 332) continue to be reported, a number of reports indicate that cancer should be considered a risk factor as well.

Table 3 lists the cases of *Capnocytophaga* bacteremia associated with underlying neoplasia that have been reported (6, 9, 102, 105, 110, 118, 119, 137, 138, 144, 146, 197, 216, 224, 235, 243, 269, 315, 316, 325). The association with hematologic malignancies, leukemia and lymphoma, is amply demonstrated. Bacteremia due to *C. canimorsus* has now been documented in patients with Hodgkin's disease (146, 197, 325), leukemia (102, 216), multiple myeloma (110), and heart valve myxoma (325).

Martone et al. (197) presented evidence that a patient who was splenectomized and treated with chemotherapeutic and radiation regimens acquired the organism from contact with his pet dog. Holmes and Kozim (146) described another patient with Hodgkin's disease who had been splenectomized and who developed a *C. canimorsus* bacteremia after whirlpool immersion. Ndon (216) reported a fatal case of *C. canimorsus* bacteremia in a patient with hairy-cell leukemia following a dog bite, and Pletschette et al. (235) described a case of a 36-year-old man with T-gamma-lymphoproliferative disorder and a refractory anemia who experienced *C. canimorsus* bacteremia successfully treated with penicillin.

Hickling et al. (144) reviewed 41 cases of DF-2 infection and noted five cases of cancer: three cases of Hodgkin's disease and two cases of chronic lymphocytic leukemia. There appears to

be an especially pronounced association of *C. canimorsus* bacteremia with Hodgkin's disease patients.

The unnamed *Capnocytophaga* species called DF-3 has been shown in some studies (25, 118, 311) to be associated with gastrointestinal disease. Gill et al. (118) showed that 1.6% (11 of 690 cultures) of stool cultures were positive for DF-3. Ten of the 11 patients with DF-3-positive stool cultures in this study had underlying neoplastic disease: two each with common variable hypogammaglobulinemia, lymphoma, sarcoma, and breast cancer and single cases of angioblastic lymphadenopathy, metastatic colon cancer, and AIDS. To date, a single documented case of DF-3 sepsis has been reported (9) in a patient with acute lymphocytic leukemia who was also granulocytopenic.

CLOSTRIDIUM SPP.

In 1969, Alpern and Dowell reported the results of a seminal study of *Clostridium septicum* isolates submitted to Centers for Disease Control and Prevention laboratories for confirmation (3). They showed that of 28 patients with *C. septicum* infections, 21 had bacteremia and 23 had an underlying malignancy, including 14 with some type of leukemia. Of the nine other patients, five had carcinoma of the colon and one each had carcinoma of the rectum, disseminated reticulum cell sarcoma with intestinal involvement, carcinoma of the larynx, and carcinoma of the breast. In five cases, malignant disease was found at the time the organism was cultured, and in three cases, a bowel carcinoma was found 1 to 2 months after the first isolation of *C. septicum*. This work substantiated earlier isolated findings that indicated an association of *C. septicum* with malignancy (33, 163, 198, 272, 300). Seven of the 28 patients in the series presented with a bowel disorder, making a barrier break of the intestinal wall the most likely portal of entry for *C. septicum* to the bloodstream. Later, the same authors reported on the clinical correlation of nonhistotoxic clostridium species from blood (4). Excluding consideration of "known histotoxic species," namely, *C. perfringens*, *C. septicum*, and *C. novyi*, these authors showed that recovery of a variety of relatively uncommon clostridial species was associated with underlying disease: 41% of patients had an intra-abdominal disorder, and 14% had a malignant tumor or leukemia. However, other workers have shown that the designation of an organism as histotoxic is somewhat arbitrary. In a survey of blood cultures positive for *Clostridium* species, Pietrafitta and Deckers (233) showed that among 29 of 53 patients with clostridial isolates, no hemolytic disease process, characteristic of histotoxic strains, was evident, although multiple isolations of *C. perfringens* (26) and one isolation of *C. septicum* were made.

Schaaf and colleagues (262) reported six patients with *C. septicum* sepsis: three with bowel carcinoma, two with leukemia, and one with aplastic anemia. Kornbluth et al. (179) conducted a comprehensive review of the literature in 1989 and reported the finding of 162 cases of *C. septicum* infection at that time. Of these, 40% had a hematologic malignancy or a premalignant condition and 34% had a colorectal carcinoma, with nearly half of these having a cecal carcinoma. These investigators pointed out that *C. septicum* myonecrosis often occurs at a site distant from the presumed portal of entry. Of 162 patients summarized in their review of the literature, 38 cases of distant myonecrosis (an infection in muscle tissue occurring at an anatomic site removed from the suspected portal of entry) were recognized, and there was a significant association with an occult malignancy in these patients. This finding indicates that *C. septicum* bacteremias occur frequently enough in patients with undiscovered malignancies to initiate infectious processes at sites far distant from the bowel. Distant myonecrosis has been documented with *C. perfringens* bacteremias associated with colon carcinoma as well (198).

As described previously, the study by Bretzke and colleagues (42) showed the high incidence of malignancy (52.6%), including colon and rectal carcinoma, in a group of patients with *C. septicum* bacteremia and gas gangrene. Although the infection ensued after trauma in 3 of 19 patients (16%), a spontaneous event occurred in 13 of 19 patients (68%). Koransky et al. (178) reported a study of 59 patients with *C. septicum* bacteremia. Fully 71% had a malignancy, one-half with hematologic disease and the remainder with solid tumors. Of the 21 solid-tumor patients, 14 (67%) had colon carcinoma.

Studies of cancer patients has shed light on the frequency of clostridial bacteremias and their underlying pathogenic antecedents. Wynne and Armstrong (327) described 15 episodes of clostridial bacteremia among cancer hospital patients, of whom 47% had leukemia or lymphoma. To these authors, all bacteremias seemed to originate in the bowel and were precipitated by anticancer chemotherapy, radiation therapy, and various other surgical and diagnostic procedures. *C. perfringens* was recovered in 11 of 15 episodes, and *C. septicum* was recovered in two; there were single isolates of *C. multifermentans* and *C. tetanomorphum*. The authors attributed the predisposition to bacteremia in this group to advanced stage of disease, chemotherapeutic measures that depressed already compromised cellular and humoral immune defenses, the ulcerating effects of drug on bowel mucosa, and thrombocytopenia, which promotes internal hemorrhage, especially of the gastrointestinal tract. Bodey et al. (31) reported on a 12-year experience at a cancer hospital which involved 136 episodes of clostridial bacteremia. The most common species recovered was *C. perfringens*, responsible for 32% of the 82 monomicrobial bacteremias, followed by *C. septicum*, responsible for 20%. Lesser numbers of other species were also found: *C. sporogenes*, nine cases; *C. tertium*, five cases; *C. innocuum*, four cases; *C. sphenoides*, two cases; *C. paraputrificum*, two cases; and bacteremia due to *C. sordellii*, *C. irregularis*, *C. butyricum*, *C. limosum*, *C. paraperfringens*, *C. hastiforme*, *C. cadaveris*, *C. clostridiiforme*, and *C. aminovalericum*, one case each. Polymicrobic bacteremias accounted for 39% of all episodes. Leukemia and other hematologic malignancies were the underlying disease for 44%, while solid tumors at various sites (genitourinary, gastrointestinal, head, neck, muscle, and lung) accounted for the remaining cases. A history of abdominal complaints, which support the gastrointestinal tract as the source for the organism, was found in 70% of patients with *C. perfringens* bacteremia and in 76% of the patients with *C. septicum* bacteremia. Caya and coworkers (56) reported on a series of 47 patients with leukemia and clostridial sepsis. In 48 episodes involving 36 adults and 11 children, they found 29 isolates of *C. septicum*, 14 isolates of *C. perfringens*, and 5 isolates of other *Clostridium* species. The predominance of *C. septicum* infections among patients with leukemia (3, 5, 187, 188, 262) speaks strongly for a pathogenetic association between the leukemia process and this particular species.

Other studies of clostridial bacteremia show a high frequency of underlying neoplastic disease but are encumbered by a failure to delineate the species of *Clostridium* recovered (50, 126).

Whereas clostridial bacteremias classically have been associated with traumatic wound infections and postabortal and postpartum sepsis, the spectrum of patients has shifted to those with underlying disease, especially malignancies. *C. septicum*, on the basis of numerous studies, exhibits a striking association with hematologic malignancies, while the clinical situations associated with *C. perfringens* sepsis are more diverse.

For example, Ramsay (242) stated that circulating *C. perfringens* was of no pathogenic consequence by virtue of a failure to document histotoxic clostridial infection in women with postpartum infections. Ellner and O'Donnell (93) reported 16 cases of nonfatal *C. perfringens* bacteremias. Five of these cases occurred in young women with uterine infections; the remaining eleven were in generally elderly patients, three of whom did have cancer. Other investigators have provided evidence for clinical situations in which *C. perfringens* bacteremia was judged without clinical gravity (242), unrelated to clinical situation (123), or a contaminant (321).

Gorbach and Thadepalli (123) cautioned, "Clostridial bacteremia was often unrelated to the clinical situation and was found in alcoholics with aspiration, or *S. pneumoniae* pneumonia, pulmonary tuberculosis, empyema, meningococcemia, and infantile gastroenteritis."

However, explosive infections caused by *C. perfringens* with intravascular hemolysis occur frequently in cancer patients (31, 123, 327). Decisions as to the significance of an isolation of a *Clostridium* species from blood must be tempered by the fact that single positive blood cultures are the rule (31) and, collectively, clostridial bacteremias are an uncommon event (96). The comparison of *C. septicum* and *C. perfringens* is worthy of highlight. *C. perfringens* is the most common clostridial species recovered from blood cultures and its recovery can signal a wide spectrum of clinical contingencies, from the benign to the life-threatening; *C. septicum* is strikingly associated with underlying neoplasia.

CORYNEBACTERIUM SPP.

As is often the case with *Bacillus* isolations from blood cultures, the isolation of a *Corynebacterium* species is usually regarded as a contamination event unless the patient has a prosthetic heart valve (114, 302). However, evidence which shows an association between *C. jeikeium*, previously known as the JK group, and malignant disease has accumulated.

In 1976, Hande and colleagues (135) reported sepsis due to a previously undescribed *Corynebacterium* species which grew very slowly on laboratory bacteriological media and exhibited pronounced resistance to antibiotics, except vancomycin. Of the four patients described in this report, three had leukemia in relapse; the fourth had a porencephalic cyst and ventriculoatrial shunt. Pearson et al. (227) followed with a report of sepsis with this organism in 12 patients; 9 of these patients had leukemia, 2 had aplastic anemia, and 1 had multiple myeloma. Factors that appeared to predispose to infection included breaks in mucocutaneous surfaces, extended duration of granulocytopenia, and antibiotic treatment. These investigators located the primary site of infection in 10 of the 12 cases, noting skin or mucous membrane breaks due to a drug-induced toxic reaction, instrumentation, and other invasive procedures. The first definitive microbiologic characterization of JK group isolates, predominantly from blood, was reported by Riley et al. (254) in 1979. Information on infections continues to point to the predilection of *C. jeikeium* to cause infections secondary to cardiac surgery (76) and heart protheses (128, 302).

Gill et al. (117) presented data to show that the skin is the source of *C. jeikeium* and, by means of cultures taken at intervals from various anatomic sites of hospitalized patients, that this organism frequently colonizes patients at admission and, once present, persists for weeks or months. Among 57 patients colonized with *C. jeikeium*, 84% were cancer patients: 40% with hematologic malignancies and 44% with solid tumors. Inguinal, axillary, and rectal specimens most frequently resulted in recovery of the organism. However, of 15 blood culture isolates, 13 were recovered from patients with hematologic malignancies, 1 was recovered from a sarcoma patient, and 1 was recovered from a neuroblastoma patient. Thirteen of these patients were also granulocytopenic, and 14 of the 15 expired within 2 weeks of contracting *C. jeikeium* bacteremia.

A number of other reports now document the ability of *C. jeikeium* to cause infection, often with bacteremia, in patients with leukemia (74, 259), Hodgkin's disease (130), aplastic anemia (85), and medulloblastoma (2). It is clear, however, that patients without neoplastic disease have had documented *C. jeikeium* bacteremias when a skin barrier break has occurred due to trauma (2, 73), Hickman catheter use (239), and other procedures (203).

Clearly, recovery of *C. jeikeium* from blood must be judged a significant event until proven otherwise. This is especially important when isolation is obtained from multiple blood culture sets, as has been documented in the studies discussed. The ability of *C. jeikeium* to invade cancer patients when that invasion is facilitated by an intravenous catheter is evident from the reported studies.

Our literature search also revealed a case of *C. diphtheriae* endocarditis in a patient with chronic lymphocytic leukemia (158). Although recovery of this species seems to occur most often with patients with congenital heart disease (75, 194), the rarity of recovery of *C. diphtheriae* and other *Corynebacterium* species should prompt a clinical investigation to determine if a malignancy is present in patients without long-term intravenous catheters or prosthetic heart valves.

LISTERIA MONOCYTOGENES

In 1967, Louria et al. reported a series of 18 cancer hospital patients with infection with *L. monocytogenes* (193). The organism was recovered from blood in all but two patients. Eight patients had Hodgkin's disease (44.4%), two had reticulum cell sarcoma, five had leukemia, and one each had breast carcinoma, multiple myeloma, and lymphosarcoma. These investigators compared these findings with a review of 100 cases in the English literature. Of these 100 cases, 26 had underlying disease and 6 (23%) of these had neoplastic disease. Meningitis was the most common infection in both the cancer patients and the literature review. In the same year, Simpson et al. (274) reported listeriosis complicating the clinical course of four patients, including three with Hodgkin's disease and one with subacute lymphocytic leukemia. A decade later, Bottone and Sierra (37) described a series of 37 patients with *L. monocytogenes* infections. Neoplasia was again prominent, accounting for 43% (16 of 37) of the patients. Nearly 70% of these were lymphoma or leukemia cases. Kalis et al. (164) reported an additional four cases, three of whom had lymphoproliferative disorders. In 1978, Nieman and Lorber (219) reviewed the reports accumulated since the review by Louria et al. (193). They pointed to the value of blood cultures to detect *L. monocytogenes* infections and the apparent increasing frequency of primary *Listeria* bacteremias. Of 176 patients, 25% had an underlying malignancy. Lymphomas, leukemias, and plasmacell dyscrasia were found in 76% of patients, while the remainder had solid-tumor malignancies. Meningitis was the most common infection and 25% of these patients had cancer. Similarly, in patients with primary *Listeria* bacteremia but without a localized infection, a third had an underlying malignancy. In contrast, none of 14 patients with *Listeria* endocarditis had malignancy. Bayer and coworkers reported similar findings (19).

The occurrence of *L. monocytogenes* infections in normal individuals has been noted by several groups (37, 206, 219) and

includes outbreaks associated with food and dairy products (113). However, the spectrum of susceptible patient groups includes infants, the aged, pregnant women, renal and bone marrow transplant patients, immunosuppressed patients, alcoholics, diabetics, and patients with collagen-vascular disease, sarcoid, idiopathic thrombocytopenia purpura, ulcerative colitis, and asthma (37, 48, 58, 113, 267). Those with underlying malignancies make up a small but increasingly significant segment. Several authors have presented evidence that the gastrointestinal tract is the source of *L. monocytogenes* infection (47, 202, 252). The ability of listeria organisms to penetrate the gut mucosa (241) may be a singular attribute which obviates the need for a predisposing factor in the host to allow a bacteremia to be initiated.

In rare instances, *L. monocytogenes* bacteremia has been reported in patients with AIDS (51, 245, 246) and with iron overload (51, 213). Patients with combinations of these risk factors have included a patient with AIDS, iron overload, and listeria sepsis (51) and an AIDS patient with rectal carcinoma and listeria sepsis (245).

MYCOBACTERIUM SPP.

In a study of hospitalized cancer patients, Feld et al. (99) found 59 cases of mycobacterial disease among patients at M. D. Anderson Hospital in the period from 1968 to 1973. Although relatively rare, these infections occurred at a rate three times higher than in the general population. No attempt was made to recover mycobacteria from blood in these patients; specimens consisted primarily of sputum and bronchial washings. Of the 59 infections, 29 were due to *Mycobacterium tuberculosis* and 30 were due to a variety of nontuberculous mycobacteria, principally *M. kansasii* (12 cases) and *M. fortuitum* (7 cases). This finding of an increased rate of mycobacterial infection among cancer patients was reported before the significant advances in mycobacterial blood cultures that occurred in the 1980s.

This group has also reported a relationship between *M. fortuitum* bacteremia and cancer patients with long-term indwelling venous catheters (152). Four patients had a variety of neoplasms: oat cell lung carcinoma with a previous history of chondrosarcoma, acute myelogenous leukemia, Burkitt's lymphoma, and bladder transitional cell carcinoma. This study pointed to the use of long-term central venous catheters and instrumentation on the patients as most likely to have provided the portal of entry for the infecting mycobacteria, and this agrees with previous reports that *M. fortuitum* infections are associated with traumatic or surgical barrier breaks. More recently, a number of studies have described *M. fortuitum* and *M. chelonae* catheter infections, often with septicemia, in cancer patients, especially leukemics (40, 205, 240, 253). Wallace et al. (312) described recovery of *M. chelonae* subsp. *abscessus* from the blood of five patients with disseminated disease, including one with acute myelogenous leukemia and one with lymphoma. Other cases were two renal transplant patients and a chronic hemodialysis patient.

In recent years, the AIDS epidemic has spurred improvements in the diagnosis of mycobacterioses, especially disseminated infections, and a number of new taxons have been established (320). It is worth noting that an association of tuberculosis and lung carcinoma has been recognized since the early 1960s (256, 287).

Localized and disseminated mycobacterial disease in AIDS patients is increasingly diagnosed by means of blood cultures. This includes *M. tuberculosis* (256), *M. avium* complex (150, 170), *M. haemophilum* (8, 295), and *M. genavense* (70). The improvement in blood culture detection technology has been coupled with an increasing recognition that a laboratory diagnosis of disseminated mycobacterial disease can be made by blood culture. Kiehn et al. (170) documented *M. avium* complex bacteremias in 3 patients with leukemia as well as in 30 patients with AIDS and 2 with congenital severe combined immunodeficiency syndrome. Further developments in this arena may provide increased numbers of documented cases of mycobacteremia and allow for study of the underlying neoplastic diseases that give rise to these events.

RHODOCOCCUS EQUI

Rhodococcus equi, formerly *Corynebacterium equi*, is an aerobic, gram-positive, nonmotile, partially acid-fast, gram-positive bacillus that is closely related taxonomically to the genera *Mycobacterium* and *Nocardia*, sometimes referred to as the *Corynebacterium-Mycobacterium-Nocardia* group. Because the rhodococci have the appearance of a "diphtheroid," isolates from human specimens may be regarded as clinically unimportant contaminants or commensals. *C. equi* was recognized as early as 1923 as an agent of bronchopneumonia in horses (foals) and later was found to cause pulmonary infections in swine, cattle, and sheep as well (191). The primary habitat of *R. equi* is the soil (18). It is an exceedingly rare blood culture isolate but may be recognized more frequently in laboratories in which diphtheroids recovered from blood cultures are identified before a judgment is made as to whether the isolate is a contaminant.

Only a few human infections with *R. equi* have been reported. The portal of entry is thought to be the respiratory tract, most commonly following exposure to infected animals, and human infections occur in immunocompromised hosts (21, 301). Van Etta et al. (301) reviewed 12 cases of human infections through 1983, including two of their own, all occurring in patients who either were recent renal transplant recipients or had underlying hematologic malignancies, primarily lymphosarcoma, and Hodgkin's disease. Eleven of the patients in this series were receiving one or more immunosuppressive drugs, including corticosteroids.

The primary infections in all of the reported cases were in the lungs, manifesting initially as a slowly progressive lobar infiltrate and later developing into single or multiple cavitary lesions, from which *R. equi* was often recovered from percutaneous needle aspiration specimens. The clinical course of one patient was also complicated by the development of a brain abscess from which *R. equi* also was recovered in culture. In only four of these cases reported by Van Etta and colleagues was *R. equi* recovered in blood cultures, always a secondary event following the evolution of cavitary pulmonary disease. A current literature search reveals only one additional reported case of *R. equi* bacteremia; in a patient with AIDS who also had a primary cavitary pneumonia caused by this organism (94).

In summary, *R. equi* bacteremia is a rarely reported event, occurring in patients with severe immunosuppression and virtually always complicating cavitary pulmonary disease. In discussing a case of *R. equi* infection in a patient with Hodgkin's disease, Carpenter and Bloom (53) theorize that the organism is perhaps carried as a commensal in the upper respiratory tract, becoming pathogenic in select cases only with the onset of the underlying neoplastic disease and/or immunosuppression.

SALMONELLA SPP.

In the 1950s and 1960s, reports that documented *Salmonella* infections complicating the course of neoplastic disease appeared in the literature (23, 148, 154, 221, 265). Reports of unusual infections caused by *Salmonella* spp., namely, of tumor tissue itself, appeared in the 1950s (115, 125, 225), although this observation had been made as early as 1936 (127).

Heineman and coworkers (140) described three cases of Hodgkin's disease complicated by *S. typhimurium* infection. Blood cultures were positive in two cases. Han et al. (134) reported on a series of 20 patients with salmonellosis encountered during a 6-year study of cancer patients at Roswell Park Memorial Institute. Seven had a bacteremia, including five with *S. typhimurium*. Unlike in many other studies, these investigators presented denominator data that showed that *Salmonella* infections were seen in patients with lymphoma, leukemia, and pelvic malignant neoplasm eight times more frequently than in patients with other malignant neoplasms.

In 1969, Cherubin et al. (59) presented the results of an analysis of 2,192 cases of salmonellosis, including 101 cases of bacteremia. Nearly half of the sepsis cases had underlying disease: malignancies, liver disease, alcoholism, and chronic heart and kidney disease. However, *S. typhimurium* sepsis was clearly associated with Hodgkin's disease and other malignant lymphomas, while bacteremia due to other *Salmonella* serotypes was more often found in patients with sickle-cell disease, alcoholism, and liver disease.

In a study of cancer hospital patients, Wolfe et al. (323) described 100 episodes of *Salmonella* bacteremia and similarly showed its strong association with lymphoma and leukemia. Of 35 episodes of *S. typhimurium* bacteremias, 32 (91%) occurred in patients with neoplasms, predominantly lymphoma, including nine patients with Hodgkin's disease and leukemia. Bodey's group contributed a five-patient series that also provided testimony to the strong association of *S. typhimurium* sepsis and Hodgkin's disease (35).

Cases of *Salmonella* sepsis have been reported for AIDS patients (38, 120, 159, 236, 284). *S. typhimurium* and *S. enteritidis* (310) are the most frequently recovered isolates. However, with the advent of zidovudine therapy, the frequency of these *Salmonella* bacteremias appears to have declined. Sperber et al. (290) have reported that this drug inhibits *Salmonella* spp. at clinically achievable levels.

A compromised cellular immune mechanism seems to render AIDS patients, who commonly acquire Kaposi's sarcoma, and cancer patients susceptible to invasion with *S. typhimurium.*

STREPTOCOCCUS BOVIS

In 1951, McCoy and Mason (200) reported a single case of enterococcal endocarditis accompanied by carcinoma of the sigmoid colon. This report and a report by Barry and Scarpelli (17), which seemed to indicate an association of nonbacterial endocarditis with colonic neoplasms, presaged the elucidation of a unique association of a single streptococcal species and colonic cancer in the 1970s.

In 1973, Ravreby et al. (244) reported the clinical features of 18 patients with "enterococcal" bacteremia. These authors offered that incomplete identification of group D streptococcus, which included the common enterococcal species *S. faecalis* and *S. faecium* as well as the nonenterococcal species *S. bovis* and *S. equinus*, would not allow appropriate evaluation of the clinical features of patient groups infected with individual species. Of the 19 patients in their study, 11 were infected with enterococcal species, while the remaining 8 had *S. bovis* bacteremias. Of the enterococcal bacteremia patients, nine had serious underlying disease, including five with widespread neoplasia. All *S. bovis* bacteremia patients had subacute bacterial endocarditis, and two had neoplastic disease: multiple myeloma and metastatic melanoma. Keusch (169) drew attention to the observations of Roses et al. (257) and Roberts' group at New York Hospital-Cornell Medical Center (215) which seemed to indicate an association between *S. bovis* endocarditis and colorectal carcinoma. Klein et al. (177) reported similar findings for two patients and demonstrated that fecal carriage of *S. bovis* was increased in colon carcinoma patients compared with other patient groups. This group followed with a prospective study of 29 patients with either *S. bovis* endocarditis or bacteremia which lent support to the previous study (176). In 30 episodes of bacteremia in the 29 patients, 15 were fully evaluated. Of these, eight patients had carcinoma of the colon, three patients had adenomatous polyps without carcinoma, and two patients had esophageal carcinoma. These authors stated: "The results of our study suggest that all patients with *S. bovis* bacteremia need aggressive evaluation of the gastrointestinal tract, especially the colon." Murray and Roberts (215) reported on a study of 36 patients with *S. bovis* endocarditis and bacteremia. Of these, 25 either had undergone a manipulative procedure or had a documented gastrointestinal lesion. Four patients had either colon carcinoma or potentially malignant villous adenomas.

It is worth noting that other studies of group D streptococcal endocarditis (149, 207, 270, 318) published during the same time period did not indicate the striking association with gastrointestinal disease shown in the previously described studies but did point to genitourinary or dental problems as possible sources for the invading organism. A study of enterococcal bacteremia reported by Shlaes and colleagues (270) lacked species information to discern the significance of relationships between underlying disease and the species of streptococcus. Similarly, Leport et al. (189) reported that 67% of 32 patients with group D streptococcal endocarditis demonstrated either polyps or a neoplasm on endoscopy. Subsequently, a study by Reynolds et al. (249) contributed an additional 19 cases of bacteremia due to *S. bovis*. Eight patients had diverticulosis, four had benign adenomatous polyps, and three had adenocarcinomas of the gastrointestinal tract.

A succession of case reports (43, 71, 81, 89, 108, 112, 143, 151, 220, 250, 260, 273, 286, 292, 314, 322) next provided ample supportive evidence for the pathogenetic relation of *S. bovis* endocarditis and bacteremia and colorectal neoplastic disease. Hønburg and Gutschik reported that 15 (16%) of 92 *S. bovis* bacteremia patients had gastrointestinal cancer (147). These reports and the principal multicase studies are summarized in Table 4. A spectrum of disease from diverticulosis to cancer is evident. To date, cases that link *S. bovis* endocarditis with both nonmalignant disorders, such as diverticulosis (89, 249) and adenomatous polyps (89), and adenocarcinoma of the oropharynx (112), pancreas (143), and liver (220) have been reported. Dunham et al. (89) reported *S. bovis* infection of a porcine prosthetic heart valve. *S. bovis* endocarditis occurred in a case in which a successful surgical cure of colonic carcinoma had apparently been performed 21 months previously (250). Klein et al. (176) posed the question of whether *S. bovis* produces a carcinogen that induces bowel cancer or if growth of the organism is promoted by a preexisting carcinoma. Brooks et al. (43) added additional descriptive information regarding a patient previously reported in the series by Ravreby et al. (244). This patient had a malignant melanoma that metastasized to the colon, suggesting that the latter hypothesis is

TABLE 4. *S. bovis* bacteremia and neoplastic disease

Total no. of patients	Total no. of cancer patients	No. of patients with neoplastic disease and other disorders[a]						Reference
		Gastrointestinal				Other sites		
		Carcinoma	Adenoma	Polyps	Other gastrointestinal disorders	Lymphoma	Other diseases	
36	10	3	2	4	10	1		215
29	12	11		4		1		176
24	9	1		4		8[b]		331
19	3	3		4	8			249
19	7	6		5	1	1[b]		331
14	0			4	2			149
14	4	2	2					177
14	0			1			8	207
8	1	1						244
5	0			2	1			108
3	0				1		1	318
3	2	2						190
2	2	2						273
2	2	1	1					286
2	2	1			1			89
1	1	1						292
1	1					1		314
1	1	1		1				112
1	1	1						143
1	1	1					1	220
1	1	1						71
1	1	1						151
1	1	1						322
Total 202	62	40	5	29	24	12	10	

[a] More than one disorder present in some patients.
[b] Leukemia or lymphoma.

correct. Levy et al. (190) reported three cases of *S. bovis* endocarditis, two of which had colonic carcinoma. One of the latter cases was of particular interest: an 80-year-old man with a history of surgical treatment of both prostatic carcinoma and colon carcinoma prior to the *S. bovis* endocarditis who later died of lymphosarcoma.

Table 4 summarizes all relevant reports for which identification of isolates appears to have been performed appropriately (71, 89, 108, 112, 143, 149, 151, 176, 177, 190, 207, 215, 220, 244, 249, 273, 286, 292, 314, 318, 322, 331). Nearly half (48.5%) of all cases of *S. bovis* bacteremia or endocarditis had a demonstrated gastrointestinal disorder, and nearly half of these (40.8%) had colonic adenocarcinoma.

GROUP G STREPTOCOCCI

Bacteremia due to group G beta-hemolytic streptococci occurred in 3.5% of all patients with bacteremia at three major Boston University Medical Center-affiliated hospitals (319). This organism accounted for 8% of all beta-hemolytic streptococcal and enterococcal bacteremias, a value consistent with the 8% incidence reported 15 years earlier by Duma et al. (88) and the 10.8% incidence reported by Auckenthaler et al. (10). Alcohol abuse, diabetes mellitus, and neurological diseases have been underlying diseases most commonly reported in association with group G streptococcal bacteremia; the association with cancer is less consistent on the basis of several reports in the current medical literature (319). For example, in nine cases of group G streptococcal bacteremia reported by Armstrong et al. (7), only one was associated with cancer; in contrast, an association of 83% was reported by Duma et al. (88), one of 65% was reported by Auckenthaler et al. (10), and one of 45% was reported by Skogberg et al. (279). Watsky et al. (319) mentioned specifically that only 6 of 26 patients (less than 25%) with group G streptococcal bacteremia had cancer, 4 with solid tumors and 2 with hematologic malignancies, in sharp contrast to the higher rates mentioned above. In smaller studies, Packe et al. (223) reported that two of seven patients with group G streptococcal bacteremia had cancer, in one case its isolation being the first manifestation of the underlying disease; and Dickie et al. (83) reported that three of six patients with group G streptococcal bacteremia had cancer, concluding that "malignant disease must be considered when this organism is recovered in blood cultures." In contrast, none of nine patients with group G streptococcal bacteremia reported by Bucher and Gustad had associated malignancies (44).

Colonization of the skin and asymptomatic carriage in the oropharynx, the gastrointestinal tract, and the female genital tract are the most likely ports of entry into the bloodstream for group G streptococci. Watsky et al. (319) estimate that colonization of the skin with group G streptococci was probably the port of entry in 79% of the 26 patients with group G streptococcal bacteremia who made up their study, although this was not confirmed by culture. Cellulitis of the lower extremities and decubitus ulcers were the most common conditions found in these patients.

In their patient series report, Auckenthaler et al. (10) described a variety of barrier breaks of skin and mucous membranes secondary to invasive procedures such as placement of indwelling devices which included an Omaya reservoir, Broviac catheter, and chest tubes and surgical operations such as transurethral prostate resection, laryngotomy, thoracentesis, and esophagogastrectomy that probably served as the portal of entry. Cellulitis of the lower extremities, decubitus ulcers, and

TABLE 5. Group G streptococcal bacteremias associated with cancer

Total no. of patients	No. of cancer patients	No. of patients with associated neoplastic disease					Reference
		Hematologic neoplasia			Solid tumors		
		Leukemia[a]	Lymphoma	Other	Carcinoma	Other	
37	24	4 (ALL, 1; CLL, 1; AGL, 1; myeloid, 1)	8 (lymphocytic, 2; follicular, 1; histiocytic, 1; Hodgkin's IIIb, 1; myeloma, 1; myelofibrosis, 1; histiocytoma, 1)		10 (laryngeal, 1; prostate, 1; breast, 1; squamous, tongue, 1; squamous, esophagus, 1; squamous, anus, 1; squamous, vulva, 1; pancreas, 1; endometrium, 1; colon, 1)	2 (melanoma, 1; seminoma, 1)	10
6	3	1 (AML)	2 (non-Hodgkins, 1; Hodgkin's, 1)				83
18	4	1 (PML)		1 (aplastic anemia)	2 (laryngeal)	1 (melanoma)	303
38	17			4 (unspecified)		13 (unspecified)	279
15	1				1 (prostate)		182
4	3				3 (breast, 2; cervix, 1)		88
3	1				1 (colon)		328
9	1				1 (ear)		7
Total 130	54	6	10	5	18	16	

[a] Includes ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia, AGL, acute granulocytic leukemia; AML, acute myelogeneous leukemia; PML, promyelocytic leukemia.

postradiation infections and cancers of the mucous membranes, such as carcinoma of the larynx, tongue, esophagus, skin, vulva, anus, and ear, were other conditions found among their study patients. All of these conditions could have provided a means for direct entry of colonizing group G streptococci, although the exact mechanisms for entry into the blood are yet to be worked out (83). Table 5 summarizes the findings of these studies.

Why group G streptococci, in preference to other Lancefield groups of beta-hemolytic streptococci, are selectively associated with cancer remains unexplained. The only possible virulence factors that may contribute to this selectivity are surface proteins analogous to the M proteins of group A streptococci. Bisno et al. (22), in an electron microscopic study of seven strains of group G streptococci isolated from clinically severe bacteremic infections, demonstrated fibrillae similar to those observed in M-protein-rich group A streptococci. By whatever mechanisms it employs, the group G streptococcus has become a more prevalent pathogen (44, 303). Auckenthaler et al. (10) raise the question of whether patients with underlying malignancy are more prone to colonization with group G streptococci, although proof is still lacking. As can be seen from Table 5, a wide variety of solid tumors, particularly those involving mucous membranes, are associated with group G bacteremia (7, 10, 83, 88, 182, 279, 303, 328). Watsky and coworkers concluded that the breach of anatomical barriers may be more important than specific immune defects in the pathogenesis of bacteremia (319). Although exact mechanisms of pathogenesis must still be elucidated, the recent literature does show a distinct association between group G streptococcal bacteremia and cancer, to the extent that the recovery of this organism from the blood should at least alert the clinician that a hidden or overt underlying neoplastic disease may be present.

ACCURACY OF IDENTIFICATION

This survey has provided ample evidence for the value of clearly defined taxons and accurate identification of blood culture isolates. Where clear taxonomic delineation was lacking, such as was the case for *Capnocytophaga* and *Campylobacter* spp. in early studies of these genera, useful information on the association of individual species with underlying disease such as leukemia is virtually impossible to discern. In studies in which the identification to species is not performed, only the most general association of spectrum of disease with the genus of infecting organisms can be made. The association of *S. bovis* bacteremia with colonic carcinoma or that of *C. septicum* with leukemia and other neoplasms would not be discerned if laboratories merely identified these organism to the genus level. It is important to recognize that the characterization of new groups of microorganisms that can cause human disease begins with the referral of unusual isolates to the public health laboratory system or recognized laboratories of academic medical centers. Frequently, characterization of previously unrecognized isolates is done by the laboratories of the National Center for Infectious Disease at the Centers for Disease Control and Prevention.

Laboratorians should be circumspect about identification results rendered by commercial identification systems when uncommon organisms are indicated. These isolates may be correctly identified only with the use of conventional media or other reference methods. Many investigators have reported that commercial identification systems occasionally provide incorrect results with very uncommon organisms (14–16, 107, 285, 291). Laboratories that are unequipped to conduct identification studies using reference methods should refer select isolates to their state public health laboratories for identification.

UNUSUAL BACTERIA NOT YET ASSOCIATED WITH NEOPLASMS

While we have reviewed many reports that provide evidence for the association of bacteremias caused by rare bacteria with neoplastic disease, we also think it is worthwhile to consider microorganisms for which an association with cancer has yet to be found. Investigations designed to elucidate the pathogenetic mechanisms employed by the organisms described in this review may benefit from a consideration of negative data, namely, the characteristics of organisms that are recovered

TABLE 6. Microorganisms associated with cancer

Organism	Associated neoplasms	Source	Endogenous source	Infection risk factors	Primary infection	Probable mechanism
Aeromonas hydrophila	Leukemia, carcinoma	Water, fish	GI tract[a]	Liver disease	Gastroenteritis, trauma wound	GI mucosal penetration
Bacillus spp.	Leukemia, lymphoma, carcinoma	Soil	Skin	Trauma, hemodialysis, neonates, i.v. catheterization,[b] i.v. drug abuse, neutropenia	Septicemia, pneumonia, trauma infection, ocular infection	Skin barrier break
Campylobacter spp.	Leukemia, solid tumors	Cattle, sheep, swine	GI tract	Alcoholism, neonates, elderly, immunosuppressants, cardiac disease, liver disease, kidney disease	Gastroenteritis	GI mucosal penetration
Capnocytophaga ochracea	Leukemia	Oropharynx	Oropharynx	Oral lesions, granulocytopenia	Mucosal lesion	Oral mucosal barrier break, IgA[c] degradation?
Capnocytophaga canimorsus	Hodgkin's disease, leukemia	Dogs	None	Dog bite, asplenia, alcoholism, hemochromatosis	Skin wound	Skin barrier break
Clostridium septicum	Leukemia, colonic carcinoma	Soil	GI tract	Age?	Bacteremia, myonecrosis	GI barrier break
Corynebacterium jeikeium	Leukemia, lymphoma	Skin	Skin	i.v. catherization, heart surgery	Catheter infection, bacteremia	Skin barrier break
Listeria monocytogenes	Leukemia, Hodgkin's disease	Water, soil, foods	GI tract	Neonates, pregnant women, elderly, immunosuppressants, alcoholism, diabetes, renal disease, liver disease, iron overload, decreased gastric acidity, AIDS	Meningitis, sepsis, focal infection	GI mucosal penetration
Mycobacterium fortuitum, *M. chelonei*	Leukemia	Soil	Skin	i.v. catheterization, trauma	Septicemia, catheter infection	Skin barrier break
Rhodococcus equi	Leukemia, lymphoma	Soil, animals	Skin		Pneumonia	Inhalation
Salmonella typhimurium	Hodgkin's disease, leukemia	Animals (rodents), food, eggs	GI tract	Liver disease, alcoholism, chronic heart disease, kidney disease, AIDS	Septicemia	GI mucosal penetration
Streptococcus bovis	Colon carcinoma	GI tract	GI tract	Colonic cancer	Endocarditis, septicemia	GI barrier break
Group G streptococci	Carcinoma, lymphoma, leukemia	Respiratory tract, Skin	Respiratory tract, skin	Surgery, i.v. catheterization	Septicemia, endocarditis	Mucosal break, skin barrier break

[a] GI, gastrointestinal.
[b] i.v., intravenous.
[c] IgA, immunoglobulin A.

from blood, but not in the setting of cancer. We present a consideration of two species and their known risk factors.

Cover and Aber (69) reviewed infections caused by *Y. enterocolitica* in 1989 and presented literature citations to substantiate the prominent role underlying disease plays in *Y. enterocolitica* bacteremias. Predisposing factors include cirrhosis, hemochromatosis, acute iron poisoning, transfusion-dependent blood dyscrasias, deferoxamine therapy, immunosuppressive therapy, antibiotic therapy, diabetes mellitus, alcoholism, and malnutrition (36, 69, 97). Bacteremia has been documented in apparently normal individuals as well (36, 60, 69). Our search resulted in the finding of only two cases of malignancy associated with *Y. enterocolitica*: a single case of leukemia (209) and a single case of surgically treated uterine myoma (289).

Similarly, reports of *Gardnerella vaginalis* bacteremia (52, 55, 210, 247, 304) typically cite prenatal and postpartum problems as predisposing factors for entry of this organism into the bloodstream. Our search yielded a single case of *G. vaginalis* bacteremia in a patient with cancer, a man with a prostatic adenoma (80).

Our assignment of the microorganisms considered here to be rare may be debated and other candidate species of bacteria might be added to this list. The case for *Acinetobacter* or *Bacteroides* sp. may be made. It is our somewhat arbitrary decision that recovery of isolates of these genera from blood occurs frequently enough so as not to warrant separate consideration even though the frequency of isolation from blood is increased in cancer patients (277).

SUMMARY

Table 6 is a summary of the organisms discussed with a listing of the environmental source, the endogenous source, the predisposing factors including neoplasms, and the postulated mechanisms by which the organism can gain access to the circulation. The evidence considered indicates that the entrance of one of these microorganisms into the bloodstream of a human being depends on the presence of a multiplicity of predisposing factors. In the majority of cases of bacteremia due to one of these unusual organisms, two or more predisposing factors are present. Certain predisposing factors, such as cancer chemotherapy or intravenous catheterization, often provide a barrier break, while others, such as liver disease, may render the host immune system less capable of clearing organisms from the circulation. For organisms such as *Campylobacter*, *Listeria*, and *Salmonella* spp., attributes that allow the invasion of a healthy host are present and seem to be enhanced by the simultaneous presence of a predisposing condition, such as liver disease, in the host.

Although somewhat fragmentary, a number of individual case reports describe bacteremia due to one of these organisms occurring weeks to years after surgery and after other therapeutic measures had effected a supposed cure of a cancer. It may be speculated that cancer patients, even after a cure, are still susceptible to bloodstream invasion by one of the aforementioned organisms by virtue of the presence of one or more predisposing metabolic, physiologic, or immunologic factors, even though these factors may be cryptic.

The predominance of hematologic malignancies among cases of bacteremia due to these unusual organisms is also apparent. Although, as pointed out by Keusch (169), the reduction in the performance of immune function in hematologic malignancies compared with solid tumors is likely to be responsible, other associations of certain organisms with specific neoplasms warrant further examination. The frequency of bloodstream infections of *Salmonella typhimurium* and *Capnocytophaga canimorsus* in Hodgkin's disease patients seems likely due to a particular mechanism which infection by these species is favored. The specific nature of these mechanisms remains to be determined.

The recovery of any unusual bacterium from blood should warrant a careful consideration of the possibility of underlying disease, especially cancer. Microbiologists should advise clinicians of the unusual nature of the identified organism and provide the counsel that certain neoplastic processes, often accompanied by neutropenia, render the human host susceptible to invasion by almost any bacterium. The recovery of such organisms as *C. septicum* or *S. bovis* should prompt the clinician to aggressively seek to identify an occult neoplasm if one has not yet been diagnosed.

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