HISTORY

Germs, Dr. Billings, and the Theory of Focal Infection

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Our understanding of infectious diseases continues to expand rapidly, and has led to the realization that microorganisms are responsible for, or at least contribute to, numerous diseases that were never before associated with infectious etiologies. However, a review of medical history reminds us that this is not so novel an idea. Not long after the widespread acceptance of bacteriology and the germ theory and with an increased awareness of public hygiene, there was a period during which it seemed that nearly all diseases would prove to be the result of infections. One popular proposal that championed such an idea was the theory of focal infection. This article reviews this theory by considering the key concepts and developments that likely inspired it, and examines the work of the theory’s most visible proponent, Dr. Frank Billings.

I have been made happy by discovering that I have only added to the observations of other physicians, in pointing out a connection between the extraction of decayed and diseased teeth and the cure of general diseases.

—Benjamin Rush, 1809

The author of a recent perspective on infectious diseases noted “a quieter revolution [that] has been taking place in our understanding of human-microorganism interactions: the discovery that transmissible agents are responsible for diseases that were never suspected of being infectious in origin” [1]. Actually, this is not such a novel idea. During the early 1900s, shortly after the widespread acceptance of the germ theory and the principles of bacteriology, and with an increased awareness of public hygiene, there was the expectation that most illness would prove to be the result of infections. This idea crystallized in the theory of focal infection. In brief, the theory proposed that circumscribed foci of bacteria, localized to various parts of the body, could result in a myriad of systemic diseases. Upon review of this theory, the lesson for the modern practitioner is clear: therapeutic interventions, even if based on current science, may not benefit patients.

As is true for theories today, the theory of focal infection was a product of the intellectual environment of its time. The theory was most dependent on the then recently developed germ theory, but it was influenced as well by earlier ideas associated with contagion and bacteriology. Another important influence was probably that surgery was the primary therapy available during that era. Finally, its acceptance depended in large measure on the proselytizing efforts of the theory’s most visible proponent, Dr. Frank Billings. This article reviews the theory of focal infection by considering the key concepts and developments that served as its inspiration, and by examining the life and work of Dr. Frank Billings.

Bacteriologic Influences

Frank Billings was born in 1854. In his home state of Wisconsin, he was employed as an elementary and high school teacher, and he was destined to become a leader in medical education. He entered the Chicago Medical College (now Northwestern University Medical School) in 1878 and graduated in 1881 [2, 3]. At the time that Dr. Billings was completing his medical studies, scientists were making enormous progress in the field of bacteriology. Many had demonstrated the presence of bacteria in various disease states, observations that led to the suspicion that bacteria were involved in pathologic processes. The nature and extent of this involvement were the source of heated debates among European academic circles. In America, the germ theory continued to be largely ignored [4].

Robert Koch’s discovery of the etiology of tuberculosis was seminal in convincing many of the causal role of bacteria in disease and bringing recognition of the germ theory to America [3]. This discovery occurred while Dr. Billings was completing his internship at Cook County Hospital in Chicago and beginning his work as a demonstrator in anatomy at his alma mater [2, 4]. In 1885, Dr. Billings, like many other American physicians before and after, sought to further his medical education...
at the great European universities. He moved to Vienna for a year of clinical study and attended the lectures of influential clinicians such as the venerated surgeon, Theodore Billroth. Subsequently, he traveled to clinics in Paris and London and met Louis Pasteur and Joseph Lister [4]. Given the recent dramatic discoveries and the opportunity to learn from many of the scientists who had made them, it is easy to imagine that Dr. Billings’ ideas concerning health and disease would be greatly influenced by the field of bacteriology as he embarked on a career in academic medicine.

Dr. Billings manifested an appreciation for infectious diseases, from both a clinical and a public health perspective. In two articles published in 1898, Dr. Billings seems to draw parallels between sanitation for a city and hygiene for the body. With respect to sanitation, he discussed the remarkable decline in rates of cholera and other contagious diseases in Vienna after the source of the water supply was changed from the sewage-contaminated Danube River to pristine water from the Alps. ‘‘Most of the infectious and contagious diseases may be classified as preventable: most of them are filth diseases, and they cannot exist in the presence of perfect cleanliness,’’ [5]. Concerning hygiene, he wrote ‘‘It is probably fair to state that the great majority of diseases which we study in our office patients are caused by bad hygiene.’’ Unhygienic states, he theorized, could lead to inflammation ‘‘of mucous membranes or of the skin possibly, through the agency of bacteria, which find a proper soil for development in or upon such weakened tissues. When once under way, a resulting local process may aggravate the complex whole and appear as a primary cause’’ [6]. He defined hygiene in a broad sense to include diet, air quality, work habits, sleep patterns, social stressors, exercise, shelter, and use of alcohol and tobacco.

In these articles, and in the subsequent development of the theory of focal infection, Dr. Billings’ opinions reflect many of the tenets of the hygienist Max von Pettenkofer, whose ideas were well received in America [7]. Pettenkofer graduated with a degree in medicine from the University of Munich in 1843, and he began to conduct research in the field of medical chemistry at his alma mater in 1847. By the time he opened the first Hygienic Institute in 1879, he had studied diverse topics such as nutrition and metabolism; restoring aging paintings; copper dental amalgam; the ventilation of houses; and the relation of the atmosphere to clothing, habitations, and the soil. His work with Munich’s water and sewer systems is credited for the dramatic decrease in the city’s mortality rate associated with typhoid fever between 1870 and 1898 [8].

Pettenkofer was extremely interested in the epidemiology of intestinal diseases, particularly cholera. He believed that a germ, which he termed X, must develop virulence in appropriate soil (moist, porous soil with decaying organic matter was especially effective) termed Y, before it became the toxic infectious substance termed Z. He also believed that individual susceptibility or disposition to infection was an important factor in developing an illness. Included among the important contributing factors suggested by Pettenkofer were advanced age, poverty, weakness, bad air, unclean water, poor nutrition, improper clothing, physical or mental strain, and excesses of all kinds [8].

Pettenkofer accepted the germ theory as it was being derived by Koch and others but with some caveats. For example, he accepted Koch’s comma bacillus as the germ (X) for cholera, but believed that patient-to-patient transmission could not occur until the bacillus became infectious (Z) by developing virulence from the soil (Y). Pettenkofer believed so strongly in his ideas that in 1892, at the age of 74, he drank one milliliter of fresh culture derived from a patient who was dying of cholera. Subsequently, Pettenkofer developed only mild diarrhea and thus felt further confirmation that the comma bacillus did not cause cholera without first gaining virulence in the soil [8, 9].

It is of interest that Pettenkofer broached the idea of a cholera carrier as early as 1869. He suggested that the germ could be carried by a healthy person from a cholera region to an area free of disease. There, an epidemic could ensue when the germ became infectious after it was transmitted from that person to the appropriate soil [8]. By the time Dr. Billings was writing about focal infection, the concept of the ‘‘healthy’’ disease carrier had been well established by investigators in Europe and America [10].

### Focal Infection

In an article published in 1906, Dr. Billings speculated that some gastric and duodenal ulcers were caused by a bacterial infection of the mucous membranes that rendered the cells prone to digestion by the gastric juices [11]. A few years later, he published a series of 12 cases of chronic endocarditis. He noted that in four of these cases, tonsillitis or alveolar abscesses occurred shortly before the onset of cardiac symptoms. Cultures of blood from each patient had yielded streptococci, and Dr. Billings postulated a relationship between the focal infections, the positive blood cultures, and cardiac disease [12].

In 1912, in the introduction to the first article in which the term focal infection was used in the title, Billings noted that the principle that focal infection leads to acute systemic disease was well established in medical science (table 1). However, he

### Table 1. Focal infections leading to acute systemic disease noted by Dr. Billings in 1912.

<table>
<thead>
<tr>
<th>Focal site or type of infection</th>
<th>Systemic disease</th>
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<tr>
<td>Tonsil</td>
<td>Rheumatic joint infections</td>
</tr>
<tr>
<td>Tonsil</td>
<td>Endocarditis</td>
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<tr>
<td>Upper respiratory passage</td>
<td>Pneumonia</td>
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<tr>
<td>Nasal mucosa</td>
<td>Epidemic meningitis</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Nephritis</td>
</tr>
<tr>
<td>Gentitourinary tract</td>
<td>Gonorrheal arthritis</td>
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<tr>
<td>Tuberculosis</td>
<td>Disseminated (miliary) tuberculosis</td>
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was concerned that the concept of long-standing focal infection leading to chronic systemic disease was not appreciated. He wrote: ‘I think there can be no doubt that the insidious slow degenerative processes which occur in many patients who arrive at the meridian of life are due to slow intoxications from chronic focal infections variously located’ [13]. He proposed that ‘cardiovascular degeneration’ was often caused by unappreciated chronic appendicitis. In this same paper he cited 16 cases of arthritis and nephritis among which foci of prolonged infection were removed and clinical improvement followed [13]. One year later, Billings published a general review of arthritis deformans based on a study of 70 patients and opined that this condition had an infectious etiology. In addition, he indicated that improvement could be expected after removal of the responsible focal infection [14]. To support his ideas, Dr. Billings pointed to the work of Dr. Edward C. Rosenow, a colleague with whom he collaborated extensively.

Rosenow, who was born in Wisconsin 21 years after Billings, graduated from Rush Medical College in 1902 (where Dr. Billings was Dean) and served his internship at Presbyterian Hospital (where Dr. Billings was an attending physician). From 1904 to 1915, Rosenow was a member of the staff of the McCormick Memorial Institute for Infectious Diseases (where Dr. Billings served as the president of the board) [4, 15]. In Dr. Billings’ words:

In acute rheumatism the bacteria obtained from joint exudate and from rheumatic nodes have been studied by Dr. Edward C. Rosenow. . . . He has found that organisms from rheumatism appear to occupy a position between S. viridans and S. hemolyticus. They are more virulent than the former and less virulent than the latter. Three types of organisms have been isolated from rheumatism. . . . By varying the condition of growth, these types may be changed quite readily, one into the other. [14]

In animal studies, Dr. Rosenow sought to fulfill Koch’s postulates. First, he cultured an organism from the implicated site of focal infection (e.g., teeth or tonsils) or distant systemic lesions (e.g., joints) of patients. Next he injected animals intravenously with the bacteria cultured from the human lesions and found that the bacterial strains produced lesions in the organs of animals that corresponded to those organs of patients from whom the bacteria were isolated. On the basis of these observations he set forth the theory that specific bacteria had a pathogenic affinity for certain tissues, a characteristic he termed elective localization [16]. Dr. Rosenow also coined the term bacterial transmutation to explain the observation that streptococci and pneumococci appeared to change from one to the other. He found this to be especially common on serial passages of the bacteria through animals or with variations in oxygen tension or temperature. For Dr. Billings and Dr. Rosenow, bacterial transmutation explained the discordant results among the studies by many investigators who had described a variety of streptococcal organisms isolated from arthritic patients [14].

While searching for the etiology of polio, Rosenow found a pleomorphic coccus isolated from the adenoids and tonsils that formed all gradations between a large coccus or diplococcus on aerobic culture to exceedingly small, almost ultramicroscopic, ‘‘globoid’’ forms, on anaerobic culture [17]. Contributing to the clinical importance of transmutation was the fact that this transformation could apparently occur in a primary focus of infection such as a tonsil. Thus, theoretically, a nonvirulent bacteria could become virulent and cause systemic disease, or a germ could mutate, thereby changing its elective localization and cause disease in a different target organ. Clinical application of this concept of transmutation provided the impetus to remove all focal infections, even those that occurred without current systemic illnesses [18].

The ideas of Billings and Rosenow were consonant with the concept of a disease-carrier state. In their scenario, however, the carrier does not transmit the germ to another, but rather harbors an organism that has the potential to cause disease within the carrier at any time. Their scenario also echoes Pettenkofer’s idea that to become infectious germs require some other factor from the soil. In this case the ‘‘soil’’ would be the inflamed and weakened tissues of the body. Like Pettenkofer, Billings and Rosenow believed that individual susceptibility to infection occurred on the basis of a variety of hygienic factors, and that bacterial virulence could change given the right conditions.

**Pleomorphic Bacteria**

The notion that bacteria were pleomorphic was not new. In the mid-1800s it had been observed that the same fungus appeared in several different forms. Furthermore, early culture methods could not produce pure cultures. Hence, initially one organism might become apparent, but soon the culture would yield a variety of organisms. Because these additional organisms were not recognized as contaminants, the concept emerged that fungi and bacteria could readily change their morphology and transform from one into another [19, 20].

During the mid-1800s, Ernst Hallier, a botanist and prolific writer in Germany, believed that microscopic organisms were stages in the development of more complex fungi, and that transformations were brought about by changes in medium, moisture, and temperature [19]. Billroth, whose lectures Billings had attended in Vienna, was a strong proponent of the position that all round and rod-shaped bacteria were stages of the same organism, which he called Coccobacteria septica, because of the occurrence of the organism in putrid fluids and septic wounds. In addition, he believed that changes in the organisms occurred according to different environmental conditions. Edwin Klebs, a professor of pathological anatomy at Rush Medical College from 1896 to 1900 (likely to have known Billings), was a supporter of Billroth’s idea [19]. Despite the opposition of some (e.g., Koch and Ferdinand Cohn) the concept of pleomorphic bacteria was widely held in America in
Table 2. Diseases resulting from focal infections according to Dr. Billings in 1914 and 1915 and later by others.

<table>
<thead>
<tr>
<th>In 1914</th>
<th>Additions as of 1915</th>
<th>Suggested by others</th>
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<tr>
<td>Arthritis</td>
<td>Chorea</td>
<td>Psychoses</td>
</tr>
<tr>
<td>Myositis</td>
<td>Appendicitis</td>
<td>Phobias</td>
</tr>
<tr>
<td>Acute rheumatism</td>
<td>Erythema nodosum</td>
<td>Melancholia</td>
</tr>
<tr>
<td>Nephritis</td>
<td>Herpes zoster</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Visceral degeneration</td>
<td>Spinal myelitis</td>
<td>Arrhythmias</td>
</tr>
<tr>
<td>Septicemia</td>
<td>Osteomyelitis</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Gastric and duodenal ulcers</td>
<td>Iridocyclitis</td>
<td>Cardiac insufficiency</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>Angina</td>
<td></td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Paresthesias</td>
<td></td>
</tr>
<tr>
<td>Endocarditis</td>
<td>Hodgkin’s disease</td>
<td></td>
</tr>
<tr>
<td>Thyroiditis and goiter</td>
<td>Polio</td>
<td></td>
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<tr>
<td>Pancreatitis</td>
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The nature of the discussions that followed the presentations of these articles concerning focal infection implied that the theory might explain any poorly understood disease. Indeed, the theory of focal infection was considered by many physicians as an explanation for psychosis/mental illness [24], phobias, melancholia, insomnia [25], arrhythmias, angina, cardiac insufficiency [25, 26], paresthesias [26], high blood pressure [27], anemia [28], Hodgkin’s disease [29, 30], and polio [17]. Repeated, thorough physical examinations were recommended to search for a focus of infection in any patient with a puzzling systemic disease. The roentgen ray; ear, nose, and throat specialists; fluoroscopic bismuth tests; and bacterial cultures were suggested as promising methods to find these elusive foci [31]. Dr. Rosenow recounted his search for a focus of infection in one patient this way:

The recommended management of focal infections included both methods of prevention and eradication. Prophylactic measures focused on both individual hygiene and environmental
considerations. According to Dr. Billings, “carious teeth are an inexcusable evidence of faulty personal cleanliness in those otherwise healthy” [31]. The use of crowns and other dental measures, which would likely harbor infectious foci, were to be abandoned [31]. Enlarged or infected tonsils and adenoid overgrowth were considered a menace to health. In fact, the abundance of lymphoid tissue in children was believed to explain the frequency of rheumatic fever, diphtheria, and tonsilitis at that time of life [13]. Environmental factors were also considered important in the prevention of infection. Pure air and wholesome foods were recommended to replace the protein of wasted tissues and to boost the immune system. Overfatigue and exposure to extreme temperatures, especially prolonged exposure to cold temperatures, were believed to lower host resistance and increase bacterial virulence and should thus be avoided [14, 16, 23].

If a focal infection was found, the therapy was surgical removal. Although autogenous vaccines and polyvalent streptococcal horse serum had been used therapeutically, the value of these were limited by side effects (including anaphylaxis), and neither seemed effective without removal of the infection focus [31]. More than a decade earlier, Billings had lamented that therapeutic medicine was rarely able to intercede in infectious disease. Thus, he became an unabashed champion of surgery: “bacteriology has made possible a knowledge of true cleanliness which has enabled the surgeon to invade with impunity every part of the human body. Hence, the horizon of surgery is wide and its limitations now are few” [5]. Dr. Billings described some of the measures used to remove focal infections:

Tonsillectomy: oral surgery for alveolar abscesses (roentgenography will show jaw disease); drainage or other measures to cure sinusitis; vasectomy to drain and to use the vas deferens to wash out infected seminal vesicles and to drain the prostate gland; and any other measures necessary to surely remove all possible streptococcal foci of infection have been made use of. [14]

The net result of the influence of the focal infection theory was a boom in tonsillectomies, tooth extractions, and sinus procedures. So widespread was this practice that one contemporary is quoted as saying, “If the craze for violent removal goes on, it will come to pass that we will have a gutless, glandless, toothless, and I am not sure that we may not have, thanks to false psychology and surgery, a witless race” [33].

The Theory of Focal Infection in Perspective

By the early 1900s the field of bacteriology had provided etiologies for many diseases not previously understood. In addition to tuberculosis and cholera, other diseases discovered in the early years of clinical bacteriology were diphtheria, tetanus, plague, dysentery, syphilis, and whooping cough. An increased understanding and practice of public hygiene resulted in decreased rates of disease. With such an auspicious start, the germ theory may have been seen as the key to deciphering most, if not all, diseases. The theory of focal infection was an extension of the germ theory that offered physicians potential explanations for poorly understood illnesses. Indeed, the theory has proven to be valid in some instances (e.g., streptococcal pharyngitis and acute rheumatic fever). More recently recognized examples include Guillain-Barré syndrome after infection due to Campylobacter jejuni [34], hemolytic-uremic syndrome after infection due to Escherichia coli O157:H7 [35], and cryoglobulinemia associated with hepatitis C infection [36].

As it turned out, the germ theory was not the key to every disease. Dr. Rosenow’s work, viewed from the perspective of modern bacteriology, was obviously flawed; it was fraught with contamination, which affected the isolation and identification of organisms. However, in that era, his efforts appeared to represent significant advances in a new technology with great potential. Frequently, the theory of focal infection was presented in lead articles in the Journal of the American Medical Association, and the theory was accepted by other prominent physicians of the period such as Charles Mayo and Russell Cecil, thereby further enhancing its credibility [24, 37].

Logically, our concept of disease dictates our response to disease. It may also be true that the ways in which we are able to respond to disease at least in some measure shape our concepts of disease. The theory of focal infection not only explained puzzling disease, but also advocated treatment that was available to patients at that time, namely, surgery and attention to individual hygiene. A contemporary pathologist described a focus of infection as “anything that is readily accessible for surgery” [38]. It could also be argued that economics may have contributed to the acceptance of this theory. One bacteriologist stated that “The age of specialization stimulates surgery. Operations carry the best fees with them, and without intimidating that economics play a role in the specialist’s decision, nevertheless it is only reasonable to regard him as human—if he is the proud possessor of surgical skill, he is more prone to use it” [33].

In addition, when considering the popularity of the theory, it should be noted that Dr. Billings was a prolific and well-respected contributor to academic and organized medicine, both locally and on a national level. Early in his career he was professor of physical diagnosis and medicine at Northwestern University Medical School. Later he was professor of medicine and dean of the faculty at Rush Medical College, and he was an attending physician at Cook County Hospital, St. Luke’s Hospital, and Presbyterian Hospital. He served as both president of the Chicago Medical Society and as president and treasurer of the AMA during a time of rapid membership growth. In 1900 there were 8,000 members of the AMA; by 1910 there were 70,000 members, as many as 50% of American physicians [39]. Billings was accorded the distinct honor of receiving an invitation to deliver the Shattuk Lecture in Boston during his tenure as AMA President. He spoke about medical
education, a result of his involvement in creating the Council on Medical Education and Hospitals, which eventually led to the famous Flexner Report [2, 3].

The Decline and Epilogue

Eventually the support for the theory of focal infection declined. Even at the zenith of the theory’s popularity, some expressed concern: “Since the discovery of a positive relationship between tonsil infections and secondary manifestation in other organs and parts, tonsils have been removed wholesale, in some instances on slight provocation. Their removal has, we fear, become almost a fad” [40]. By the mid-1920s more were beginning to believe that the theory was being carried too far [41]. With further progress in the field of bacteriology, the research that supposedly supported the theory was increasingly discounted. The studies were not reproducible and questions arose concerning mixed cultures in Dr. Rosenow’s work. In 1928, W. L. Holman effectively discredited the concept of elective localization. He pointed out inconsistencies among the data of studies supporting the theory, including incongruities in tables that reported results. In addition, he noted the difficulties in applying results of animal studies to human disease, and questioned the variability in bacterial doses used in the studies and the timing of animal sacrifice [42].

During the 1930s the perspective of focal infection changed in relation to arthritis. In a review of chronic arthritis in 1935, Chester Keefer indicated that he doubted that focal infection was related to arthritis [43]. Others who reviewed the data found them controversial but favored a more conservative therapeutic approach than advocated earlier [44]. Russell Cecil reversed his view on focal infection. In 1938, in a study of 200 cases of rheumatoid arthritis Cecil and D. Murray Angevine found that for 70% of cases there was absolutely no evidence of focal infections. Retrospectively, they found that 46% of the patients had had their tonsils removed (although only 15% provided any history of tonsillitis or complained of sore throats), and 26% had had teeth removed because of arthritis. Prospectively, among those patients with focal infections treatment of such did not provide any benefit for the arthritis. In addition, when attempting to duplicate Rosenow’s studies, these investigators were unable to induce significant arthritis in animals with use of bacteria obtained from patients with rheumatoid arthritis. They concluded that chronic focal infection was relatively unimportant in rheumatoid arthritis and that complete reevaluation of the focal infection theory was indicated: “Many of us who originally accepted the theory of focal infection with enthusiasm have watched with interest and some trepidation its rapid development in the various fields of medicine but are now wondering if the time has not arrived for a reevaluation of the whole theory” [38].

In 1940, Hobart A. Reimann and W. Paul Havens systematically reviewed the literature and made a case against indiscriminate removal of teeth and tonsils. They documented other studies that supported Holman’s discrediting of elective localization and detailed the difficulties in assessing bacteriologic and radiological criteria for infected teeth and tonsils. They cited multiple observational and controlled studies that demonstrated a lack of benefit with removal of teeth and tonsils, and the potential harm associated with such procedures [41].

A review of two texts of the period illustrates the rise and fall of this theory. In the 1915 edition of Osler’s The Principles and Practices of Medicine, there is no specific reference to focal infection. The only local infections referred to are tetanus, diphtheria, erysipelas, and pneumonia [45]. The 1920 edition contains a discussion of focal infection that is consistent with Dr. Billings’ concepts [46]. However, in the 1940 edition, the discussion is preceded by a comment that focal infections as an explanation for many subacute and chronic diseases is on the wane and many are skeptical of such a relationship [47]. Similarly, in 1934, the Merck Manual discusses focal infection and mentions 35 conditions that may result [48]. In the 1940 edition, focal infection is included only as a subset of septicemia, and there is no mention of the role of focal infection in chronic disease [49]. The 1950 edition makes no mention of focal infection [50].

At the turn of the century, during the dawn of bacteriology, it appeared that most if not all diseases might be infectious in origin. In time it became clear that the theory of focal infection carried this concept to an extreme. Ultimately, it was demonstrated that the science on which the theory was based was flawed. Indeed, infections could not explain all diseases. However, the last chapter in this interesting story may not yet be written. Current technology has demonstrated an association of specific infectious agents to many diseases not recently considered infectious. There is a reconsideration of the association of infectious agents in ulcer disease, neurologic illnesses, some types of arthritis, malignancies, vascular disorders, and even coronary artery disease [1]. History reminds us to consider whether these apparent associations might be merely the result of our lack of experience with new technologies. History also demonstrates that therapeutic interventions, even if based on the most current scientific understanding of etiology and pathologie, may not result in improved health of patients. Prospective studies still need to be undertaken. Nevertheless, the words of Dr. Billings from 1915 sound almost prophetic: “Modern bacteriology and clinical research are adding day by day incon-testable proof that bacterial invasion and infection of tissue is the fundamental cause of many of the systemic diseases, which have been classed as toxic, metabolic or nutritional” [23].

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References