Role of Bacteria in Oncogenesis

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INTRODUCTION

Although scientific knowledge in viral oncology has exploded in the 20th century, the role of bacteria as mediators of oncogenesis is less well elucidated. Yet for every human cell, the human body carries 10 bacterial cells (217). How these bacteria might affect disease development in the human host is rightly a vigorous area of research. As cancer continues its climb as the leading cause of death in developed nations, understanding the long-term effects of bacteria has become increasingly important as a possible means of cancer prevention.

A transmissible cause of cancer was suspected as early as the 16th century (263). However, it was not until the late 20th century that reproducible, peer-reviewed work definitively identified a bacterial cause of malignancy. Pinpointing specific bacterial causes of cancer, however, has been challenging. The colon alone, for example, harbors more than 500 species of...
bacteria (24). Furthermore, the decades-long and variable period between infection and presentation of cancer makes singling out a culprit organism formidably difficult. Consequently, much effort has been applied to understanding the bacterial mechanisms that might influence oncogenesis. Posited mechanisms include deleterious alterations in physiological host processes such as inflammation, antigen-driven lymphoproliferation, and induction of hormones that increase epithelial cell proliferation. Bacteria may also promote cancer through direct effects on cell transformation or through the production of toxic, carcinogenic metabolites. An overview of the mechanisms of oncogenesis affected or promoted by bacteria is shown in Fig. 1. On the other hand, recent work has emerged on a protective role of bacterial infection in cancer. Although this area is not very well explored, there is mounting evidence that bacteria can alter host physiology and thereby reduce the risk of some cancers.

ALTERATIONS OF NORMAL HOST RESPONSES

Chronic Inflammation

Virchow first described the irritation hypothesis of oncogenesis in the 19th century. He understood that cancer cells were derived from human cells rather than being foreign invaders. He further postulated, after seeing the inflammatory
reaction in schistosome-related bladder cancers, that chronic irritation stimulated the cancer cells to grow (17, 54). The inflammatory process is characterized by damage caused by the host’s immune response to the infection rather than by the infecting organism itself. Over 100 years since Virchow’s discoveries, the “chronic irritation hypothesis” remains a widely supported mechanism for carcinogenesis by infectious agents.

During a normal response to infection, inflammation is created as a means for the host to combat invading pathogens. Inflammation is first initiated by the recruitment of phagocytes to the site of infection. The phagocytes recruited to the site of infection also secrete proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), and chemokines that attract more phagocytes and other cells of the immune system to the site of infection to amplify the inflammatory response. These cells respond through physiological processes mediated by the cellular enzymes NADPH oxidase, superoxide dismutase (SOD), myeloperoxidase, and nitric oxide synthase (NOS). The result is the release of reactive oxygen and nitrogen oxide species (ROS and RNOS) to kill potential pathogens. The free radicals and secondary products derived from them, such as secondary amines, HNO₂, N₂O₃, and peroxynitrite, may damage DNA, proteins, and cell membranes and indirectly induce cell repair (54).

Areas of tissue injury and inflammation trigger regenerative cell division from tissue and marrow-derived stem cells. Increased cell division may lead to point mutations, deletions, or translocations as damaged DNA escapes the repair system; the aberrant DNA is then propagated by subsequent cell division. This can result in disordered cell differentiation and, ultimately, oncogenesis. Hence, chronic inflammation instigates a cycle of cell damage, repair, and compensatory proliferation that promotes the development of cancer cells (54).

The inflammatory mechanism is not specific to bacteria. In fact, viruses as well as noninfectious irritants also share similar pathways toward cancer development. For example, the non-specific role of chronic inflammation in oncogenesis is well supported by studies of the role of hepatitis B and C viruses in the development of hepatocellular carcinoma (48, 83, 151) and by studies of the role of asbestos in lung cancer (an example of a noninfectious irritant) (208). The inflammation theory is further supported by the cancer-preventive effect of agents that decrease oxidative stress and diminish inflammation. For example, population studies have shown that long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) reduces the risk of colon cancer by 40 to 50% (245). Epidemiological studies also suggest that NSAIDs may protect against several other cancers as well, including esophagus, stomach, lung, and prostate cancers, among others (75, 122, 231).

In almost all examples of bacterial inflammation and human cancer, the implicated bacteria reside in the host for many years and create an environment of persistent inflammation. Specific bacteria that have been shown to cause chronic inflammation and an increased risk of cancer include Helicobacter pylori (gastric adenocarcinoma) and Salmonella enterica serovar Typhimurium or Paratyphi (biliary cancer). In addition, other types of chronic infection have been observed to be associated with cancers in some studies, but without an identified specific bacterial pathogen. Examples are chronic ulcers and osteomyelitis sinus tracts (squamous cell carcinoma), chronic urinary tract infections (UTIs) (bladder cancer), and chronic prostatitis (prostate cancer).

**Helicobacter pylori and gastric cancer.** *H. pylori* is a spiral Gram-negative rod that infects and colonizes the human stomach in 50% of the world’s population. In response to the overwhelming evidence linking *H. pylori* infection and human cancer, in 1994 the International Agency for Research on Cancer listed *H. pylori* as a definite human oncogenic agent (115a). *H. pylori* causes over 60% of all stomach cancers, which corresponds to more than 5.5% of all cancers in the world (186). In a meta-analysis of 12 nested case-control studies, *H. pylori* was a strong risk factor for noncardia intestinal-type gastric adenocarcinoma, with a summary relative risk of 3. When serology was tested at least a decade before diagnosis, when the stomach might have been less disrupted by the progression to cancer, the summary relative risk was even greater, at 5.9 (103a). In a cohort study in Japan that evaluated both intestinal-type and diffuse-type cancers, only *H. pylori*-infected subjects developed stomach cancer, making the risk ratio infinite (249).

Chronic *H. pylori* infection in the human stomach is characterized by chronic inflammation. The development of gastric adenocarcinoma, particularly of the intestinal type, is preceded by the development of chronic gastritis, atrophic gastritis, intestinal metaplasia, and dysplasia. The changes in the gastric mucosa are notable for recurrent cell necrosis and regeneration and for changes in cell differentiation. The inflammation by *H. pylori* is mediated by epithelial cell release of ROS and RNOS as well as interleukin-8 (IL-8) and Gro-a, chemokines that attract and activate neutrophils and macrophages (74). Accompanying this response is activation of macrophages and release of ROS and RNOS, activation of lymphocytes, and induction of a Th1-predominant cellular immune response that includes secretion of proinflammatory cytokines such as IL-1β, TNF-α, and gamma interferon (IFN-γ) (137). In studies that measure ROS release by chemiluminescence, the degree of inflammatory response correlates with the density of *H. pylori* organisms present on the mucosal surface. A marker of oxidative damage by ROS, 8-hydroxy-2’-deoxyguanine (8HdG), leads to G-to-T DNA transversions (47). In biopsy samples, the gastric mucosae of *H. pylori*-infected adults and children had larger amounts of 8HdG than the mucosae of those without infection. After *H. pylori* eradication, the levels of 8HdG return to baseline, confirming the role of infection in the formation of this mutagenic metabolite and lending support for the inflammation theory of oncogenesis (96). *H. pylori*-infected patients also have higher levels of cyclooxygenase-2 gene expression. These levels return to normal after antibiotic treatment (35). Some in vitro work, however, argues against a nonspecific accumulation of DNA mutations caused by chronic inflammation. Meyer-ter-Vehn et al. suggest instead that *H. pylori* may cause cancer through constitutive activation of mitogenic signal transduction pathways, such as those mediated by the proto-oncogenes c-fos and c-jun (162).

Few of those infected with *H. pylori* actually develop gastric cancer, and differences in bacterial strains explain some of the differences in cancer risk. Some *H. pylori* strains contain a functional cytoxin-associated gene (cag) pathogenicity island (PAI). The PAI encodes a type IV secretion system that allows *H. pylori* to insert the CagA protein into the host cell.
process results in increased transcription of host genes, altered host cell structure, an increased inflammatory response, and a higher risk for gastric adenocarcinoma (100, 194). In addition, only CagA-positive *H. pylori* strains were found to induce activation of the proto-oncogenes *c-fos* and *c-jun* (162).

Host genetic polymorphisms also play a role in gastric cancer development and highlight the importance of chronic inflammation in the carcinogenic process. IL-1β is known to reduce gastric acid secretion. Polymorphisms of the IL-1β gene are linked with an increased risk of chronic hypochlorhydria and gastric cancer (72, 260). Other gene polymorphisms that are associated with increased risk for gastric cancer involve the proinflammatory cytokines TNF-α, IL-8, and IL-17 and the anti-inflammatory cytokine IL-10 (156). Polymorphisms in genes encoding other cytokines, cytokine receptors, and antigen recognition receptors, such as Toll-like receptor 4 (TLR4) or mannann-binding lectin, are the targets of active research (110, 259). Each of the ensuing phenotypes is marked by increased or unchecked inflammation initially induced by *H. pylori* infection (220).

The use of antibiotics against *H. pylori* has been examined as a means of preventing gastric cancer. In animal models of *Helicobacter*-induced gastric cancer, eradication of infection is beneficial. Studies using C57/BL6 mice (infected with *Helicobacter felis*), hypergastrinemic transgenic INS-GAS mice (infected with *H. pylori*), or Mongolian gerbils (infected with *H. pylori* strain 7.13) have consistently demonstrated that antibiotic treatment reduces or prevents gastritis and premalignant lesions (37, 38, 145, 209) and, in some cases, can even abort the progression of gastric cancer (37, 145, 209). With treatment of early infection, the risk of gastric cancer may become similar to that for uninfected animal controls. In contrast, deferred therapy decreases histological abnormalities but does not prevent gastric cancer. This suggests that the timing of antibiotic intervention might be crucial and needs to take place before irreversible oncogenesis steps have occurred.

Even though animal studies do not fully represent human disease, epidemiological studies of humans are also encouraging. These studies show that antibiotics are associated with a lack of progression of some precancerous lesions and can lead to regression of both atrophic gastritis and intestinal metaplasia (52, 63, 148). However, the first randomized controlled trial (RCT) in a high-risk region of China found that eradication of *H. pylori* did not prevent gastric adenocarcinoma, except in those with no precancerous lesions on endoscopy (264). Since then, however, additional RCTs have reported more encouraging results. You et al. found a decrease in the combined endpoint of atrophic gastritis, intestinal metaplasia, dysplasia, and gastric cancer in those receiving *H. pylori* antibiotic treatment. When they examined only dysplasia and gastric cancer, however, the association was weaker (270). In a Japanese study of patients who received endoscopic resection for early gastric cancer, in the 3 years of follow-up *H. pylori* treatment prevented the development of metachronous gastric cancer (cancer that arises in other parts of the stomach after resection of the initial cancer) (odds ratio [OR], 0.35) (80). It is possible that treatment of *H. pylori* may prevent or decrease early precancerous lesions but may not alter more advanced lesions (63). Because initiation of oncogenesis may occur early and may not be amenable to antibiotics, use of vaccines in young children to prevent acquisition of infection has been suggested as a means to prevent gastric cancer (7, 211).

**Chlamydia trachomatis and cervical cancer.** *Chlamydia trachomatis* is an obligate, intracellular, Gram-negative bacterium that can be transmitted sexually. Different serovars have tropisms for different tissues. Serovars A to C infect the eye, while serovars D to K colonize the urogenital tract. Genital infection in women is often asymptomatic, but the chronic inflammation generated can cause cervicitis, cervical erosions (33), pelvic inflammatory disease, fallopian tube scarring, and infertility (8). Although human papillomavirus (HPV) is the prevalent cause of cervical cancer, there is some evidence that *C. trachomatis* may act as a cofactor in some cases.

The best epidemiological studies to date use prospective or nested case-control designs, use precancer diagnosis serology, and control for the effects of HPV and smoking. Some studies have also controlled for other possible confounders, such as human herpesvirus 2 infection, parity, and number of Papanicolau smears. *C. trachomatis* increases the risk of squamous cell carcinoma only, not adenocarcinoma, and the risk increases with higher antibody titers (227). Similar to the *H. pylori* serology studies of gastric cancer, the risk of cervical cancer with *C. trachomatis* infection is greater with increasing time from serum sampling to cancer diagnosis (136). This is likely because *C. trachomatis* serology wanes with time after antibiotic treatment (177, 195), and more-recent serum testing may miss the presence of past infections that resolved after already initiating the oncogenic process.

When seven studies from different countries were pooled, a positive association remained, with an adjusted OR of 1.8 (227). Individual studies have shown that *C. trachomatis* infection confers an increased risk of squamous cell carcinoma, with ORs between 2.2 and 6.6 after adjusting for HPV infection and smoking, and depending on the serotype involved (8, 65, 107, 177, 184, 257). It appears that there is some variation of risk depending on the serotype as well. Serotypes B, D, E, G, I, and J have been found to increase the risk of squamous cell cancer (14, 158), while serotypes C, F, H, and K have not.

How exactly *C. trachomatis* enhances oncogenesis in the setting of HPV infection is not fully understood but likely falls under the aegis of chronic inflammation and metaplasia (131). Other mechanisms have also been proposed. *C. trachomatis* may promote the persistence of HPV infection (213, 224). *In vitro* infection of fibroblasts and cervical tissue that were free of HPV showed decreased expression of the tumor suppressor gene caveolin-1 and increased expression of the proto-oncogene *c-myc*, indicating other possible ways that *C. trachomatis* may promote oncogenesis (218).

**Helicobacter species and biliary tract cancer.** Enterohepatic *Helicobacter* species, such as *Helicobacter bilis* and *Helicobacter hepaticus*, are bile-resistant organisms that can colonize the gallbladder (229). They have been isolated from bile and biliary tract tissue and have been implicated in the development of biliary cancers. Eight studies of humans have evaluated the presence of *Helicobacter* species in biliary tracts of cancer patients versus controls. These studies have had significant differences in their methods of bacterial detection, including culture, DNA amplification, and immunohistochemistry (58, 98). Controls have typically comprised subjects with biliary tract diseases such as gallstones or cholecystitis. Since these diseases
have also been linked to enterohepatic \textit{Helicobacter}, the use of these patients as controls may be inadequate (98). With these caveats, there has been wide variability in the study findings, from no association to a 6-fold increase in the odds of gallbladder cancer with \textit{Helicobacter} infection. Only two studies used controls with no biliary tract disease (28, 134). One of these showed an increased prevalence of \textit{Helicobacter} species in gallbladder cancer patients compared to that in controls (134).

**Chronic osteomyelitis, sinus tracts, skin ulcers, and squamous cell carcinoma.** In 1828, French surgeon Jean Nicholas Marjolin first described the development of raised tumors in chronic ulcers caused by vascular insufficiency (160). Not long after, Hawkins described cases of similar tumors arising in scar tissue from trauma and burn wounds as well as from infected bone (101). In these examples of chronic inflammation, infection plays a minor role. Since then, the development of malignancy has been described extensively in the setting of various infections, including chronic osteomyelitis, chronically draining sinus tracts, tropical (Buruli) ulcers due to \textit{Mycobacterium ulcerans}, and leprosy. The term “Marjolin ulcer,” initially coined by Da Costa in 1903, is now used to indicate malignant transformation that occurs in the setting of any chronic inflammatory lesion (20). Usage of the term, however, is not uniform. For example, although it is common in the burn literature, it is not used as frequently in case reports of carcinomas arising from chronic osteomyelitis or fistulous tracts.

A predominant feature of Marjolin ulcers arising from infection is the prolonged latency between the onset of infection and malignancy, which usually averages 3 decades or more. In the case of osteomyelitis, carcinomas typically derive from infections that began in childhood. Hence, the true incidence of Marjolin ulcers is unknown but is estimated to lie between 0.2% and 1.7% (20, 219). With improvements in antibiotic and surgical therapy of chronic osteomyelitis and chronic ulcers, the incidence of these cancers in industrialized countries has decreased substantially. Today, most cases are reported in areas with poor access to health care, where tropical ulcers, leprosy, and inadequate burn and wound care are more common (127, 226). The tumors in Marjolin ulcers are generally very aggressive, and metastases are found at diagnosis in 14% to 40% of cases. A recent review of 26 studies with a total of 443 cases found that, on average, 27.5% of cases had metastases at the time of presentation (127). Almost exclusively, the histopathology of the carcinoma is of the squamous cell type (161), either spindlecellular or verrucous (20, 252). However, basal cell carcinoma has also been reported (226).

The exact mechanisms leading to oncogenesis in Marjolin ulcers are unknown, but they likely rely on the processes of inflammation-induced DNA damage, repair, and increased proliferation described above. In the case of osteomyelitis and nonhealing ulcers, development of carcinoma is directly related to the duration of infection and drainage. In infected sinus tracts, the cells lining the tract undergo epithelial metaplasia, from which the squamous cell carcinoma arises (32, 164). Examination of chronic wound tissue has shown increased expression of the \textit{c-fos} and \textit{c-Ha-ras} proto-oncogenes, which are frequently involved in various human cancers (183). Investigators have also proposed that the avascular scar tissue in chronic wounds interferes with lymphocyte mobility and immune surveillance against damaged or precancerous cells (127). The latter mechanism is supported by findings of Marjolin ulcers in old, “healed” scar tissue, where inflammation is no longer an active process. Ultimately, however, no specific bacterial infection is the culprit. Rather, the general inflammation associated with chronic infection initiates the pathway to malignancy and is likely promoted by other factors which have yet to be identified.

**Colonic microflora and colon cancer.** The inflammation theory has also been applied to colorectal cancer, the third most common cause of death from cancer in the world (266a). Colorectal adenocarcinoma, similar to gastric adenocarcinoma, develops in a stepwise fashion. It begins in small areas of colonic epithelium with abnormal glandular architecture, known as aberrant crypt foci, from which benign adenomas arise. These can develop into dysplastic adenomatous polyps and, finally, into adenocarcinoma. The best evidence supporting the inflammation theory in colorectal cancer is seen in the augmented risk of patients with inflammatory bowel diseases (IBD), i.e., ulcerative colitis and Crohn’s disease. The cumulative incidence of colon cancer in IBD is as high as 18% at 30 years postdiagnosis (70). After the hereditary cancer syndromes, familial adenomatous polyposis and hereditary non-polyposis coli, IBD imparts the highest risk for colorectal cancer (250). Epidemiologic studies show that the severity and duration of inflammation in IBD dictate cancer risk (212).

The role of the colonic microflora in colon cancer is strongly suggested by various animal models. In the mouse model of familial adenomatous polyposis, for example, germfree mice develop colon cancer at half the rate of control mice (68). Several different experimental mouse models of IBD have been developed, and in all of them, germfree mice do not develop colon cancers, unlike mice raised in normal environments (73, 251). Investigation has thus turned to how colonizing bacteria may promote tumors. Toll-like receptors found on the surfaces of macrophages and dendritic cells may be involved. For example, mice deficient in myeloid differentiation factor 88 (MyD88) adapter protein, critical for Toll-like receptor signal transduction, have fewer and smaller adenomas than wild-type mice in experimental models of colon cancer (198). Additional studies now indicate that the commensal bacteria in the colon engage in complex interactions with the host’s innate, adaptive, and regulatory immune responses (73), and they may promote carcinogenesis through these interactions.

No specific bacterial organism has been identified as the culprit in colon cancer. In mice, inoculation with \textit{Citrobacter rodentium} leads to mucosal hyperplasia in the colon and to promotion of colon cancer (18), but there are no such findings for humans. Enterotoxigenic \textit{Bacteroides fragilis} (ETBF), which produces a metalloprotease toxin, has also been explored in relation to colon cancer. ETBF causes acute diarrhea but can also be part of the normal flora in up to 30% of adults (19). Mice that are chronically infected with ETBF develop colitis and colonic tumors 4 weeks after infection, whereas mice infected with non-toxin-producing \textit{B. fragilis} do not (269). The inflammation caused by ETBF in mice is mediated through Stat3 signaling and is accompanied by increased levels of IL-17-secreting CD4+ T cells.

Human data are scarce. Cross-sectional studies have found differences in colonizing \textit{Clostridium} species between patients
with colon cancer and controls, but a causal relationship remains to be proven (29, 171). In one study, ETBF was found more frequently in stools from colon cancer patients than in those from age- and gender-matched controls (246). Ultimately, because of the large number of bacteria colonizing the gastrointestinal tract, identifying a single species or even genus that is responsible for colon cancer is a daunting task. Nevertheless, modulation of the gut microflora as a means to prevent colon cancer is an area of intense investigation.

**Urinary tract infections and bladder cancer.** Bladder cancer is the fourth most common cancer in men (34). The predominant histology is that of transitional cell carcinoma, which accounts for 93% of cases. Squamous cell carcinoma and adenocarcinoma also occur, but at much lower frequencies—2% and 1%, respectively. Chronic bladder inflammation caused by the parasite *Schistosoma hematothium* has been reported to cause squamous cell cancer since 1911 (76). Indeed, the association between bladder inflammation and cancer was described by Virchow in the late 19th century (199). Demonstrating a role for bacteria, on the other hand, has been much more problematic. Experimental studies of bacterial infection and bladder cancer are scarce but evocative. Injections of *Escherichia coli* and other coliforms into rat bladders led to inflammation, papillary hyperplasia, and squamous metaplasia, suggesting chronic inflammation as the possible mechanism for carcinogenesis (34). Most of the data available, however, are limited to epidemiological studies of gonorrhea, nonspecific bacterial urinary tract infections (UTIs), and urinary tract stones.

(i) *Neisseria gonorrhoeae*. *Neisseria gonorrhoeae* is a Gram-negative diplococcus that causes urethritis in men and cervicitis in women. Urethritis in men often recurs after antibiotic treatment (30), and the chronic inflammation that can ensue has been considered a risk factor for carcinogenesis. Although *N. gonorrhoeae* primarily infects the lower urogenital tract, ascending infection into the bladder has been demonstrated in patients with gonococcal urethritis. In these patients, gonorrhea has been isolated from urine collected via suprapubic puncture, suggesting that urethral inflammation facilitates the propagation of bacteria into the bladder, where they may establish chronic infection as well (189, 190). Only three epidemiological studies have examined the possible role of gonorrhea and bladder cancer, and all of them were studies of men. Two case-control studies reported ORs of 2.1 and 2.42 (143, 165). For comparison, *syphilis*, which does not cause urethritis, was also examined in one of the studies, and no association was found (143). Case-control studies may be subject to recall and detection biases, however, as symptoms of bladder cancer and urethritis may be similar. Recently, however, a prospective study also reported an increased risk of bladder cancer (primarily of transitional cell histology) in those with a history of gonorrhea (relative risk [RR], 1.92). In addition, the finding of a stronger association between invasive bladder cancer (RR, 2.38) and a history of gonorrhea argues against possible detection bias in the study (163). In some of the patients with gonococcal urethritis, high counts of bacteria other than *N. gonorrhoeae* were cultured from urine collected by suprapubic puncture (189). It appears that the inflamed urethra becomes more permissive to ascending bacteria in general. If that is the case, then the association between bladder cancer and gonorrhea may be due to chronic inflammation caused by *N. gonorrhoeae* itself or perhaps by other ascending bacterial infections that result from urethritis.

(ii) Nonspecific urinary tract infections. The irritation caused by chronic UTIs and chronic indwelling catheters has been implicated in bladder cancer in spinal cord injury patients (34). This population is subject to frequent bacterial infections, and during screening cystoscopy, chronic cystitis and squamous cell metaplasia have been found at high frequencies (4). As with metaplasia from *H. pylori* infection in the stomach or from osteomyelitis and draining sinus tracts, such metaplasia connotes abnormal differentiation of cells in response to a chronic, adverse stimulus. Bladder cancer in spinal cord injury patients also has a much higher ratio of squamous cell carcinoma to transitional cell carcinoma (34), reflecting a similar inflammatory pathogenesis to that seen with bladder schistosomiasis. However, other than suggestive case reports, no epidemiological evidence of a causative relationship is currently available. With regard to nonspecific acute UTIs, there is controversy that they are associated with bladder cancer. Case-control studies have found positive (34, 89), null (124, 132, 193), and inverse (125) associations.

(iii) Urinary tract stones. Approximately 7% of urinary tract stones result from bacterial infections that raise the urinary pH and allow formation of struvite (179). Cytology of bladder washings from persons with stones and UTIs has shown squamous metaplasia, indicating a possible increased risk for malignancy. However, the association between bladder stones and bladder cancer is even more controversial than that of UTIs and cancer. Only two of seven case-control studies have found a positive association (ORs of 1.8 to 2.8) (34). With regard to kidney stones, a single case-control study reported an increased OR for cancer in women (OR, 3.7) but not in men (132).

Given the paucity of data from prospective studies, causative relationships between UTIs or stones and bladder cancer have not been established. As in all case-control studies, recall and selection biases may explain the positive associations that have been seen. In the studies reporting the higher ORs for cancer, UTIs were reported less than 4 years from cancer diagnosis, which suggests a possible detection bias (4). In addition, studies of bladder cancer may be subject to reverse causation and detection biases: early symptoms of bladder cancer may mimic UTI symptoms, and those with more frequent urinary tract infections may undergo more frequent evaluation with cystoscopy. Kantor et al. reported a stronger association of UTIs with the squamous cell type than the transitional cell type of tumors (126). It is possible that the association, if it exists, is limited to squamous cell carcinomas only and that including transitional cell carcinomas in the analyses obscures the findings through misclassification. Potential confounders such as the antitumor effects of NSAIDs or antibiotics used by patients may also need to be assessed (125).

**Sexually transmitted infections, prostatitis, *Propionibacterium acnes*, and prostate cancer.** Much like the case for bladder cancer, epidemiological studies have long suggested chronic inflammation from infection as a risk factor for prostate cancer (204, 239), but a causative infectious agent has remained elusive. Bacterial pathogens have been examined, with inconclu-
sive results. Gonorrhea, syphilis, Chlamydia trachomatis, and Propionibacterium acnes have all been implicated by various investigators, as has nonspecific inflammation from chronic prostatitis.

Histologically, inflammation in the prostate is accompanied by infiltration of mononuclear cells, epithelial atrophy, a low apoptotic index, and increased cellular proliferation. These inflammatory changes are frequently seen adjacent to and are presumed to give rise to cancerous prostatic lesions (59). The hypothesized mechanisms for inflammation-related carcinogenesis in the prostate involve accumulating mutations in the tumor suppressor gene p53, gains in centromeric DNA sequences on chromosome 8, and CpG island hypermethylation (130). In addition, studies of prostate cancer have found abnormalities in several genes that are involved in control of infection and inflammation. MSR1, TLR-4, and RNase L increase susceptibility to bacterial infection, MSR1 and PON1 are linked to the oxidative burst in response to infection, OG1, CHEK2, and BRCA2 are involved in DNA repair, and MIC1 and MSR1 are necessary to control the inflammatory response to infection (133, 139). An increased number of single nucleotide polymorphisms in many genes in the inflammatory pathway in prostate cancer patients also supports the infection/inflammation theory for prostate cancer (277).

(i) Sexually transmitted infections. Since the 1970s, sexually transmitted infections (STIs) have been investigated as risk factors for prostate cancer. In some individuals, levels of prostate specific antigen (PSA) rise shortly after acquisition of gonorrhea, nongonococcal urethritis, chlamydial infection, and trichomoniasis, suggesting prostatic inflammation (240). Chlamydia trachomatis is a candidate pathogen for prostate cancer because it causes urethritis and epididymitis with marked tissue inflammation (256), and extension of bacterial infection into the prostate is biologically plausible. Some investigators have found C. trachomatis in prostatic tissues from patients with prostatitis, albeit with some variability in methods and results (262). However, positive associations have not been found between C. trachomatis and prostate cancer in nested case-control studies (15, 60, 66, 237). Rather, in one of them, fewer men with positive serology for C. trachomatis developed prostate cancer (15).

Syphilis and gonorrhea have also been studied independently, although most studies combine several STIs to assess the risk for prostate cancer. Meta-analyses have found a positive association for gonorrhea (OR, 1.35) but variable results for syphilis (61). However, the case-control studies on which these meta-analyses are largely based may have inherent recall, detection, and selection biases. Three prospective studies have evaluated syphilis, gonorrhea, and prostate cancer, all of them with null findings (236). In a recent study that followed a multiethnic cohort, only a subgroup (foreign-born Latinos with either gonorrhea or any STI) showed an increased risk of prostate cancer. Ultimately, the association between prostate cancer and STIs may be increasingly difficult to study in developed countries, where rates of infections have significantly decreased. If recurrent infections and the duration of infection have an effect on cancer risk, studies in countries where access to diagnosis and medical care is often delayed may provide the answer.

(ii) Prostatitis. Along with STIs, clinical prostatitis has also been considered a risk factor for prostate cancer. A meta-analysis of 11 case-control studies from 1966 to 2000 found a summary risk of 1.57 for prostate cancer (62). However, as in the case of STIs, both positive and null associations were found in subsequent case-control studies (56, 204). The largest risk (OR, 4.93) was identified in a study of African-American men (215). More typical, however, are studies that find elevated risks only for subsets of individuals, e.g., men younger than 59 years of age (RR, 1.87) (236) or those with a long duration of symptoms (46). Moreover, when results are stratified by the presence of benign prostatic hypertrophy, thereby increasing the likelihood of prostate cancer screening, the association between prostatitis and cancer is attenuated.

(iii) Propionibacterium acnes. Recently, attention has turned to P. acnes as a possible agent in the pathogenesis of prostate cancer (50). Typically associated with acne, P. acnes is a Gram-positive bacterium that colonizes the urinary tract in some men following puberty (222) and can persist for years in the prostate gland (10). A small study showed that high antibody titers for P. acnes were predictive of high PSA levels in men with benign prostatic hyperplasia (BPH), suggesting the presence of tissue inflammation with infection (221). Furthermore, P. acnes has been cultured from one-third of prostate cancer specimens, particularly those with histological evidence of inflammation (50). In another study, fluorescence in situ hybridization combined with confocal laser microscopy identified P. acnes in 5 of 10 samples of prostate cancer and identified intracellular aggregates of P. acnes in prostate tissues with both prostate cancer and BPH (10).

Epidemiological data linking P. acnes to cancer are sparse. Using PCR analysis of archived specimens, Alexeyev found no difference in P. acnes RNA in benign prostatic hypertrophy patients who went on to develop prostate cancer and those who did not (9). In studies of acne history and prostate cancer, two early case-control studies found no association or a protective effect (86, 152). Prospective studies have been more suggestive of a positive association (82, 238). However, the level of androgen hormones, an important potential confounder, was not assessed (118) and needs to be considered in any future research in this domain.

Overall, infectious links with prostate cancer are weak. Many of the studies to date are hampered by limitations of study design (case-control studies with recall and detection biases); selection of controls (and possibly overlapping cases with controls with BPH, who may be too similar in exposure to the cases); definitions of prostatitis and infections (many of them by self-report); overlapping symptoms between infection, BPH, and cancer; difficulty in accounting for potential confounders (e.g., testosterone or antibiotic treatment for acne); and the high likelihood of undiagnosed asymptomatic infections and inflammation (109). In addition, all of the pathogens suggested so far may not be causative agents themselves but may be markers of an as yet unidentified infection, either bacterial or viral, that does promote prostate cancer. The finding that NSAIDs, including aspirin, reduce the risk of prostate cancer (55, 159) suggests that inflammation may play a role, but given the available evidence, a causative association between bacterial infection and prostate cancer remains highly speculative.
Pyothorax-associated lymphoma. First described in Japan in 1987, pyothorax-associated lymphoma (PAL) is a non-Hodgkin's B-cell lymphoma arising in the pleural cavity in patients more than 20 years after their treatment for tuberculosis with artificial pneumothorax (16). A procedure used in the preantibiotic era, artificial pneumothorax consisted of introducing air in repeated treatments over 1 to 2 years into the pleural space to compress the infected lung. It was thought to allow the infected lung to rest and heal and to decrease the bronchial spread of tuberculosis (102). The chronic inflammation induced by the treatment led to chronic pyothorax in the pleural cavities of patients. This chronic pyothorax, rather than the original infection, is considered to underlie the development of lymphoma. Instead of the original infection, is considered to underlie the development of lymphoma. Instead of the original infection, chronic inflammation due to chronic infection (123). Bacterial infection has been associated strongly with PAL and has been found in 70% to 85% of the tumors in case series from Asia (174, 181). In one small study, EBV latent gene products, such as Epstein-Barr nuclear antigen 2 and latent membrane protein 1, were found in all four cases of PAL versus none of 50 other control B-cell lymphomas, and EBV genomic material was found to be clonal (216). In another study, EBV genomes were found in 28 of 33 PAL cases and only 1 of 16 controls with pyothorax (181).

Antigen-Driven Lymphoproliferation

Antigen-driven B-cell proliferation can be thought of as a T-cell-initiated process that occurs within the context of chronic inflammation due to chronic infections (123). Bacterial antigens drive the generation of the Th1-type cytokines IFN-γ and IL-2, stimulating epithelial and endothelial cells to secrete the IFN-γ-induced chemokines CXCL9 and CXCL10. These chemokines then attract more Th1 cells to the site of inflammation (137). The excess immune stimulation by persistent antigens creates T-cell-driven B-cell hyperplasia, from which a malignant cell undergoes unchecked clonal expansion and gives rise to mucosa-associated lymphoid tissue (MALT) lymphomas (120). Both the T cells recruited to the site of inflammation and the B cells of MALT lymphomas express CXCR3, a receptor for IFN-γ-induced inflammatory chemokines (196, 235, 253). After some time, MALT lymphomas may progress to a state that then becomes independent of the underlying chronic infection that instigated its initial growth.

MALT lymphomas, also known as extranodal marginal-zone B-cell lymphomas, make up 7 to 8% of adult non-Hodgkin's lymphomas. They can occur at multiple sites, including the lung, gastrointestinal tract, salivary gland, thyroid, liver, ocular adnexa, and skin. Chronic infections with Helicobacter pylori, Chlamydia phila psittaci, and Borrelia burgdorferi have been found with gastric, ocular/adnexal, and skin MALT lymphomas, respectively. MALT lymphomas arise in organs typically devoid of lymphoid tissue. They are generally indolent tumors that resemble antigen-selected B cells and express mutated immunoglobulin genes, mostly of the IgM isotype, frequently with rheumatoid factor reactivity (23). Many of them regress with antiinfective treatment, supporting the role of bacterial infection and oncogenesis. The discovery of some causative infections in MALT lymphomas has allowed significant progress in understanding the pathophysiology of this malignancy.

Several specific chromosomal abnormalities have been described for MALT lymphomas, involving t(11;18), t(1;14), t(14;18), and t(3;14). Some of the translocations, such as t(11;18)(q21;21), are found only in MALT lymphomas, but at variable frequencies depending on the organ tissue involved. The oncogenic properties of the identified chromosomal aberrations lead to a common final pathway, i.e., activation of NF-κB in lymphocytes. NF-κB physiologically checks the tumor suppressor gene p53 and effectively renders cells impervious to senescence and apoptosis. Some upstream events have been elucidated involve deregulation of the BCL10 and/or MALT1 gene. BCL10 is a nuclear transcription factor necessary for B- and T-cell development, with effects on NF-κB activation. MALT1 is involved in antigen receptor-mediated activation of NF-κB. Alterations in both of these proteins appear to work in concert to activate the NF-κB signaling pathway (157). The most recently identified translocation, t(3;14)(p13;q32), affects FOXP1, which encodes a transcription factor involved in B-cell development and differentiation (69). Overall, however, translocations are present in only a minority of MALT lymphoma cases. In addition to translocations, genomic screens of MALT lymphoma tissue have identified entire chromosome or large segment gains involving chromosomes 1, 3, 12, 18, 22, and X (25, 280). Smaller discrete gains have also been seen with chromosomes 1, 9, 11, and 17 (279). It is still unclear which pathways are altered by these chromosomal gains (or occasional losses), but it is hypothesized that they involve proteins that lead to dysregulation of NF-κB activation, similar to what has been observed with the translocation abnormalities. Based on studies of transgenic mice, these chromosomal abnormalities alone, however, seem to have weak oncogenic potential. Oncogenesis requires additional immunologic stimuli via antigen receptors and, perhaps, CD40-mediated costimulation (69). Chronic inflammation caused by persistent infection is thus permissive but not sufficient for malignancy.

Helicobacter pylori and gastric MALT lymphoma. The stomach is the most common site of MALT lymphoma, accounting for approximately 50% of all cases. Histologically, the tumors are characterized by diffuse and/or nodular infiltrates of small neoplastic lymphoid cells that infiltrate the gastric epithelium and lymphoid follicles (77). An etiologic relationship between MALT lymphoma and H. pylori was first hypothesized with the recognition that patients with H. pylori-associated chronic gastritis accumulated lymphoid follicles in the stomach, with B-cell infiltration of the epithelium, a characteristic of MALT. Immunohistochemistry also revealed H. pylori in 92% of MALT lymphoma tissue samples, a frequency much higher than the typical 50 to 60% background prevalence of infection (268). Subsequent epidemiological studies supported these findings. Since then, ample evidence in various geographic cohorts has confirmed the association between H. pylori and gastric lymphoma (67). In a nested case-control study in the United States, patients with gastric lymphoma were 6.3 times more likely than matched controls to have had H. pylori infection (187).

As described above, chronic infection with H. pylori creates a chronic inflammatory response that is associated with increased expression of certain cytokines (e.g., TNF-α), leading to upregulation of NF-κB and other proinflammatory pathways. Chronic inflammation of the gastric mucosa can lead to chronic gastritis, which in turn can promote the proliferation and accumulation of B lymphocytes in the gastric mucosa. Over time, this process can lead to the development of MALT lymphoma. This association has been confirmed in large epidemiological studies, with an increased risk of MALT lymphoma associated with H. pylori infection. The association is stronger in countries with a higher prevalence of H. pylori infection, and the risk is highest in patients with chronic gastritis.

The discovery of H. pylori as a causative agent has led to significant advances in the treatment and prevention of MALT lymphoma. Eradicating the infection using antibiotics can lead to resolution of the chronic gastritis and regression of MALT lymphoma in some cases. This has led to the development of guidelines for the management of MALT lymphoma, emphasizing the importance of eradicating H. pylori infection when it is present. However, the natural history of MALT lymphoma can be complex, with some cases progressing to higher-grade lymphomas, including diffuse large B-cell lymphoma (DLBCL). Therefore, close monitoring and follow-up are essential for patients with MALT lymphoma to ensure early detection and appropriate management of any progression.

Several studies have investigated the molecular mechanisms underlying the development of MALT lymphoma after H. pylori infection. Chromosomal abnormalities, including translocations and gains, are common in MALT lymphoma and can contribute to oncogenesis. In particular, the t(1;14) translocation, which affects the BCL10 gene, is frequently observed in MALT lymphoma. This translocation leads to the deregulation of the NF-κB pathway, contributing to the malignant transformation of B cells.

In conclusion, the discovery of H. pylori as a causative agent for MALT lymphoma has had a profound impact on the understanding of the disease and its management. The association between H. pylori infection and MALT lymphoma has led to a paradigm shift in the treatment and prevention of this lymphoma, emphasizing the importance of eradicating the infection when present. However, the natural history of the disease remains complex, and close monitoring and follow-up are essential for patients to ensure early detection and appropriate management.
lymphomas proliferated when grown with *H. pylori* antigens and *H. pylori*-specific T cells (115). Interestingly, though, the immunoglobulin produced by MALT lymphoma reacts with autoantigens rather than with *H. pylori*. It appears that T cells are the ones to react with *H. pylori* antigens and then provide contact costimulation of the malignant B cells (114). The roles of various *H. pylori* virulence factors in MALT lymphoma have been examined, but with no clear indication of any one gene being involved in pathogenesis. A combination of alleles of the icaA1, sabA1, and hopZ genes increased the odds of developing MALT lymphoma 10-fold, but this combination is rare in the population (146). The open reading frame for CagA, which confers increased risk of gastric adenocarcinoma, does not have equally strong links to lymphoma (77). Aberrant cellular DNA methylation has also been examined in gastric MALT lymphoma. DNA methylation at islands of cytosine followed by guanine dinucleotides (CpG) is an essential cellular process for normal development and serves to suppress gene expression. However, excess DNA methylation seen in the CpG island methylator phenotype (CIMP) has been linked to inactivation of tumor suppressor genes in various cancers. For gastric MALT lymphomas, CIMP was observed in 100% of high-grade MALT lymphomas, 61.9% of MALT lymphomas, and none of the control group specimens. Furthermore, the number of methylated genes and the incidence of CIMP increased significantly with *H. pylori* infection (135). Exactly how *H. pylori* infection leads to increased CpG island methylation, however, is still under investigation.

Treatment of *H. pylori* infection is very successful in treating MALT lymphomas, especially during the early stages of the disease (234). A recent pooled analysis of approximately 1,300 patients with gastric MALT lymphoma showed that successive attempts at *H. pylori* antibiotic treatment achieved eradication of infection in 98.3% of cases and that 77.8% of the *H. pylori*-cured patients achieved lymphoma remission (284). Unfortunately, reinfection with the same strain of *H. pylori* can reactivate the growth of the lymphoma. High-grade gastric lymphomas, on the other hand, are generally believed to be *H. pylori*-independent tumors evolved from low-grade lymphomas (234). Although more rare, regression of high-grade gastric lymphomas after the cure of *H. pylori* infection can also occur. MALT lymphomas that do not respond to antibiotics often have chromosomal translocations t(1;14)(p22;q32) and t(11;18)(q21;q21) as well as other genomic changes (267). Increasing chromosomal damage may allow MALT lymphomas to become independent of *H. pylori* infection (81). Yet such damage is found in only half of antibiotic-resistant cases of MALT lymphoma, and more research is needed to identify other markers and causes of treatment nonresponse.

**Non- pylori Helicobacter species and MALT lymphoma.** Gastrointestinal forms such as *H. suis*, *H. felis*, *H. salomonis*, *H. bizzozeronii*, and "Candidatus Helicobacter heilmani," can occasionally infect humans. Approximately 0.1% to 0.6% of human gastric *Helicobacter* infections are attributed to these non-*pylori* species (95, 182, 225), sometimes concomitant with *H. pylori* infection (117). Non-*pylori* gastric *Helicobacter* organisms cause chronic gastritis and inflammation that are less severe than those caused by *H. pylori*. In humans, 5 to 10% of gastric MALT lymphomas that are negative for *H. pylori* may be due to other *Helicobacter* infections (167). Case reports of gastric MALT lymphoma attributed to non-*pylori Helicobacter* species have been described in Japan and Europe (202, 233, 247), but no large series has been published. In the scattered reports, the response of non-*pylori Helicobacter*-related MALT lymphoma to antibiotic treatment is similar to the response of *H. pylori*-associated disease (182), and similar oncogenic mechanisms are posited.

**Helicobacter pylori and gastric DLBCL.** Primary diffuse large-B-cell lymphoma (DLBCL) of the stomach is another form of extranodal non-Hodgkin’s lymphoma that can occur in gastric tissue. DLBCL is clinically aggressive, and tissue examination shows a large number of transformed cells. This cancer has been thought to arise from gastric MALT lymphoma that has undergone high-grade transformation and lost the need for *H. pylori* antigen drive to proliferate. However, histopathology studies have suggested that DLBCL does not always arise from low-grade MALT lymphoma or lose dependence on *H. pylori* antigens. Consequently, DLBCL has been classified as a separate entity (40). The pathways to oncogenesis involving *H. pylori* infection in primary DLBCL are likely similar to those described for gastric MALT lymphoma. Examination of DLBCL tissue has shown overexpression of B-cell activating factor of the TNF family (BAFF), which physiologically mediates BCL10 expression and indirectly activates NF-κB. In addition, BAFF overexpression was found in 70% of DLBCLs that did not respond to *H. pylori* treatment and 18.8% of those that did respond, indicating that it may allow DLBCL to gain *H. pylori*-independent growth (140). Similar to the case for gastric MALT lymphoma, excess methylation and CIMP are highly prevalent in DLBCLs (93.3%) (135). Although DLBCL is often refractory to antibiotic therapy, complete remission with *H. pylori* eradication has been described, but the overall success rates (57.9 to 68.9%) with antibiotic therapy are lower than those for gastric MALT lymphomas (40).

**Chlamydocephila psittaci and ocular adnexal MALT lymphoma.** The ocular adnexa, composed of the conjunctiva, lacrimal gland, orbital fat, eyelid, and lachrymal sac, are also susceptible to the growth of MALT lymphomas. These types of tumors are on the rise, with an incidence of >6% in some areas. They appear after the 4th decade of life and are more common in women. Like the case for gastric MALT lymphoma, occasional chromosomal translocations are found in ocular adnexal MALT lymphoma, but with a lower frequency. More common are discrete chromosomal gains and trisomies, especially involving chromosomes 3, 6, 9, and 18 (69, 232).

There is some suggestion that *Chlamydia* species may be responsible for ocular adnexal MALT lymphoma. Chlamydiae are small intracellular bacteria that cause human disease in lung, genitourinary, and ocular tissues. They can establish persistent infections in humans and are a known cause of chronic conjunctivitis. Comparable to *H. pylori*, *Chlamydia* can establish chronic infection and cause lymphoid aggregates in mucosa-associated sites. Also like *H. pylori*, *Chlamydia* species have been implicated as cofactors in the development of adenocarcinoma (224).

Using immunohistochemistry coupled with DNA amplification, studies in Italy and Korea found a high prevalence (80 to 87%) of *C. psittaci* in human ocular adnexal MALT lymphoma tissues (77, 234). In addition, *C. psittaci* DNA was found in 43% of peripheral blood mononuclear cells (PBMCs) of pa-
tients, but not in healthy donors. Studies in other parts of the world, however, have yielded mixed results (45, 232, 254). A meta-analysis of 11 published studies with 458 cases of ocular adnexal MALT lymphoma found that *C. psittaci* was present in 25% of the tissue samples, although 90% of the positive specimens came from only 3 of the studies (113). Some of these discrepancies may be due to the different detection methods that were used, including immunohistochemistry, immunofluorescence, electron microscopy, and DNA amplification. In the studies with the highest prevalence of infection, *C. psittaci* DNA was detected using a monoclonal antibody against *Chlamydia* lipopolysaccharide coupled with PCR analysis.

The response of some cases of ocular adnexal MALT lymphoma to antibiotics has suggested that *C. psittaci* infection is causal (6, 78, 234). In a meta-analysis of four studies, 20 patients were reported to have responded to antibiotic therapy, another 20 patients had stable disease, and 2 progressed during antibiotic treatment (113). During more than 12 months of follow-up, lymphoma recurred in seven patients. The clinicopathologic characteristics, recurrence rate, progression-free survival, and overall survival did not differ in patients with and without *C. psittaci* infection. On the whole, the studies to date suggest that if the association between *C. psittaci* and ocular adnexal lymphoma is real, then there is wide geographic variability. Moreover, it is possible that another unidentified organism, treated concurrently, is actually responsible for ocular adnexal MALT lymphoma. Alternatively, doxycycline alone, which has known anti-inflammatory properties that include inhibition of T-cell activation and T-cell proliferation (214), might permit regression of lymphomas independent of any underlying infection. Larger prospective trials with standardized and objective response criteria are needed to clarify the role of antibiotics in the treatment of ocular adnexal MALT lymphoma.

*Borrelia burgdorferi* and MALT lymphoma of the skin. *B. burgdorferi* is the tick-borne spirochete that causes Lyme disease. Studies from Scotland and Italy have reported an association between *B. burgdorferi* and primary cutaneous B-cell lymphoma (PCBCL), a type of MALT lymphoma (78, 92). Similar to *H. pylori* in gastric MALT lymphoma, *B. burgdorferi* is thought to provide chronic antigen stimulation leading to the development of MALT lymphoma of the skin. In one study, *B. burgdorferi* infection was demonstrated in skin biopsy lesions of two patients prior to the development of PCBCL, suggesting a temporal relationship between infection and development of lymphoma (91). Bacterial culture or DNA amplification methods have found evidence of infection in up to 80% of patients with PCBCL (78). However, studies in the United States (265), Asia (149), and parts of Europe (94, 243) have found little evidence of *B. burgdorferi* in PCBCL patients. Perhaps the variable prevalence of infection in PCBCL is explained by the different prevalences of *Borrelia* strains across the world or by differences in techniques used for detection of infection.

The molecular genetics of cutaneous MALT lymphoma differs somewhat from that of the other MALT lymphomas. Notably, translocations are uncommon (69). Activation of NF-κB may occur through mechanisms such as TLR2 signal transduction elicited by the outer surface proteins of the bacterium (150, 266). PCBCLs also appear to differ from other MALT lymphomas in other ways: they tend to produce switched immunoglobulins that lack rheumatoid factor reactivity, they do not express CXCR3, and they produce a cytokine profile that appears biased toward the Th2 type of cellular response (253). Unlike gastric MALT lymphoma, only a few cases of PCBCL have responded to antibiotics (42, 57, 91, 141, 266). As in the case of *C. psittaci* and ocular adnexal MALT lymphoma, if *B. burgdorferi* is truly associated with PCBCL, then there is wide geographic variability and other factors are probably involved.

**Campylobacter jejuni infection and IPSID.** Previously known as alpha-heavy chain disease, immunoproliferative small intestinal disease (IPSID) is a rare form of MALT lymphoma with a predilection in Mediterranean areas with poor sanitation. A characteristic of this disease is the finding of alpha-heavy chains in the sera of 20 to 90% of patients (11). The cause of IPSID has been ascribed to *Campylobacter jejuni*, a Gram-negative rod that causes diarrhea and is associated with chronic autoimmune diseases such as Guillain-Barré syndrome and reactive arthritis. Although *C. jejuni* infection has been shown to persist in the mouse (144), human infection is thought to be transient, except in immunocompromised persons. This aspect of *C. jejuni* infection distinguishes it from all other examples of bacterial antigen-induced MALT lymphoma, where chronic infection is the hallmark. However, it is possible that chronic *C. jejuni* infection occurs more frequently and is simply undetected or underrecognized (188). *C. jejuni* has been found in five of seven tissue samples from patients with IPSID. IPSID, similar to other MALT lymphomas, can regress with antibiotic treatment (11, 144).

**Other associations.** Other associations between bacterial infection and B-cell proliferation have been examined in a few studies. Among these, *H. pylori* seropositivity in childbearing women has been linked with childhood acute lymphocytic leukemia in their offspring (147), and *Chlamydia pneumonia* has been associated with lung MALT lymphoma (44) and the Sézary syndrome (5). However, the lack of sufficient data precludes any conclusions about these associations at this time.

**Effects Mediated through Human Gastrin Hormone**

Gastrin is a hormone peptide produced by neuroendocrine G cells in the antrum of the stomach. It is released in response to different stimuli, including intraluminal protein and calcium. During normal physiology, gastrin stimulates enterochromaffin-like cells to release histamine, which in turn stimulates parietal cells to increase acid secretion. The increased acidity creates a negative feedback loop by stimulating neuroendocrine D cells to release somatostatin, which then inhibits gastrin release. Gastrin is first released as a precursor protein that undergoes posttranslational modification through protein cleavage and the addition of glycine or amide moieties (35). There is growing evidence linking gastrin and its precursors to gastrointestinal tumors. Disease states that feature hypergastrinemia, such as the Zollinger-Ellison syndrome or autoimmune atrophic gastritis, are associated with gastric malignancies, most notably gastric neuroendocrine (carcinoid) tumors. Some posit that chronic infection with *H. pylori* also causes cancers through this mechanism. Human experimental studies have shown that infusion of supraphysiological levels of gastrin causes increased gastric cell proliferation (99), and increased
gastrin expression is found in developing gastric cancer cells (104). Besides stimulating acid secretion, gastrin has been found to (i) drive proliferation of the gastric mucosal epithelium, particularly in the gastric antrum; (ii) interfere with apoptosis of normal and transformed gastric epithelial cells; (iii) enhance expression of cyclooxygenase-2, thereby increasing angiogenesis; and (iv) regulate tissue remodeling and invasion (35). In addition to local action on gastric mucosa, gastrin has also been found to have more distal trophic effects on various tissues, such as the colon, pancreas, and lung (12, 35, 242).

*Helicobacter pylori*, **gastrin, and gastric adenocarcinoma.** In some hosts, *H. pylori* leads to atrophic gastritis and achlorhydria; the ensuing decrease in acidity can lead to compensatory elevations in serum gastrin. Yet even at comparable gastricacidities, persons with *H. pylori* infection have higher gastrin levels than uninfected controls (228). Hence, a plausible alternate mechanism is that *H. pylori* infection causes a loss of somatostatin inhibition of gastrin release, leading to hypergastrinemia. This is supported by the finding that *H. pylori* antibiotic treatment leads to lower gastrin expression levels and concomitantly higher somatostatin gene expression levels in infected patients (168). *H. pylori* infection acts in concert with gastrin to induce the secretion of growth factors, such as heparin-binding epidermal growth factor (HB-EGF), that promote cell cycling and proliferation (64, 255).

In animal models, gastrin appears to act in synergy with *H. pylori* in the development of gastric cancer. Transgenic mice that overproduce gastrin develop gastric cancer, but *Helicobacter* infection significantly accelerates the process (241, 261). Although studies with animal models and human cancer cell lines are promising, there are insufficient data regarding the effect of *H. pylori*-induced hypergastrinemia on gastric adenocarcinoma in humans.

*Helicobacter pylori*, **gastrin**, and **colorectal adenocarcinoma.** In the various premalignant colonic lesions (adenomas, dysplastic polyps, etc.), gastrin and its receptor, cholecystokinin-2 (CCK-2) receptor, have been found to be upregulated, and these proteins are believed to play a significant role in the development of colorectal cancer (242). Because *H. pylori* increases gastrin levels, an association between *H. pylori* infection and colorectal neoplasia has frequently been sought. Although the findings are still debated, *H. pylori* infection appears to increase the risk of colonic adenomas, particularly in the more distal colon (31, 36, 85, 169, 223). The postulated mechanism is similar to that derived for gastric cancer: *H. pylori*-induced hypergastrinemia influences precancerous lesions toward malignant transformation. However, the actual association between *H. pylori* infection and colorectal cancer is highly debated. Epidemiological studies of *H. pylori* infection and colorectal cancer are conflicting and fraught with limitations. Several had poor matching of cases and controls or did not consistently adjust the comparisons for confounders. At least nine have shown no association, while in those with positive associations, the odds ratios have ranged from 1.7 to 3.8. The three largest studies, which were also the only nested case-control studies, found no association between *H. pylori* infection and colorectal cancer (154, 205, 244). Although in one of these studies above-normal gastrin levels increased the risk of colorectal cancer (OR, 3.9), *H. pylori* infection was not linked to colorectal cancer, despite being correlated highly with hypergastrinemia (244). A meta-analysis found a significantly increased risk of colon cancer in *H. pylori*-infected patients (OR, 1.5) (276), but if an association does exist, it is relatively weak for an infectious agent.

*Helicobacter pylori*, **gastrin**, and **lung cancer.** The effect of *H. pylori* infection on cancers outside the gastrointestinal tract has garnered some attention as well. The respiratory epithelium shares a similar embryological origin with gastrointestinal epithelium, and gastrin can increase the proliferation of bronchial epithelium. Serum gastrin levels are higher in lung cancer patients than in controls and correlate with tumor stage (278). Resection of the tumor leads to decreases in serum gastrin levels. Although the hypergastrinemia in these patients is likely of tumor origin, there have been speculations that hypergastrinemia induced by *H. pylori* infection also contributes to the development of lung cancer. A link with *H. pylori* infection has been sought in only four small case-control studies. Two studies reported a positive association (71, 87), whereas the other two found no association. In the studies with null associations, there were no adjustments for important confounders such as smoking or sex (173, 192). Pooled analysis of the studies suggests that *H. pylori* infection increases the risk of lung cancer 3-fold. However, the data available thus far are quite limited (281).

**DIRECT BACTERIAL EFFECTS ON ONCOGENESIS**

**Oncoproteins and Cell Transformation**

*Mycoplasma species* and human cancers. Mycoplasmas are the smallest known free-living bacteria. Averaging 0.25 μm in diameter, they are less than one-third the size of *Escherichia coli*. The genus *Mycoplasma*—with 13 different species that infect humans—ubiquitously colonizes the respiratory and urogenital tracts. Several serious disease entities are associated with mycoplasmas, including pneumonia, urethritis, prostatitis, endometritis, and arthritis. Since the 1960s, *Mycoplasma pneumoniae* has been postulated to cause human leukemia. However, seroepidemiological studies of leukemia patients and controls found no association, and difficulties remained in establishing this organism as an etiologic agent of any cancer (49). The finding of mycoplasma seropositivity in leukemic patients could simply represent opportunistic infections of the immunocompromised. Furthermore, mycoplasmas are difficult to detect and diagnose because they are typically noncultivable. The recent development of molecular amplification techniques and immunoassays allowed mycoplasmas’ role in malignancy to be assessed more accurately.

Mycoplasmas, in particular *Mycoplasma fermentans*, *Mycoplasma penetrans*, and *Mycoplasma hyorhinis*, were reported to have oncogenic potential when in vitro cultures showed cell transformation in a variety of experimental cell lines. Skepticism remained about their oncogenic potential because most of the initial studies were carried out with cell lines that are highly prone to spontaneous mutagenesis. However, experiments using cells with low levels of mutagenesis have also shown similar cell transformation effects with prolonged infection. In studies using CH3 cells (of murine embryonic origin), mycoplasma infection appears to transform cells through increased expres-
sion of the c-Ras and c-myc oncogenes (271). After a long period of latency of infection, the cells undergo both reversible and irreversible chromosomal changes during their malignant transformation (272). The gene alterations occur in a stepwise fashion, with an accumulation of abnormalities which parallel the phenotypic changes of the cells (273). Other investigators have reported similar findings. In some experiments, cells are not transformed after infection of CH3 cells with *M. fermentans* and *M. penetrans* but accumulate chromosomal abnormalities with prolonged infection. This suggests that at the very least, *Mycoplasma* promotes the progression of malignant transformation in the mouse (248).

Since the initial murine studies, investigators have examined the oncogenic effect of mycoplasma infection in experimental human cell lines. Malignant transformation and immortalization occur in bronchial epithelial cells (200), human prostate cells (with *M. hyorhinis* (90, 175), and cervical cells (275). Most provocative of all, mycoplasma-induced transformation is also seen in PBMCs from healthy donors (274). Normal PBMCs do not survive beyond a few weeks *in vitro*. However, if infected with EBV, PBMCs occasionally spontaneously immortalize—a step that is considered necessary for malignant transformation. In their study, Zhang et al. showed that 6 weeks of *in vitro* infection with *M. fermentans* led to the malignant transformation of 74% of EBV-positive human PBMCs from healthy donors, in contrast to 17% at baseline. The transformed PBMCs displayed prominent chromosomal changes, including losses, gains, and translocations, and tended to be monoclonal (274).

In tissue specimens from actual patients, mycoplasmas are found in precancerous lesions as well as in malignant tissues, such as those from stomach, colon, ovarian, and lung cancers (43, 112, 129, 142, 191). The prevalence of mycoplasma infection is significantly higher in stomach and colon cancer tissues (43, 112, 129, 142, 191). The prevalence of mycoplasma infection is significantly higher in stomach and colon cancer tissues than in their respective precancerous lesions (112). Stomach and colon cancer tissues with evidence of infection also have more inflammatory infiltrates (142). Not all studies have positive findings, however. When the presence of *M. genitalium* was examined in 186 frozen ovarian tissues obtained from patients with diseases ranging from benign conditions to borderline tumors and ovarian cancer, none of the samples were positive (116).

How mycoplasma infection might cause cell transformation is being investigated. *Mycoplasma* likely acts through activation of NF-κB to inhibit the impact of the tumor suppressor p53 on cell cycle arrest and apoptosis of damaged cells. In a recent murine cell culture study, Logunov et al. found that several mycoplasma species, *M. arginini*, *M. fermentans*, *M. hominis*, and *M. arthritidis*, suppress host cell p53 and constitutively activate NF-κB. Most exciting was the finding that treatment of the cells with ciprofloxacin prevented transformation (155).

There are also several studies that suggest that P37, a lipoprotein present on the membrane of the bacterium, plays a key role. In mammalian tissue cultures, recombinant P37 promotes cell motility, migration, and invasion (88, 175). P37 also induces antigens of the oncoprotein human epidermal growth factor receptor related 2 (HER2) to inhibit cell adhesion. Some of these effects can be blocked completely with a neutralizing antibody to P37, corroborating the oncogenicity of the mycoplasma protein (90, 128). Overall, *in vitro* studies and examinations of human cancer tissue specimens support mycoplasmas as a plausible cause of cancer. However, significant work remains to be done in human populations to validate this hypothesis.

**Helicobacter pylori CagA protein and gastric cancer.** We previously described the epidemiology and effect of *H. pylori* and chronic inflammation in the oncogenesis of gastric cancer. In particular, we described how the *H. pylori* strains that produce CagA protein create more inflammation and increase the risk of gastric cancer 2-fold compared to CagA-negative *H. pylori* strains (111). CagA, however, also has direct effects on the host cell that impart it with oncogenic properties. During chronic infection, *H. pylori* injects its CagA protein into the host cell, where it undergoes phosphorylation. Once phosphorylated, CagA is able to interact directly with the host cellular tyrosine kinase SHP-2, which then aberrantly activates the Ras–mitogen-activated protein (MAP) kinase cascade to regulate growth factors and cell motility and induces the cells to undergo morphological changes. Activation of the MAP kinase cascade also increases expression and activation of the proto-oncogenes c-fos and c-jun. CagA-negative strains do not exhibit these oncogenic effects (162). CagA also modulates transcription through activation of NF-κB and nuclear factor of activated T cells (NFAT). It also disrupts gastric epithelial cell tight junctions and causes a loss of cellular polarity (100). Strong evidence of CagA's oncogenic properties has been garnered from experiments using transgenic mice that constitutively express the *H. pylori* CagA protein in the absence of infection (180). Mice that express CagA in the stomach grow and behave like normal mice, but gastric polyps and adenocarcinomas develop in some of the transgenic mice and none of the wild-type mice. Transgenic mice that express CagA systemically can also develop hematological malignancies, similar to the human cancers that occur with SHP-2 gain-of-function mutations (197). The oncogenic effect appears to be dependent on phosphorylation of the CagA protein, since transgenic mice with phosphorylation-resistant CagA expression behave like wild-type mice. The oncogenic properties of CagA appear weak, though, as even in transgenic mice the development of cancers is delayed and occurs in a minority of individuals. However, these findings support a direct effect of the *H. pylori* CagA protein in oncogenesis that is dependent on CagA phosphorylation and deregulation of SHP-2.

**Toxic Bacterial Metabolites**

**Nitrosamines.** Host cellular DNA damage from toxic bacterial metabolites is another method that can instigate oncogenesis. Previously, we described the effects of chronic inflammation and the creation of ROS and RNOS by host immune cells in response to infection. RNOS are metabolized into N-nitrosamines, compounds that are strong mutagens. Bacteria themselves, however, can also generate N-nitrosamines as part of their metabolism. Some bacteria, such as *E. coli*, produce reductases which catalyze the conversion of nitrates into nitrites and allow the formation of N-nitrosamines (282). Nitrosamines are well-recognized perpetrators of bladder carcinogenesis in infections with the parasite *Schistosoma hematothium*. A few of the associations between bacterial infections and human cancer that we have described may also involve this mechanism of
carcinogenesis. A similar mechanism is postulated for bacterial infections and bladder cancer. For example, N-nitroso compounds from bacterial metabolism have been shown to cause urinary bladder cancer in animal models, and urine samples from patients with chronic urinary tract infections were found to have higher levels of nitrosamines than those of controls (34). With gastric cancer, hypochlorhydria caused by *H. pylori* has been proposed to allow overgrowth of other bacteria that produce nitrosamines (39, 282). Both nitrate-reducing bacterial counts and nitrite levels are higher in patients with chronic atrophic gastritis (39); hence, this mechanism may contribute to the genesis of *H. pylori*-induced gastric cancer. Colon cancer is thought to be potentiated by this mechanism as well. Although no specific bacterial culprit has been pinpointed, investigators have suggested that nitrates and nitrites from the diet are metabolized and reduced to carcinogenic nitrosamines by the bacterial flora in the intestine. This model of oncogenesis has been shown in rats as well as in the human colon carcinoma cell line Caco-2 but has not been validated in human studies (103, 153).

**Bile acid degradation products.** Colonizing bacteria in the gastrointestinal and biliary tracts can metabolize primary bile acids and produce secondary bile acid products (203). The most prominent biochemical reactions by which this occurs are deconjugation of bile acids and the removal of 7α-hydroxyl groups to generate deoxycholate and lithocholate, both of which are mutagenic in mice and colonic cell lines (108). Secondary bile acid products also increase the release of ROS through activation of enzymes on host cell membranes. The consequent conversion of arachidonic acid into prostaglandins results in the release of ROS. Similarly, bile acid degradation products can damage mitochondria, also causing the release of ROS. In addition, bile acids increase nitrosative stress through increased transcription and activation of inducible and endothelial nitric oxide synthases. The increased reactive oxygen and nitrogen species that are produced can then create DNA damage and promote mutagenesis (26).

Despite the many potential pathways to cancer related to secondary bile acids, studies of animals indicate that these products alone are insufficient for cancer development. Rather, secondary bile acids are thought to promote and expedite tumor formation in the presence of other carcinogens. For example, in mice, bile acid degradation products increase the development of colon cancer after exposure to nitrosamine (176). This process has been implicated in the development of both colorectal and gallbladder cancers in humans.

(i) **Colonic bacterial flora and colorectal cancer.** As previously discussed, colorectal adenocarcinoma develops in a multistage fashion, beginning with the formation of adenomas, from which adenocarcinomas arise. Epidemiological studies of humans have consistently found that high-fat diets increase the risk for colon cancer (84). Fat intake stimulates the secretion of bile acids into the gut, which then can be metabolized by resident colonic bacteria into toxic secondary compounds. In vivo, individuals who consume a high-fat diet have higher fecal concentrations of secondary bile acids than persons who do not (93, 172). Although the secondary acid compounds may promote the growth of colonic adenomas from which adenocarcinomas may eventually arise (106), epidemiological studies of humans have been conflicting. Some case-control studies have found increased levels of fecal or serum bile acids in patients with colorectal adenomas or cancer (21, 22, 119, 201), whereas others have not (105, 170, 171). The studies have varied significantly in methodology, choice of controls, the type of bile acid measured (primary, unconjugated, secondary, deoxycholate, etc.), and the method of fecal collection, thus making interpretation of the overall findings difficult. Furthermore, patients diagnosed with colorectal adenomas or cancer may develop alterations in fecal bile excretion as a result of their cancer. The studies with the strongest methodology (using age-matched controls screened for polyps and adjusting for cholecystectomy) report a positive association between secondary bile products and colon cancer (22, 119). Prospective studies of colon cancer, however, have failed to confirm this association (53, 97).

(ii) **Salmonella enterica serovars Typhimurium and Paratyphi and gallbladder cancer.** *Salmonella* is a Gram-negative rod that causes typhoid fever and diarrheal disease. In the late 19th century, it was realized that in a minority of persons, a chronic carrier state could occur that was characterized by asymptomatic infection. Since then, strong epidemiological evidence has linked infection with *Salmonella* serovars Typhimurium and Paratyphi with gallbladder cancer (138). Most prominently, a large cohort study of a typhoid outbreak in 1964 showed a markedly increased risk of gallbladder cancer in chronic carriers—as high as 167 times that of noncarriers (41).

(iii) **Other bacterial infections and gallbladder cancer.** In case-control studies, gallbladder cancer patients have higher levels of the secondary bile acids lithocholate and deoxycholate than do individuals with just gallstones. Those with positive bacterial cultures from their bile also have higher levels of secondary bile acids (138, 185). Although the evidence linking bacterial infection to gallbladder cancer is strongest with *Salmonella*, several other bacteria have also been implicated. Mixed bacterial infections with *Escherichia coli*, *Enterococcus faecalis*, and *Klebsiella* and *Enterobacter* species are found at a significantly increased frequency in patients with gallbladder cancer than in healthy controls (138).

**PROTECTIVE EFFECTS OF BACTERIAL INFECTION**

Bacterial infection is not always detrimental but can also impart protection against disease, perhaps by altering normal host physiology. For example, a surprising beneficial association between *H. pylori* and esophageal adenocarcinoma has surfaced.

*Helicobacter pylori* and esophageal adenocarcinoma. Esophageal adenocarcinoma is the most rapidly increasing cancer in the developed world (27). Adenocarcinoma of the esophagus arises as a complication of chronic acid injury from esophageal reflux disease. The acidic damage elicits columnar metaplasia in the lining of the esophagus to resemble the gastric mucosa, a state known as Barrett’s esophagus. It is from these metaplastic cells that adenocarcinoma develops. Because the latter is a disease stemming from acid reflux disease, researchers have examined whether the diminishing prevalence of *H. pylori* infection, which can cause hypochlorhydria from atrophic gastritis, is a contributor to the increasing incidence of esophageal adenocarcinoma.
A considerable number of studies have examined the association of *H. pylori* infection and Barrett’s esophagus. Initial studies have been heterogeneous and often hampered by methodological limitations. Most of the studies did not use age-matched cases and controls. Because age is associated with both the prevalence of *H. pylori* infection and decreased acid output, this confounder should be considered in analyses. Another cause for heterogeneity is the varied selection of controls in the different studies. Most studies selected controls from patients undergoing endoscopy for gastrointestinal complaints, including reflux disease or peptic ulcer disease. Some selected healthy blood donors with no endoscopy results. As a result, meta-analyses of these studies have been difficult to conduct, and the findings are inconclusive (258). More recently, however, several well-designed case-control studies have shown *H. pylori* to be associated inversely with all stages of Barrett’s esophagus (13, 51).

The studies of the relationship between *H. pylori* and esophageal adenocarcinoma, on the other hand, have been fairly consistent despite originating from various areas around the world. Although *H. pylori* has no effect on esophageal squamous cell carcinoma, it has a clear inverse relationship with esophageal adenocarcinoma. Two meta-analyses with a partial overlap of selected studies found summary ORs of 0.52 and 0.56 (121, 207). In a pooled analysis of five studies reporting simultaneous *H. pylori* serology and CagA status, the inverse association was noted only for patients infected with CagA-positive strains (121). Because CagA-positive strains cause more gastric atrophy, this finding is consistent with the hypothesis that *H. pylori* infection may protect against esophageal adenocarcinoma through hypochlorhydria.

However, many questions remain about the underlying mechanisms of this association. Does *H. pylori* truly prevent esophageal adenocarcinoma or is it a marker of some other active process? If a reduction of gastric acidity and therefore of precursor esophageal lesions were the sole method of protection, then the negative association would be less notable for persons without gastric atrophy. However, Anderson et al. found that even after adjusting for the presence of gastric atrophy, the association between *H. pylori* and esophageal adenocarcinoma remained (13). This implies that other processes besides hypochlorhydria might be important. As a result, attention has focused on the gastric hormones ghrelin and leptin, which are both suppressed by *H. pylori* infection (210). Ghrelin is a hormone secreted by X/A cells of the gastric mucosa to stimulate appetite. It has been hypothesized that lower ghrelin levels may lead to lower obesity, a known risk factor of reflux disease and esophageal adenocarcinoma. Ghrelin also stimulates gastrin-releasing hormone and, as a result, increased acid production. Leptin, a hormone produced mainly by adipocytes to suppress appetite, is also produced by the gastric mucosa. Esophageal cells have high leptin receptor expression, and leptin has been shown to induce the growth of esophageal adenocarcinoma cells in vitro (178, 230). Gastric leptin levels were significantly higher in persons with Barrett’s esophagus than in healthy controls, suggesting that *H. pylori* may protect against esophageal adenocarcinoma through this hormone (79).

**CONCLUSION**

In 2006, Parkin estimated that 18% of the global cancer burden is attributable to infectious agents (186). Although this estimate includes viruses and parasites in addition to bacteria, we believe it to be quite conservative, as it is based on only a few well-established causative pathogens. The estimate does not include the many types of cancers reviewed here for which a bacterial etiology is suspected but has not yet been proven definitively. It also does not include cancers for which a single pathogen is not the culprit but which result from chronic inflammation caused by various bacterial infections. We can also surmise that as more bacteria are discovered as a result of advances in technology, new causative relationships will also be revealed.

The challenge of finding and understanding the true associations between bacterial infections and human cancers is indeed great, but it also promises great rewards. Unlike viral infections, bacterial infections are typically curable, and the prospect of antibiotic treatments to prevent, alleviate, or cure cancers is obviously alluring. Many of the bacterial infections that promote oncogenesis, i.e., *H. pylori*, *Chlamydia*, and *Mycoplasma* infections, are often asymptomatic. When the pathways toward malignancy are initiated and when they become irreversible, though, are not fully understood. Vaccination against etiologic pathogens to prevent infection and thus eliminate the risk of cancer is yet another hopeful prospect for researchers.

In this review, we have illustrated prominent ways that bacteria can modulate oncogenesis. Besides instigating cancer by derailing the host’s normal defense processes—inflammation, antigen recognition, and gastric acid production—some bacteria have also demonstrated production of oncoproteins and by-products of metabolism that have direct mitogenic or mutagenic effects. There are also other possible mechanisms that we have mentioned only briefly, such as the role of bacterial infections as cofactors in the development of malignancy. As illustrated with *C. trachomatis* and cervical cancer, bacteria may potentiate the oncogenic effect of other pathogens (bacterial, viral, or other), as well as that of noninfectious irritants. The possibility that some bacterium-cancer relationships may be beneficial, such as *H. pylori* in esophageal adenocarcinoma, underscores the need to better understand how the bacterial flora modulates disease development. Also provocative is the discovery that a bacterium that can cause several types of cancer may protect against another. These interactions become even more complex when taking into account subtleties in host genetics, such as the IL-1β polymorphisms that increase the risk of gastric cancer with *H. pylori* infection. Hence, much work still remains in elucidating the interactions of the complex flora and genetics of the human host and their effects on human oncogenesis.

**REFERENCES**

1. Reference deleted.
2. Reference deleted.
3. Reference deleted.


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