There is increasing recognition that microbial infections are important contributors to a wide range of chronic conditions. Peptic ulcer disease may be due to the bacterium *Helicobacter pylori* rather than to emotional stress and diet. For years the conventional wisdom had been that no microbe could survive the acidic conditions of the stomach. Until recently the blood-brain barrier was considered impenetrable to plasma proteins, such as antibody and complement. Now it is purported that several neuropsychiatric disorders of childhood are rooted in a microbe-triggered autoimmune response. Clearly, a contributing role for microbial infections in chronic diseases of the CNS needs to be reassessed.

Inflammation, sometimes accompanied by a specific immune response, is often a critical component of chronic diseases associated with infection. A role for microorganisms in autoimmunity has been suggested for decades, although for many diseases, such as multiple sclerosis and type I diabetes, the unequivocal identification of the etiological agent(s) has been met with difficulty. Perhaps the best-recognized link between autoimmunity and infection lies with acute rheumatic fever (ARF) and the bacterium *Streptococcus pyogenes*, also known as group A β-hemolytic streptococci (GABHS). Diagnosis of ARF can be tricky, and it generally includes one or more of the following major manifestations: (1) carditis, typically involving the mitral valve; (2) a polymigratory arthritis, which resolves without permanent damage to the joints; and (3) Sydenham chorea, a disorder of gross motor function.

Essential to the diagnosis of ARF is evidence of a recent GABHS infection. Documentation can take the form of a positive throat culture or an elevated antibody titer to GABHS antigens. However, exceptions are made for some cases of “pure chorea.” Unlike carditis or polymigratory arthritis, there is the possibility of a delay of several months between the primary GABHS infection and the onset of Sydenham chorea symptoms. By this time, the organism is long gone from the host and anti-streptococcal antibody titers, as well as plasma markers for...
Acute inflammation (e.g., C-reactive protein), have declined to normal levels. Inasmuch as chorea often appears during the acute stage rheumatic fever and is a clearly defined syndrome, its association with GABHS infection remains unchallenged.

Epidemiological studies were crucial in establishing the relationship between GABHS and rheumatic fever. At the close of the 19th century in the United States and Europe, diseases caused by GABHS, which notably include scarlet fever, had a public health impact that rivaled tuberculosis. Prior to the widespread use of antibiotics in the late 1940s, streptococcal infections were difficult to control. Outbreaks of ARF within the military, around the time of World War II, provided a rich source of information on the epidemiology of this disease and its association with primary GABHS infection.

ARF can follow an untreated GABHS infection of the upper respiratory tract (URT). In most instances, a host immune response that is directed specifically toward the invading organism will be mounted, resulting in clearance of the primary infection within 2 weeks. In some cases, an asymptomatic carrier state will develop, whereby the bacterium is believed to be in a quiescent state, perhaps residing within the epithelial cells lining the oropharynx and hidden from immune attack. There is a delay of 3 to 6 weeks following the primary bacterial infection and symptoms of ARF.

Not all individuals experiencing an untreated GABHS infection will develop ARF. It is estimated that only 3% of the human population has a genetic predisposition for developing rheumatic fever. Moreover, not all strains of GABHS will trigger an acute rheumatic attack, even in a highly susceptible host. This became strikingly apparent in the 1940s at Irvington House, a group home for children with rheumatic heart disease. It is here that an M-type 4 strain caused acute pharyngitis in many residents, yet failed to induce a single episode of recurrent ARF.

It is widely accepted that only a GABHS infection of the throat can induce ARF. In addition to pharyngitis, GABHS can cause impetigo, a purulent infection involving the epidermal layer of the skin. Perhaps the unique association between ARF and URT infection, but not skin infection, arises from differences in the drainage of streptococcal antigens into the ducts of the lymphatic system. There is also speculation that the apparent failure of skin infection to induce ARF is due to the fact that GABHS strains which cause impetigo are often distinct from the strains giving rise to pharyngitis. Numerous epidemiological studies on ARF outbreaks in the United States and Europe have led to the classification of several M-types of GABHS as highly "rheumatogenic."

The relative incidence of GABHS infection of the URT and skin varies in accordance with both season and geographic location. In many temperate climates, pharyngitis is common during the winter, whereas impetigo has a lower overall prevalence and peaks during the summer months. In contrast, in many tropical regions impetigo is highly endemic (Fig. 1). The highest reported rate of rheumatic fever is found among the Aboriginal people of tropical Australia. Curiously, acute pharyngitis is uncommon in Australian Aborigines, and the so-called “rheumatogenic” M-types are rarely recovered. Whether or not a throat infection by a rheumatogenic strain is a strict requirement for ARF remains a hotly contested issue.

A true GABHS infection, as opposed to carriage, can be defined in serological terms as a rise in antibody titer to GABHS antigens, such as streptolysin O or deoxyribonuclease B. However, true infection of the URT need not necessarily lead to overt clinical symptoms. It is important to note that a clinically apparent GABHS infection can trigger ARF. Beginning in the mid-1980s, the Salt Lake City (Utah) region experienced a marked increase in the incidence of ARF. Yet in about half of the cases, the patient had no recollection of a sore throat in the weeks preceding the acute attack. Were it not for outbreaks of ARF occurring in institutional settings, such as military bases, at a time prior to the availability of effective antibiotics, such as penicillin, the link between GABHS infection and ARF would probably remain elusive, or at least less certain than it is today.

There is a connection between GABHS and neuropsychiatric disorders, such as Tourette syndrome (TS), obsessive-compulsive disorder (OCD), and possibly attention-deficit/hyperactivity disorder (ADHD). Patients with these neuropsychiatric disorders have elevated levels of expression of a B-lymphocyte cell surface marker, known as D8/17, which is also elevated in rheumatic fever patients and their first-degree relatives. The specificity of D8/17 for rheumatic fever is very high when compared with several other autoimmune diseases, such as rheumatoid arthritis. Whether the D8/17 marker has a direct role in ARF is not yet known. Sydenham chorea is one of the major manifestations of rheumatic fever, and many patients with Sydenham chorea also exhibit obsessions and compulsions. Furthermore, considerable comorbidity is observed among patients with TS, OCD, ADHD, and Sydenham chorea. The basal ganglia is a primary target organ of Sydenham chorea, a feature it shares with TS, OCD, and ADHD.

A practical approach for evaluating the association between GABHS infection and neuropsychiatric disorders is to model new studies based on our current knowledge of ARF. However, the epidemiological studies that uncovered the link between GABHS and ARF may not be wholly applicable to TS, OCD, and ADHD. Most cases of TS, OCD, and ADHD are sporadic and appear in community settings. Outbreaks of acute TS, OCD, or ADHD have not been documented. Even qualifying an episode of TS, OCD, or ADHD symptoms as an acute exacerbation can be fraught with difficulties. GABHS infections are frequent within the same group afflicted with TS, OCD, and ADHD. At its peak incidence, between the ages of 5 and 7 years, it is estimated that half of all children experience an average of one GABHS infection per year. If the time delay between GABHS infection and acute episodes of TS, OCD, or ADHD...
were of the magnitude observed for pure chorea, then a temporal relationship between GABHS infection and the neuropsychiatric disorders would be difficult to establish. The “background” level of GABHS infections may be too high.

Any attempt to establish a temporal relationship between GABHS infection and an acute exacerbation of neuropsychiatric symptoms would be further complicated if only a subset of patients were susceptible to the effects of GABHS infection. Yet this is exactly what has been proposed.

Patients with PANDAS—an acronym for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections—are thought to represent only about 10% of all neuropsychiatric patients. If only some of the acute episodes experienced by a PANDAS patient were rooted in a GABHS infection, it may be impractical to design an epidemiological study that could capture the effect—a very large sample size of human subjects would be required. However, longitudinal studies of PANDAS patients are required to help clarify the etiology and to determine whether exacerbations of symptoms are secondary to repeated GABHS infections.

The molecular mechanisms underlying the development of ARF remain ill-defined. Antibodies which react with both streptococcal antigens and human host tissues, such as the brain and heart, have been identified. For some antibodies, a pathological role is well-supported by studies using experimental animal models for carditis. Because there is a strong familial pattern of rheumatic fever, as there is for TS, OCD, and ADHD, is should be possible to identify the genetic determinants of susceptibility for each of these diseases and determine whether they overlap. Significant associations between rheumatic fever and HLA markers have been observed for several human populations that share the same ethnic background; however, the HLA markers are unique to each ethnic group. Aside from the DB/17 antigen present on the surface of B-lymphocytes, there are no stable biomarkers known for rheumatic fever.

Defining the relationship between TS, OCD, ADHD, and GABHS infection is a challenging problem. But the rewards of success could be enormous. ARF is a readily preventable disease that can be managed through antibiotic prophylaxis. Identifying those individuals who stand to benefit from antibiotic therapy remains a central goal. Perhaps the answer will lie not in the classical epidemiological approach that proved so successful in decades past, but rather in the precise identification of molecular markers that allow for stratification of patients into biologically relevant subgroups.

WEB SITES OF INTEREST
http://clinfo.rocketefeller.edu/social/rf.html

ADDITIONAL READINGS

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