



Logo: Life's blood flows through the hourglass; the stopcock represents the alteration of aging and disease as biomedical research progresses.

Report of the Director

A substantial amount of current research focuses on the links between microorganisms and apparently unlikely diseases. OFAS has worked in this field for more than a decade. Our work began with a 1987 paper showing the relationship of *Staphylococcus aureus* to Toxic Shock Syndrome. Since 1989, collaborations utilizing the Serum Treasury have clearly established direct or co-factor relationships between Epstein-Barr Virus infection and Hodgkin's Disease, and between *Helicobacter pylori* infection and stomach and related cancers.

Following up on the 1908 hypothesis of Sir William Osler of an infectious cause of atherosclerosis, data is currently being analyzed from the 250-person Serum Treasury study of infection with *Chlamydia pneumoniae* or *Cytomegalovirus* and the subsequent development of heart disease. We may also be able to assay these sera for levels of the naturally-occurring, anti-inflammatory molecular messenger interleukin-10 which, in mice, are inversely related to the formation of plaque and to its rupture.

Lest one conclude that inhabiting a germ-free environment is the only means of avoiding disease, we point out the 'Hygiene Hypothesis'. Too little exposure to microbes (except colds and influenza) yields an unexercised immune system; it is less able to mount a successful attack on already infected cells or to make antibodies to defeat infective invaders before clinically evident disease.

Examples of beneficial germ exposure include:

- fewer allergies are found in children who are: in large families, in day-care before age 1, or receiving no antibiotics before age 2;
- benign helminthes (non-reproducing intestinal parasites) in the gut prevent unnecessarily extreme reactions to bacteria, viruses, and dietary proteins; such reactions are implicated in Inflammatory Bowel Disease;
- rats raised in a germ-free environment have a marked increase in diabetes and rheumatoid arthritis.

Research at OFAS continues, as well, in areas of long-standing interest: the physiology and pathophysiology of sebaceous glands, hair follicles, melanocytes, skin manifestations of diabetes, and anti-aging interventions.

We appreciate your interest and support and send our best wishes for success in the coming year.

Norman Orentreich, MD, FACP

Microorganism – Disease Links Under Investigation

ST Denotes studies using the Serum Treasury.

“Between 15% and 20% of cancers of known etiology (a higher proportion in developing countries) have been attributed to underlying infection. ... During the past 15 years alone, four new microbial causes of human cancer have been discovered.”

J Parsonnet, *Microbes and Malignancy: Infection as a Cause of Human Cancer*

Acne Rosacea

Helicobacter pylori

Some patients, after successful treatment for chronic gastritis from *H. pylori* infection, find their rosacea cleared as well. The CagA⁺ subtype of *H. pylori* is more closely correlated with severe rosacea and possibly with increased risk of stomach cancer under age 40.

Alzheimer’s Disease

Chlamydia pneumoniae

Postmortem examination of the brains of Alzheimer’s Disease (AD) patients revealed 17 of 19 were infected by *C. pneumoniae*; the inflammation indicating infection was most pronounced in those brain areas involved with AD. This bacterium appears to be a co-factor, not a cause, of AD.

ST Atherosclerosis

Cytomegalovirus and Chlamydia pneumoniae

Because a protein on the surface of the bacterium *C. pneumoniae* mimics a vascular-wall protein, the immune system attacks both, leading to inflammation and then to plaque formation. A co-factor is likely needed, as not all infections result in heart disease. Infection with *Cytomegalovirus* accelerates atherosclerosis in heart transplant patients, and antiviral therapy reduces recurrence of their heart disease. Using the Serum Treasury, OFAS is studying the prevalence of antibodies to both of these microbes in relation to heart disease.

Breast Cancer

Epstein-Barr Virus and Mammary Tumor Virus

51 of 100 breast cancer biopsies showed EBV infection, as opposed to only 3 of 30 non-cancerous biopsies. Cancers with EBV tended to be steroid receptor negative, high grade, and associated with lymph node invasion. Human Mammary Tumor Virus is not likely a directly infectious agent in breast cancer; rather, it seems this probably inherited virus is a co-factor that, interacting with genes, triggers the cancer.

ST Gastric Cancer

Helicobacter pylori

The CagA⁺-*H. pylori* subtype is more frequently associated with stomach cancer than the CagA⁻ subtype. Using the Serum Treasury, OFAS is investigating whether or not this is due to genetic alterations in cells of the hyperproliferating stomach lining.

Keratoacanthoma

Human Papillomavirus

Evidence of infection with this virus was found in 6 of 34 of these usually self-resolving, benign skin tumors. In one of the infected cases, the tumor was transforming into squamous cell carcinoma, a rare but not unprecedented event. Perhaps this viral infection is the co-factor transforming benign tumors into cancers.

Kidney Stones

Nanobacteria/Nanobes

These super-small organisms (found in 30 of 30 kidney stones) build mineralized shells that can eventually build up to be kidney stones, and, maybe, gallstones.

Multiple Myeloma

Herpes Virus

The herpes virus associated with Kaposi’s Sarcoma was found in 25% of patients with monoclonal gammopathy, the blood disorder that precedes multiple myeloma.

Prostatitis

Unidentified

Inflammation of the prostate – prostatitis – affects 22% of men under 40 and 60% of men over 40. In prostate biopsies from men with prostatic hyperplasia, almost all samples show histologic evidence of infection by an as-yet-unidentified microbe.

Psoriasis

Unidentified

Bacterial or fungal infections often coincide with psoriasis and its flare-ups. Antibiotic therapy for unrelated conditions has cleared persistent psoriasis. Acute guttate psoriasis, in particular, is often triggered by *Streptococcal* pharyngitis. Investigators, therefore, pursue these hints of causality or co-factoring.

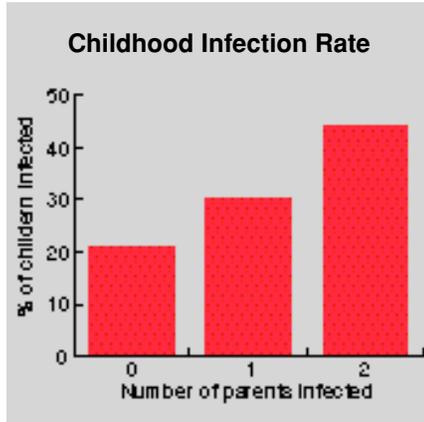
Reactive Arthritis

Campylobacter, Salmonella, Shigella, Yersinia

In septic arthritis bacteria are active in the joints, but reactive arthritis is a sterile joint condition associated with bacterial food poisoning, particularly, it seems, in persons with the HLAB2T gene. Sources of the bacteria are undercooked foods (meat, poultry, eggs, shellfish), unwashed fruits and vegetables, and unpasteurized milk products.

Common Microorganisms & Cancers

Helicobacter pylori (*H. pylori*)

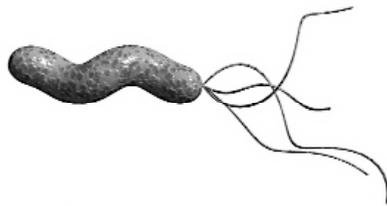
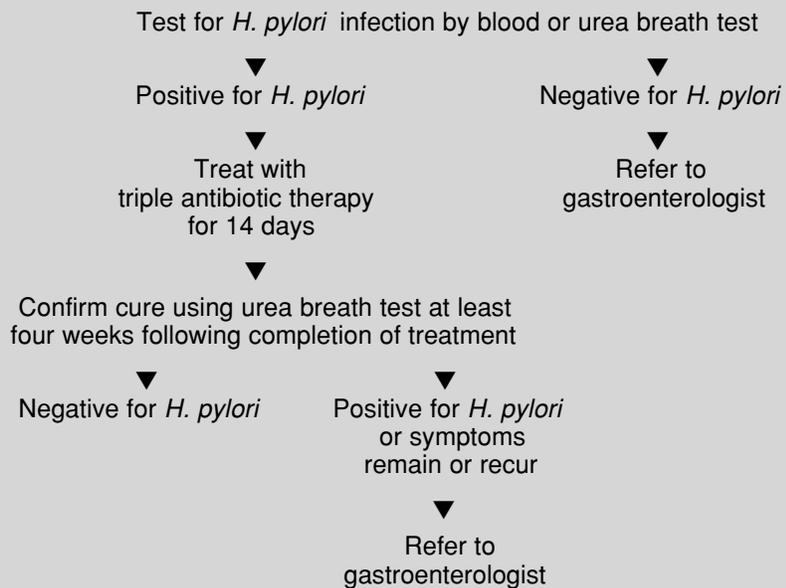


The distribution of *H. pylori* infection suggests a common source of exposure or person-to-person transmission. The infection in the US is more common in Hispanics and blacks than in whites and is generally inversely related to socioeconomic and education levels. In the US, infection of children is relatively uncommon (10-15% between 3-5 years vs. India 60%, 3-10 years), but prevalence of infection increases with age. The organism can be found in stool samples, saliva, and dental plaque.

Despite the prevalence of infection (35% over a lifetime in the US) and the risk of serious disease consequences (infected ulcers and stomach cancer), testing is rare and treatment still rarer. Gastroenterologists staying fully abreast of, and contributing to, the medical literature on *H. pylori* infection feel that every patient with chronic indigestion, including those who have or have had gastroesophageal reflux disease (GERD), should be tested for *H. pylori* infection and, if positive, treated appropriately. Although successful treatment does not reduce the symptoms of GERD, it does forestall the worsening of gastritis in the corpus of the stomach, for which chronic therapy to suppress acid production is required. The following strategy has been found consistently to save the costs of gastrointestinal medications and improve patient satisfaction.

TEST AND TREAT STRATEGY

For persons with chronic indigestion, fullness, postprandial pain, heartburn, pain on or over the stomach, bloating, or family history of stomach cancer



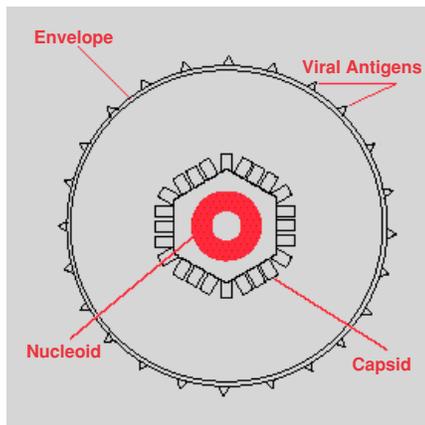
One of some two dozen species of *Helicobacter* that reside in the intestinal tract of animals and human beings, *H. pylori* is between 2.5 and 5.0 microns long and lives beneath the mucus layer of the stomach.
Courtesy of Luke Marshall, Helicobacter Foundation

In the absence of symptoms or family history of stomach cancer, treating *H. pylori* infection may be counterproductive. In fact, the infection seems to be associated with a lower rate of esophageal cancer, and *H. pylori* produces a compound that kills some other microbes.

Epidemiological studies strongly suggest a role for ascorbic acid (vitamin C) in the prevention of gastric cancers, which occur much less frequently in persons eating a diet rich in fruits and vegetables. Further, although total vitamin C levels in plasma are low in persons infected by *H. pylori*, cure of the infection does not correct the deficiency. Supplementing anti-*H. pylori* therapy with vitamins C and E increased patients' ascorbic acid levels and reduced the DNA-damaging effects of their gastric juices.

Common Microorganisms & Cancers

Epstein-Barr Virus (EBV)



The structure of the Epstein-Barr Virus. Courtesy of *The Epstein-Barr Virus*, by Werner Henle, Gertrude Henle, and Evelyne T Lynette.

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Approximately 90% of the world's population is silently infected by EBV. In the developed world mononucleosis ('the kissing disease') in adolescence is the symptomatic evidence of first infection with this saliva-transmitted virus; however, most infections occur earlier and without symptoms. The T-cells, in particular, of a healthy immune system keep the infection suppressed. When the immune system is dysfunctional (as in HIV infection or during post-transplant drug therapy), lymphoma cancers arise frequently.

EBV is strongly linked to Hodgkin's Disease (HD), which has an incidence of 5.5:100,000 in persons 20-24 years of age. Interestingly, although EBV infection triggers HD in some persons, those infected tend to live longer than HD patients who are not infected; perhaps this is because the virus stimulates the immune system.

Nasopharyngeal cancer (20% of all cancers in southern China and SE Asia vs. 0.25% in Western countries) and Burkitt's lymphoma (10:100,000 in the malaria belt of Central and East Africa vs. 100-fold less in non-malaria areas) are associated with an exceptionally high EBV infection rate. These geographically defined localizations strongly suggest the probability of essential co-factors (*e.g.*, dietary, genetic, cultural) in the development of EBV-linked cancers.

As noted earlier, EBV is a suspected co-factor in some breast cancers, and its presence in breast biopsy tissue may be an indication of negative prognosis and/or a target for therapy.

Human Papillomavirus (HPV)

Around the world, approximately 15% of cancers are the result of infections by viruses, bacteria, or parasites. In the US, only 5% of cancers are attributable to such causes.

In the case of anal, genital, and cervical cancers, however, up to 80% are the result of infection with HPV. There are approximately 100 HPV subtypes, and each prefers the cells of specific tissues of the body, such as mouth, skin, genitalia, hands, or feet. 20% of the subtypes reside in the cells of the anus, vulva, vagina, penis, and cervix. In the US, Types 16 and 18, infecting the genital and perigenital areas, are the most virulent; they account for 70-80% of genital, anal, and cervical cancers. In other areas of the world, other subtypes are more virulent; in Africa, Asia, and India, cervical cancer is the most common cancer death.

At some point in their lives approximately 75% of US and European women will be asymptotically HPV infected. Routine Pap smears miss 20-40% of HPV infections, whereas DNA testing of the same specimens can detect HPV. There is no question that HPV is the principal cause of cervical cancer, and the time for progression from infection to cancer ranges from 10-20 years. Data from the male homosexual community reveals a 60% symptomless infection rate for anal HPV with a 35:100,000 rate of anal cancer. When the immune system is compromised, as in HIV, the infection rate rises to 95%. A condom offers no protection; even in dead skin cells, HPV can remain infective for a day or so.

Cancers of the oral cavity are most frequently associated with carcinogens such as tobacco, but infection by HPV-16 is present in 16% of these cancers, and 26% of oral cancers involve HPV of some subtype. A striking 51% of oral cancer patients showed some evidence of HPV infection, whereas the control group showed a 35% rate.

On a more hopeful note: laryngeal papillomatosis, predominantly afflicting children, is usually a benign HPV infection. Often treated with awkward, delicate surgery, recent studies have shown that the condition responds to oral therapy with indole-3-carbinol (I3C), a bioactive component of cruciferous vegetables. Trials are underway for I3C treatment of other conditions caused by HPV infection.

Our Contributions

Since our 1987 work on Toxic Shock Syndrome, OFAS research utilizing the Serum Treasury has resulted in seven important papers revealing the relationships between infections with *Helicobacter pylori* or Epstein-Barr Virus and subsequent cancers.

Helicobacter pylori (H. pylori)

1991: Infection with *H. pylori* is associated with an increased risk of gastric adenocarcinoma. This bacterium is likely a co-factor in the pathogenesis of this malignancy.

New England Journal of Medicine 325:1127-1131

1993: *H. pylori* infection, when combined with a low level of Pepsinogen I, results in a markedly increased risk of distal gastric cancer.

Cancer Epidemiology, Biomarkers and Prevention 2:461-466

1994: Non-Hodgkin's lymphoma affecting the stomach is associated with previous *H. pylori* infection; this is not true of non-Hodgkin's lymphoma affecting sites other than the stomach. A causative role for the organism is plausible but remains unproved.

New England Journal of Medicine 330:1267-1271

1997: Infection with strains of *H. pylori* that express the CagA⁺ protein are associated with more inflammation and are thought to be particularly virulent. Our study found no increased risk of gastric non-Hodgkin's Lymphoma in association with CagA⁺-*H. pylori*.

Journal of Infectious Diseases 176:1641-1644

1997: When compared with uninfected subjects, persons infected with CagA⁺-*H. pylori* are at considerably increased risk of gastric cancer. Infections by CagA⁻-*H. pylori* are less strongly linked to this malignancy.

Gut 40:297-301

Epstein-Barr Virus (EBV)

1989: The development of Hodgkin's Disease may, in some patients, be preceded by enhanced activation of EBV; this can occur with immune system deficiency. Whether EBV has a direct role in the pathogenesis of the disease, or if it is simply a marker for a more fundamental factor affecting the immune control of latent infections, is unknown.

New England Journal of Medicine 320:689-695

1991: Our results suggest that neither EBV activation in the period preceding diagnosis of nasopharyngeal cancer nor detectable IgA antibody against the EBV Viral Capsid Antigen in serum are early markers for this cancer.

Cancer Causes and Control 2:125-131

Toxic Shock Syndrome (TSS)

1987: In contrast to cotton tampons, synthetic tampons provide physical and chemical conditions ideal for the development of TSS. TSS results from the production of metabolic by-products of *Staphylococcus aureus* that, when combined with endotoxins from *Escherichia coli*, become lethal.

Clinical and Investigative Medicine 10:64-70

Further Reading, Gratitudes, & Opportunities

Microbes and malignancy: Infection as a cause of human cancers
Oxford University Press, New York, 1999
J Parsonnet, editor

Edited by our collaborator on many *H. pylori* studies, this text will be most readable and illuminating to researchers in the field.

Contagion: A sometimes lethal sexual epidemic that condoms can't stop
The New Yorker, September 13, 1999:34-49
J Groopman

An important, well-written piece by a physician consultant to *The New Yorker*. Mainstream publications such as this will help to raise public awareness of a remarkably prevalent infection.

Helicobacter Today
Norris Communications, Grosse Pointe Farms, MI

Available since 1994, this newsletter from Baylor College of Medicine compiles the latest information from publications and meetings; it is addressed primarily to researchers and provides the opportunity for Continuing Medical Education credits to physicians.

Helicobacter Foundation
www.helico.com

Non-technical information is provided at this website, plus an information packet directed toward physicians.

Is your stomach bugging you? The rise and fall of the bacterium *H. pylori*
Science News, October 9, 1999:234-236
D Christensen

The pros and cons of eradicating *H. pylori*.

Nutrition Action Healthletter, October 1999
Center for Science in the Public Interest, Washington, DC

Comprehensive 7-page food safety guide including an excellent chart of the 12 most common food-borne 'bugs', their associated foods, typical symptoms, and courses of illness.

We note sadly the death this year of a great lady and truly superior friend of OFAS, Alyce Kaiser. Her unerring, gracious caring for others and generous enthusiasm persist as examples for anyone who had the pleasure to know her. In 1980, when the Kaiser Permanente Medical Care Program's serum collection was about to be discarded, Aly was prominent in effecting its successful transfer to OFAS. Started in 1964 by Morris Collen, MD and Sidney Garfield, MD, this visionary collection has evolved into the World Health Organization-acclaimed Serum Treasury. The OFAS-Kaiser Serum Treasury is an anonymous, encoded collection of some 300,000 computer-cataloged, readily-retrievable sera at OFAS and their associated medical histories through Kaiser Permanente Division of Research. The treasury provides the very rare opportunity to perform in a short time historically prospective studies that would otherwise take decades. We once again express our gratitude for Aly's vital role in the realization of this unique research resource.

INFORMATION FOR DONORS

The Orentreich Foundation for the Advancement of Science, Inc. was founded in 1961. OFAS is a non-profit institution dedicated to biomedical research to prevent, halt, or reverse those disorders that decrease the quality or length of life. It is duly registered with the United States Internal Revenue Service as an Operating Private Foundation under Section 4942(j)(3).

Your tax-deductible contribution should be mailed to:

Orentreich Foundation for the Advancement of Science, Inc
910 Fifth Avenue
New York, NY 10021-4187

INFORMATION FOR RESEARCHERS

If you have a research question relating to a human disease or disease prevention factor for which there is adequate scientific evidence of a serum marker to justify use of the Serum Treasury in pursuit of a definitive answer, please submit your proposal for consideration to:

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Scientific Affairs
Biomedical Research Station
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