Counterinsurgency Doctrine Applied to Infectious Disease

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Abstract

Recent scientific discoveries lead inexorably to the conclusion that the 'total human' incorporates a necessary body of numerous microbes, including bacteria. These bacteria play a very important role in immunity by actively resisting infections by outside bacteria; however, under certain conditions they can degrade their community. They can arrogate to themselves resources that normally flow through other metabolic pathways and form persistent biological structures. In this situation, these bacteria constitute an insurgency, with strategic ramifications.

Main Text

Introduction

Given the unconventional nature of the topic and venue, a statement of purpose is required to situate the reader. It is now many years since John Nash's introduction of game theory into applied mathematics (Nash 1951, Nash 1953). While the nominal application was perhaps recreation, there were natural applications in both economics (preexisting Nash, i.e. von Neumann and Morgenstern 1944) and military strategy. It was a larger leap to appropriate game theory into biology (Smith and Price 1973), particularly as the abstraction of strategic choices to plants and bacteria was not obvious. While aspects of the analogy are still debated, with some scholars interpreting game theory as an unnecessary or troubling rhetorical gloss layered on a theory of dynamical systems, the general perception is that game theory, especially evolutionary game theory (Taylor and Jonker 1978, Smith 1979, Weibull 1997), has provided important insights into a wide range of biological processes. Other theories derived from human behavior, such as microeconomics, have also been applied to biology, even bacteriology (Harrison 2013). These analogies, particularly when explored mathematically, provide key insights into bacterial behavior and help bridge the tremendous differences in scale that often make bacterial behavior counter-intuitive to humans.

The purpose of this text is to create a dialogue connecting the military treatment of insurgency and the medical treatment of bacterial infectious disease, demonstrating that the connection has a firm underpinning biologically and that there are already counterintuitive qualitative insights available from military doctrine.

The outline is:

1. Describe the pre-existing 'war' metaphor of bacterial infection
2. Medical strategies that develop from it
3. Refinements in the understanding of the microbiome
4. The proposed 'ecology' metaphor of infectious disease
5. A new 'insurgency' metaphor of bacterial infection
6. Appropriation of existing military doctrine to treat bacterial infection

The entire text rests on an assumption about the nature of insurgency and conflict which may not be entirely obvious. The primary distinction between insurgency and conventional war is the **fluid identities of the combatants**. If an individual is an implacable foe, the only path forward is ultimately through his destruction. Significant asymmetry at the instigation of a conflict will result in rapid resolution. However, if the 'combatants' are both drawn from the same pool and community members

can both conceal and alter their affiliation during the course of the conflict, then an insurgency has the ability to grow and the institutional regime will have difficulty eliminating it through simple destruction. This fluid identity gives rise to a wealth of asymmetric strategies familiar to the practitioners of insurgency and counterinsurgency.

The strategic ramifications of a fluid identity are enormous. Typically, the pool of inert non-combatants dwarfs the armed forces on either side. Thus, the degree to which the population is able to be recruited – or inversely, driven into the arms of the opposition – is a major factor in determining the final outcome of the conflict. Initially, an insurgency typically embraces indiscriminate destruction of community resources because those resources support the existing regime. Protracted suffering destabilizes the existing society, while periodic bouts of extreme violence and terror create grounds for escalating over-reaction by the establishment armed forces, increasing the impact of general destruction, alienating supporters of the establishment, and misdirecting the use of community resources away from the needs of the populace toward defending establishment power. Ultimately, the lack of spatial separation and partitioned civilian populations with fixed identities is such that either side can end up in possession of the entire 'pot' as the victor; there is no 'homeland' and 'foreign theater.' As a result, utter devastation diminishes the 'pot' that would sustain either victor and destabilizes the future state.

The War Metaphor and Medicine

Humans have always been surrounded and permeated by bacteria. The human is continuously co-associated with roughly ten bacteria for every eukaryotic cell (Savage 1977). These bacteria are largely necessary to human health, not just in the mildly Gaian sense that they break down detritus and skin cells in the environment, but in a much more basic sense – providing key metabolic (Claus et al 2008) and immune capacities (Naik et al 2012), and integrated with the nervous system (Ochoa-Reparaz et al 2011, Foster and Neufeld 2013), endocrine system (Lyte 2013), and most other body systems. An animal raised without any bacteria is not only grossly dysfunctional in basic nutrition, immunology and metabolism, but also developmentally (Contractor et al 1998, Dimmitt et al 2010). However, ever since they were first observed under a microscope, bacteria have been mistrusted. Some bacteria are reliably connected with disease, and the others are considered guilty by association. Eventually, the 'war' metaphor developed in which the 'war' on infectious disease was generalized as a war on all bacteria. From this sprung a public love of cleansers like Lysol[tm], sterilizers, and antibiotics.

In a seminal article, 'Infectious History,' Nobel laureate Joshua Lederberg developed the theme of the 'war metaphor' and his contrasting 'ecology metaphor.' (Lederberg 2000) His article itself frets a bit at the bonds of the 'war metaphor,' moving first to the concept that bacteria might perhaps prefer to enslave the host and grow fat as parasites rather than kill the human outright. He proceeds to describe the 'superorganism' as a mélange of parasites piled high on a 'host.' This does not repudiate the concept of 'We good; they evil' as he claims it will. Only fourteen paragraphs later does he finally turn to the 'poorly catalogued ensemble of symbionts to which we pay scant attention,' such that some bacteria in close association with people may be 'good.'

Lederberg's history, whatever its challenges in the introduction of his new chosen metaphor, does an excellent job of introducing the war metaphor, antibiotics, vaccines, and the traditions of medical microbiology. A particular highlight is the introduction of Koch's (Henle-Koch) postulates (Evans 1976, Rivers 1937), which were constructed as a procedural refutation of medical quackery and became somewhat hidebound. The Henle-Koch postulates were formulated in reaction to unsubstantiated claims about bacterial causes of disease based on case series in which microbes were observed in association with pathology. The postulates admit to a bacterial cause of disease if 1) the bacteria is present in every case of the disease in circumstances that can account for the pathology and clinical course of the disease, 2), it occurs in no other recognized disease as a non-pathogen, and 3) after the bacteria is isolated in the laboratory, the isolated bacteria can cause new cases (typically in an animal model). In this literature, all non-pathogenic bacteria were referred to as 'saprophytes' (which break down and recycle dead material), ignoring or ignorant of their symbiotic properties. Koch's postulates were acknowledged to be overly restrictive soon after their publication (Koch in 1891, Evans 1993), but ongoing outbreaks of unscientific medical claims in bacteriology reinforced their necessity and even extension later into virology as well (Rivers 1937, Huebner 1957). For each new generation of microbial detection, a new variation on Koch's postulates is proposed to quell claims of guilt by collocation (Fredericks and Relman 1996, Falkow 1988, Falkow 2004).

If Koch's postulates prescribed a method for demonstrating that particular invasive bacteria were the cause of a class of infection, they also hinted at the appropriate strategies for disease prevention and therapy: exclusion and killing. These are elements of the war metaphor. Exclusion is a common principle in military actions – spatial segregation of forces, the preservation of a defense in depth, the front and the rear. Similarly, denying bacteria entry to surgical sites, food items, and vulnerable patients is a basic principle for infection control. Sterilization of instruments and surfaces is performed without respect to the nature or identity of the organisms on the surfaces. If sterility can be practically achieved, it is. When it is not, bacteria are limited as much as possible through barriers like gloves and drapes or cleaning like hand washing.

The original studies that demonstrated massive, unambiguous health benefits to cleaning were born of noxious conditions. Semmelweis (1861; translated 1983) dealt with medical students dissecting patients who had died of infection, not washing their hands, and then treating similar patients during childbirth (Best and Neuhauser 2004). Lister was dealing with surgeons who moved between draining abscesses and performing surgery, with the same instruments (Lister 1867). In both cases, the contaminating bacteria were quite pathogenic, acutely infectious, and in great abundance at the time of infection. The war metaphor is certainly valid under such conditions. Physical barriers and exclusion present a critical element of infection control, but the best defense is a good offence. Killing the pathogenic bacteria shed from a patient by cleaning the instruments and hospital surfaces with heat, desiccation, and harsh chemicals prevents those bacteria from coming close to potential sites of infection in another patient.

A second strategy for preventing infection is 'vaccination.' This method primes the biological defense systems of the patient prior to contact with the pathogen so that an infection cannot take hold.

Developing safe vaccines is extremely challenging and is only applied to the most serious, almost universally distributed, and typically epidemic infectious diseases in a naïve population.

Once a vulnerable patient is contaminated or colonized with a bacterial pathogen, however, killing those bacteria is a priority. While some biocides or cleansers may be applied to the skin (alcohol, iodine, clorhexadine, peroxide), most are too toxic for use internally or even at sensitive exposed sites like a deep wound. Instead, in these cases, the weapons of choice are antibiotics. Antibiotics are toxic chemicals more toxic to bacteria than to eukaryotes, including humans. There are a few complications with this; first, eukaryotes are generally 'partly bacteria.' That is, the mitochondria that provide cells with energy are quite similar to α-proteobacteria (Lang et al 1999, Gray 2012), while many pathogens are also proteobacteria. As a result, antibiotics have a tendency to stress the mitochrondria and can lead to metabolic difficulties in the heart or other tissues with high respiration rates (Henderson et al 1969, Schulze-Osthoff et al 1992, Duewelhenke et al 2007, Kalghatgi et al 2013). Further, as antibiotics are somewhat toxic, the liver and kidneys attempt to process the antibiotics and are stressed during the attempt.

In treating bacterial infection, three strategies exist for resolving the dilemma that any chemical that kills all bacteria will also kill the patient. First, some antibiotics do not penetrate the patient. They are useful for skin or gastrointestinal infections, but such antibiotics cannot reach infections that are internal or disseminated and, therefore, have limited clinical application. Generally, these antibiotics could be called 'topical.' Second, some antibiotics are only active against certain sub-groups of bacteria. The range of different bacteria they will kill ('cover') is their 'spectrum of activity,' and the more kinds they kill, the more 'broad spectrum' the agent. 'Narrow spectrum' agents may help against certain infections but tend to be less toxic. They are limited in phylogeny and require the identification of the specific pathogen for each patient. Finally, a common principle in medicine is that the poison is in the dose. There may be a window of clinical utility, sometimes an order of magnitude in concentration, between effective bacterial killing and patient toxicity. The use of these antibiotics must be closely monitored. The safe window is narrowed in some patients because of liver problems, for example.

Under the war metaphor, in the world of the Koch-Henle postulates, given clinical signs and symptoms of an infection, the general solution is to apply the least toxic antibiotic that will address the infection. If a dangerous infection is of bacterial cause (or viral with suspected bacterial superinfection) and possibly systemic, then the antibiotic must reach the full body and cover all possible bacterial pathogens. If there are no such antibiotics practically available and no information on this specific patient (or no time to generate the information before the infection becomes life threatening), then the process of empirical therapy uses statistics on similar patients (for instance, pneumonia patients in this season) to infer which antibiotic is most likely to cover the relevant infection.

In cases where there is more time and antibiotic choice uncertain, diagnostics are used to assist in selecting antibiotics. Microscopy may allow bacteria to be seen and roughly identified; however, microscopy requires a relatively large number of bacteria in a sample. Bacteria from a patient sample may be grown in a laboratory. If even a few bacteria are present they will grow rapidly overnight from 1

cell to 10^9. In broth, this is turbid; on a solid media plate, a visible colony. Thus 'culture' can be exquisitely sensitive. Given a clinical sample, typically several different bacteria will grow on non-selective solid media. The selection of particular media to detect specific pathogens is an element of clinical microbiology. An experienced microbiologist will often select a representative bacterial colony from among the colonies on the initial plate, based on training, education, and experience with prior patients (Howe et al 2013). Following the initial growth and identification to the genus and species, the bacteria can be tested for sensitivity to various antibiotics. The reason for the sensitivity testing is that some closely related bacteria are resistant to some of the antibiotics at concentrations that are safe for humans. Thus their use as therapy would be unsuccessful. The process of identification and testing can take 4-7 days, or, for particularly difficult organisms, weeks.

The isolation and characterization process in the clinical laboratory is the hunt for the enemy and the careful selection of weapons to destroy it. For the decades between the innovation of antibiotics (1930s, sulfa and penicillin) and the early 2000s, it was the only paradigm of patient care for presumptive bacterial infections. Discrimination among bacteria was needed only in so much as it impacted the choice of antibiotics; antibiotics were developed to be as broad as possible to reduce the requirement for costly and time-consuming diagnostics as well as for reasons of marketing. Most antibiotics at this point are designed to treat one of two or three general classes of infection (clinical pictures), with characterized exceptions for resistant bacteria (intrinsic resistance) and additional exceptions for bacteria whose close relatives are sensitive but in whom resistance has evolved or been enhanced.

The New Science of the Human Microbiome

Environmental microbiology and medical microbiology followed different paths. With no mandate to seek and destroy pathogens, environmental microbiologists turned a curious eye toward unusual habitats and metabolisms. They found that bacteria, fungi, viruses and microeukaryotes often interacted to perform metabolic functions and that the bacteria could rarely be isolated and cultured in the laboratory using methods originally developed for clinical samples ('the great plate count anomaly', Staley and Konopka 1985, Vartoukian et al 2010). The signature strategy for environmental microbiology was the 'enrichment culture,' in which bacteria were brought into the laboratory as a group (Beijerinck 1888 and Winogradsky 1887, D'Onofrio et al 2010). Even those bacteria that could often be cultured singly proved an unexpected challenge at times (Elliot and Colwell 1985, Oliver 2005). As a result, environmental microbiologists searched for methods to count and characterize bacteria that could not be cultivated.

One of the most important 'culture-independent' methods is DNA sequencing. Each bacterial strain possesses some key genes that can be used to identify it; particularly the ribosomal RNA genes (16S rRNA), which are present universally and in high copy number (Woese and Fox 1977). By sequencing the DNA, an organism can be characterized even if it cannot be grown for biochemical testing (Seewaldt and Stackebrandt 1982). By sequencing a large variety of 16S rRNA genes from a single environmental sample, the population of bacteria in the sample can be identified and enumerated even if the bacteria themselves cannot be grown in the laboratory (Ward et al 1992). Now the method has been generalized

to other genes and even to all the DNA or RNA in a sample rather than the 16S rRNA genes alone (Qin et al 2010, Campbell et al 2013). Still the 16S rRNA sequencing method is the most common. As microbiologists imported this method from environmental microbiology to a medical context, it became apparent that many human-associated bacteria did not grow readily in the laboratory and had still not been characterized (Fodor et al 2012). Many of these had been perpetually overlooked (Relman 2002, Wylie et al 2012), particularly those that were minority organisms and thus less likely to be observed microscopically. As the diversity was better sampled, microbial ecology and medicine began to coalesce (Raes and Bork 2008, Costello et al 2012).

Following the argot of the DNA sequencing experts who pioneered the methods, the collection of bacteria in a habitat is referred to as the 'microbiome.' Collectively, the microorganisms associated with people are the 'human microbiome.' The National Institutes of Health created a program in 2008 to characterize the 'normal' human microbiome with culture-independent methods (Turnbaugh et al 2007). The International Human Microbiome Consortium (Australia, Canada, China, Europe, Japan, South Korea, and the United States) coordinated additional efforts (Peterson et al 2009). Though both data (Wortman et al 2010, Gevers et al 2012) and dozens of publications emerged during the project, the main body of publications was released in 2012. The Human Microbiome Project and numerous related programs have been wildly successful in creating vast databases of human microbiology, suggesting links to the environment and to diseases. However, the basic science is relatively recent, and its implications are still unclear in the broader field of microbiology (Fox 2012).

As a result of characterizing the full range of bacteria in samples instead of paying selective attention to those few that can be readily cultured, a new sensibility about human ecology and health has emerged. The full diversity of bacteria in association with a human had been grossly underestimated at every phylogenetic level (Mitreva et al 2012, Fitzsimons et al 2013). The bacterial populations are highly variable over time at a single site in a single person and between body sites of a single person at any given time (Zhou et al 2013). More than gender, ethnicity or geography, body site defined the bacterial diversity in a given sample (Costello et al 2009). The development of the microbiome from birth throughout life is slowly being described and modeled (Marino et al 2014). In short, the bacteria of any given body site are shared broadly across the human population. Some sites that were thought to be free of bacteria proved to have a typical population in healthy individuals (Feazel et al 2012, Ramakrishnan et al 2013, Beck et al 2013, Fouts et al 2012). Prior to the human microbiome project, it was already known that intestinal bacteria were required for healthy digestion and nutrition, but as new community data was acquired, bacteria were demonstrated to provide critical metabolic features equivalent to a second liver (Wikoff et al 2009). The immune system was shown to have a creative collaboration with the bacterial community in maintaining the integrity of tissues and the microbial population (Lee and Mazmanian 2010, Hooper et al 2012). The absence of key members required for a healthy microbiome was observed to contribute to a wide range of recognized disease conditions (Hibbing et al 2009, Cobey et al 2013, Harrison 2013, Ren et al 2013). Interactions among bacteria and fungi were discovered and described (Hoffmann et al 2013, Cui et al 2013). The microbes clearly interacted with each other in diverse and complex ways (McHardy et al 2013, Lozpone et al 2012, Zhang et al 2013).

As the healthy microbiome was explored and described, many organisms that have a reputation as pathogens were found to be daily members (Mitreva et al 2012). This has created discordant reports in the literature. Some authors emphasize that the community being described is not associated with disease; others emphasize that it includes members that have close relatives associated with disease (sometimes naming a 'reservoir,' Nistico et al 2011). One of the major issues is that the 16S rRNA genes do not permit adequate characterization of an organism to describe its ecology (Tomida et al 2013, Vanderwalle et al 2012, Preheim et al 2013, Tikhonov and Wingreen 2013). Bacteria can be closely related at the genomic backbone but have very different gene complements and behavioral potentials (Turner and Feil 2007, Joseph et al 2011, Lapierre and Gogarten 2009). Bacteria that may be healthful in one context may become pathogenic when the host or microbiome is out of balance (Littman and Pamer 2011, Nedialkova et al 2014). Mazmanian et al 2008 (continuing, Lee et al 2010) propose the term 'pathobiont' to refer to bacteria that they have observed as both long-term symbionts and participants in disease, even though almost every symbiotic bacteria possesses the potential to make a bad situation worse (Bloom et al 2011, Lhocine et al 2013). In reality, while some bacteria are obligate pathogens (not going as far as Casadevall et al 2011 in denying pathogen identity), labeling bacteria as opportunists or pathobionts is a product of selective attention to human illness.

One example of selective attention in current microbiology is the clinical focus on detecting multidrug resistant bacteria. Many bacteria are multidrug resistant, and resistance is commonly observed during culture-based surveillance for epidemiology and infection control. This suggests that there are abundant specific pathogens in the environment or the human microbiome. However, antibiotic resistance does not imply that bacteria are obligate pathogens, though many public health researchers blanch at a high frequency of MRSA or VRE carriage, for example. Multidrug resistance is a natural consequence of either having always been resistant because of some other metabolic or social requirement (Dantas et al 2008, Sommer et al 2009, D'Costa et al 2011, Bhullar et al 2012) or of having encountered and survived antibiotic therapy in the past while living as a commensal, i.e. an innocent bystander. While many recalcitrant pathogens are multidrug resistant, the simple fact of multidrug resistance does not indicate pathogenesis; it may even be in conflict with the requirements for virulence (Martínez et al 2002, Beceiro et al 2013).

The medical profession was already wrestling with compound genetic-infectious diseases (i.e. cystic fibrosis, Sibley et al 2006, Madan et al 2012, Price et al 2013, Knights et al 2013), in which

1. A genetic predisposition creates susceptibility to infectious disease and infection exposes genetic pathology,
2. Behavioral-infectious disease, in which behavior and infectious disease interact (David et al 2013, Greenblum et al 2012), and
3. Environmental-infectious disease (Cochran et al 2000), in which environmental exposures and infectious disease interact.

As a result of microbiome studies, the possibility that an infectious disease could be the result of both exposure to a pathogen and the absence of several normal bacteria, for example, became not only a

theoretical consideration but a reality (Srikanth and McCormick 2008, Lawley et al 2012, Britton and Young 2012, Ng et al 2013). This complicated the diagnostic interpretation of bacterial detection and eviscerated Koch's postulates.

The overall impact of microbiome studies on medicine is still unfolding. Immediately, the practice of medicine is making some adjustments. Some diseases had been misattributed, either to the wrong microorganisms or to other causes. These included cancers (Tjalsma et al 2012, Kostic et al 2012, Warren et al 2013, Schwabe and Jobin 2013, Zackular et al 2013, Kostic et al 2013), metabolic disorders (Cox and Blaster 2013), immune disorders (Scher and Abramson 2011, Markle et al 2013, Huffnagle 2010, Alekseyenko et al 2013), and even possibly neurological disorders (Benach et al 2012, Kang et al 2013, Finegold et al 2010, Mulle et al 2013). In the big picture, the practice of medicine will be revolutionized by new paradigms of compound and complex disease.

In an obvious extension of discovering the importance of certain bacteria for health, the impact of antibiotics on these health-associated bacteria was examined. The effect of antibiotics on those populations was confirmed (Jakobsson et al 2010, Caporaso et al 2011, Dethlefsen 2011, Jernberg et al 2013), and the impact on host health was striking. Antibiotics in childhood (in an animal model) could cause lifelong metabolic disorders (Cho et al 2012, Liou et al 2012). The disorder could be conveyed from animal to animal by infection (Turnbaugh et al 2006, Ridaura et al 2013) and treated by the administration of a balanced community of bacteria from an untreated animal. Thus, the disease was related to the entire bacterial community rather than a single pathogen, and it appeared to arise more from loss during antibiotic therapy than from an epidemic infection. This does not fit into the 'war metaphor' or square with Koch's postulates.

Ecology Metaphor

Joshua Lederberg recognized that the 'war metaphor' and Koch's postulates required revision. As an alternative to the 'war metaphor,' Joshua Lederberg proposed the 'ecology metaphor.' The ecology metaphor leads physicians to treat the bacterial community the way practicing ecologists modulate macroecological communities. The ecology metaphor is aesthetically attractive and theoretically sound – the microbiome is an actual ecology (Prosser et al 2007, Bik et al 2010, Freilich et al 2010, Smillie et al 2011, Fierer et al 2012, Costello et al 2012, Faust et al 2012, Faust and Raes 2012, Bosch et al 2013), reducing the gap between metaphor and reality. There is no inherent reason why the microbiome cannot be managed as other ecologies are managed. The problem with the metaphor is that managing other ecologies is not governed by a consistent body of theory and practice (Gosselin 2011, Mitsch 2013, Barker and Odling-Smee 2014). Over time this may change, but at present the single broader objection to the ecology metaphor in infectious disease can be refined into four more specific issues.

First, the practical goals in ecology are very diverse and are pursued by distinct communities of practitioners with their own locally adapted theories and language (Blouin et al 2013). Forestry (Heinimann 2010, Clark and Kozar 2011) and fishery biologists (Zhou et al 2010), for example, attempt to optimize one or more ecosystem service, now including carbon sequestration (Mitsch et al 2012),

reduced erosion (Mao et al 2012), and water retention (Benigno et al 2012, Palmer et al 2013). Others stabilize existing communities or optimize diversity (Chapman and Underwood 2011, Mitsch 2012). Conservation biologists attempt to prevent the extinction of a specific organism (Seddon et al 2010). Many of these goals overlap with attempts to restrict the spread of invasive species (Lu et al 2010), but not all. Famously, attempts to increase agricultural productivity or eliminate pests (biocontrol) have actually involved the introduction of invasive exotics (Simberloff and Stiling 1996, Hoddle et al 2004, Messing and Wright 2006). This has certainly led to conflict among the communities.

Second, practicing ecologists operate on a very different time scale than physicians, with opposing biases. The stakes for conservation biology may be absolute extinction of a species dependant on a complex ecology. This is an absorbing boundary to be avoided at all costs; there is little or no room for trial and error and disturbing communities is viewed as potentially irreversible. Infectious disease often has similar stakes – the death of the patient – but in the case of infection, eradicating the microbial community is considered the most conservative course of action. In each case, the precautionary principle is applied but in opposite directions, creating a serious tension in any attempt to import insights from one to the other.

Third, the 'war metaphor' is actively used in practical ecology as well as medicine (Larson et al 2005). In conservation biology invasive species are treated by exclusion and eradication (Clout et al 2002, Zavaleta et al 2001, El-Sayed et al 2006) following a 'war metaphor' such that the two metaphors are not exclusive. This limits the ability to displace the war metaphor with the ecology metaphor.

Fourth, the ecology metaphor for infectious disease has not been thoroughly explored, but in its original formulation it appears to be based on the preservation of the 'normal microbiome,' including the exclusion of 'invasive organisms,' as the guideline for health maintenance. Unfortunately, what this imports most directly from ecology is not the science of practical ecosystem management, but instead the naturalistic fallacy, which also plagues ecology (debated at length in Elliot 1982, Callicott 1992, Cowell 1993, Larson 2007). Successful disease prevention will likely result from only an abnormally healthful microbiome, certainly not a historically median microbiome. After all, one characteristic success of western medical practice has been the displacement of infectious disease at young ages by chronic illness at later ages as the characteristic causes of death (Armstrong et al 1999, Cohen 2000, Yach et al 2004). Reinterpretation of some chronic disease as infectious due to new microbiome studies may rebalance the statistics somewhat, but the overall trend has been observed over many decades. Returning to a historical microbiome would also mean returning to a higher rate of infectious disease mortality, especially given the present human population densities and global travel patterns (Colizza et al 2006, Brockman and Helbing 2013), both of which encourage periodic epidemics and pandemics.

Bacterial Insurgency

Because the 'war metaphor' is undermined in many examples of infectious disease by the presence of diverse 'pathogens' in the healthy microbiome and the 'ecology metaphor' provides little practical

guidance to clinical practice, a third metaphor is required. Given that it is the title of the article, it should be no surprise that the metaphor proposed is **insurgency**.

The typical metaphor between war and infectious disease practice was that of a 'big war' or invasion, and it still applies to many acute and deadly epidemic diseases. However, this model appears inappropriate if the pathogenic bacteria are daily occupants of the host or even necessary for health. These bacteria have a dual identity, depending on their social context. In the context of the healthy host, the bacteria are required for health; in the context of an ill or injured host, the bacteria exacerbate the disease by becoming pathogenic. Where the war metaphor has difficulty recognizing the bacteria as typically peaceful, the ecology metaphor has difficulty acknowledging them as driving disease.

This dualism can be quite subtle and hard to characterize in the unnatural environment of the laboratory. For a bacteria to change from symbiote to pathogen often requires flipping a single regulatory genetic switch (Kazmierczak et al 2005, Somvanshi et al 2010, Dolan et al 2011, Korem et al 2005, Gripenland et al 2010, de las Heras et al 2011, Richards et al 2009, Gross et al 2008, Lanois 2008), generally thrown as a result of sensing the microbial environment through diverse receptors (Lamarche et al 2008, Tamayo et al 2010). In a pathogenic state, bacteria bloom to high numbers (Cugini et al 2013), with unusual concentrations of toxic secondary metabolites produced and not detoxified (Duboc et al 2013). More complex protein toxins also cause pain (Chiu et al 2013) or host distress, often the local death of host tissues (Kim et al 2013, Farrow et al 2013) with the resulting release of nutrients (such as iron, Skaar 2010) to the bacterial community. Inflammation is present with an acute immune response, often non-specific and sometimes encouraged by the bacteria themselves (Brown et al 2008, Cheng et al 2011, Grundmeier et al 2010, Watkins et al 2011, Ellis et al 2010, Spaulding et al 2013, Babrowski 2012). Symptoms that encourage the spread of the bacteria (such as diarrhea, coughing and sneezing) are initiated (Ewald 1994).

Several known mechanisms can cause the bacteria to enter a pathogenic state. Stress hormones (Alverdy et al 2000, Karavolos et al 2013, Verbrugghe et al 2012, Alverdy et al 2010), pain neurotransmitters, narcotics (Babrowski et al 2012, Zaborin et al 2012), exposed connective tissues (Olivas et al 2012), access to abnormal sites (Alverdy and Chang 2008, Raoultm et al 2009, Al Masalma et al 2012), ischemia-reperfusion (Feinman et al 2010), free iron (Kortman et al 2012) and immune activation, and inflammation (Brown et al 2014) can each trigger pathogenesis. In addition, these mechanisms can send signals through the microbial population via microbial communication and interaction systems (Cornforth and Foster 2013). Bacteria will instigate the host to attack other bacteria (indirect antagonism; Rolfe 1984, Sansonetti 2004) and even directly attack each other dependent on the inflammation of the host (Nedialkova et al 2014). In the past, host-generated stress signals activating bacterial pathogenesis were viewed as a sign of weakness triggering opportunistic predation – literally blood in the water, at times. However, there is another paradigm that fits equally well – passengers and crew fleeing a sinking ship and prying free pieces of lumber as makeshift life-boats. This activity is well known in smaller scales, including viruses within bacteria (prophage/bacteriophage). As the bacteria decline in health, the viruses move from sometimes helpful quiescence (Wang et al 2010) to replication, more rapidly ending the life of the bacteria and producing and releasing viruses in the process (Hertman

and Luria 1967, Erill et al 2007, Choi et al 2010, Nanda et al 2014). Exceptions exist where the virus extends the life of the bacteria to enhance viral reproduction i.e. Engelberg–Kulka et al 1998, Sullivan et al 2006).

It is somewhat perverse to envision the bacteria dwelling for years in the context of the normal microbiome and participating in the health of the entire community only under pretense, a predator lurking for an opportunity to cause disease. This is, however, the image raised by terms such as opportunistic pathogen, asymptomatic infection, and pathogen carriage. These terms are the byproduct of the limitations of the war metaphor and its inherent dualism. It is reinforced by the current microbiological practice of examining mostly ill people. Since most microbiology effort is directed at characterizing people with illnesses, the bacteria are perceived in the context of illness. Instead, in general, these bacteria are members of the normal microbiome, not associated with disease, many times (asymptomatic), and in many hosts (carriers) but very much driving disease during patent infections. When symbionts are engaged in disease, it may be related to disruptions in their environment that could be viewed either as presenting an opportunity for rapid growth/invasion or as presenting a new challenge because the community is failing and the bacteria rapidly consume the local resources in anticipation of migration to another community.

In the event of a disturbance, the human will not be able to migrate; for him, the crisis is potentially terminal and the bacteria are possibly abbreviating his survival. It may be that he also expects to recover and does not share the perception that his tissues are best viewed as bacterial growth medium at this point. This creates a conflict of interests that previously did not exist between bacteria and host and even among the bacteria themselves, which previously were all aligned with the interests of the community and now experience the tragedy of the commons. The bacteria that had been checked both by each other and by the immune system of the host will now be motivated to evade the immune system and outpace each other. In short, they participate in an insurgency.

Having already discussed what may trigger a single bacterium to shift from symbiotic to pathogenic, it is reasonable to ask which scenarios might trigger an insurgency at the level of the microbial community. Some scenarios include multi-organ failure arising from metabolic or geriatric conditions, serious trauma, and severe infections by an outside bacteria (Molloy 2011, Pastar et al 2013) or virus (McHardy et al 2013, Seabloom et al 2013, Brown et al 2013) that threatens the systemic integrity of the host, thus engaging the local microbiome in superinfection. Even antibiotic use can trigger insurgency (Ayres et al 2012). When engaged in an insurgency, the bacteria themselves are likely to be stressed, to produce antibiotics, to distribute virulence factors (Charpentier 2012), pathogenicity islands (Hiller et al 2010), and antibiotic resistance factors genetically, and to release viruses (Modi et al 2013). This will increase the rate of potential evolution and destabilize the microbiome. It may ultimately serve as a hotspot in the evolution of bacterial virulence (Stecher et al 2013, Pham et al 2014).

Counterinsurgency Principles

To address insurgent bacteria, one may attempt to apply the traditional 'war metaphor' of infectious disease. Unfortunately, defense in depth does not succeed. Not only are the bacterial pathogens already on/in each host, they are even required for good health. The second principle of warfare, eradication of the foe from behind your own lines, i.e. from potential hosts, is hardly possible. In addition, the application of broad spectrum antibiotics may seriously harm the patient both directly (Cunha 2001) and indirectly. Indirect side-effects of broad spectrum antibiotic therapy include the prevention of otherwise desirable surgery (Parvizi 2012) and tens of thousands of deaths each year from antibiotic-associated infections, including *Clostridium difficile* (Zilberberg et al 2008, Oake 2010). Finally, because so many bacteria would be exposed to the antibiotics during treatment of the insurgency, antimicrobial resistance will emerge relatively quickly rendering the therapy increasingly ineffective – sometimes within a single patient (Costelloe et al 2010) and certainly within a community of patients or healthcare system (McAdam et al 2012). Finally, it may not be possible for the resistant bacterial population to evolve to antibiotic sensitivity on a relevant time scale (Andersson and Hughes 2010).

The insurgency metaphor, however, provides access to the doctrines of counterinsurgency (sometimes COIN; distinctions made in Gorka and Kilcullen 2011). Counterinsurgency as presently discussed has advocates and detractors among military professionals (Martin and Smith 2010, Nagl and Burton 2010, Vizzard and Capron 2010, Martin et al 2012, Hammes 2012, Gventer et al 2013, Petraeus 2013), but many of the concerns surrounding counterinsurgency arise from questions about whether military intervention by a democracy is practical in internal asymmetric conflicts at all (Marshall 2010) and distinctions between insurgency and civil war (Gorka and Kilcullen 2011, Gentile 2013). These discussions draw on observations about the scale of the combat, the direction of institutionalized armed forces, the political commitment of diverse nations, the moral virtues of self-determination (Porch 2011), and national or global economic concerns. Many of these realities and ramifications are either irrelevant or strangely transformed when counterinsurgency doctrines are imported to infectious disease. Outside medical intervention into infectious disease is morally less controversial (Leibovici 2012), for example, and the economics of medical interventions are important (Graves et al 2011) but certainly not the same.

Setting aside the larger strategic issue of whether to intervene, counterinsurgency doctrine was developed to pursue an apparently intractable military challenge and avoid being 'bogged down' in a conflict for which conventional warfare had no realistic solution. Many public health experts, physicians, and scientists would suggest that antibiotic resistance presents a similar risk of numerous medical interventions becoming 'bogged down' by intractable infections (Spellberg et al 2008, Boucher et al 2009, Bow 2013), many of which can be cast as 'insurgencies.' Counterinsurgency as developed by the U. S. military presents a thoughtfully developed doctrine for the prosecution of military intervention in an otherwise internal affair. The fullest expression of the doctrine are the Field Manuals (FM) 3-24/MCWP 3-33.5 (2006) and 3-24.2 (2009), "Counterinsurgency" and "Tactics in Counterinsurgency." These manuals were composed jointly by Generals Petraeus and Amos, leading teams of contributors from the US Army and Marine Corps. They represent a scholarly approach to the practical issues that a

combatant commander will meet during modern counterinsurgency. Drawing from them, one can construct a vision for novel approaches to bacterial counterinsurgency and, in broad outline, bridge military science and theory of infectious disease.

Following the field manuals, an entire counterinsurgency operation is divided into three phases: preparation, in which intelligence is the main concern; execution, in which intelligence is also the main concern; and ending the operation, in which counterintelligence appears to be the main concern. Intelligence is not only the first concern - it is the most pervasive concern. In medical terminology, the parallel of intelligence is the 'clinical picture:' the patient history, presentation, and diagnostics.

Intelligence

Under the prevailing war metaphor and Koch's postulates, by definition a successful laboratory investigation of bacterial infection reveals and identifies a single pathogen. Diagnostics are used to identify the pathogen and determine its antibiotic sensitivity before antibiotic selection. If multiple bacteria are detected, typically only one of the bacteria is deemed the primary pathogen to be characterized extensively. The others are labeled contaminants (Mirrett et al 2001, Richter et al 2002), secondary (Gjødsbøl et al 2012), co-infections (Sobel et al 2013), or superinfections, of limited clinical significance. At the extreme, certain polymicrobial infections are dismissed from infectious disease altogether (i.e. diabetic ulcers), and microbiological testing is of limited clinical utility (Gardner et al 2001, Moore et al 2010). The pathology is blamed on the host condition rather than on any of the microbes. The underlying logic is that only a severely compromised host would be open to such a diversity of opportunists and that these are unlikely to travel to nearby people who are not equally compromised.

FM 3-24 offers alternative guidance: rather than looking primarily for foes, diagnostics should be employed to identify friends and allies. The importance of holistic intelligence cannot be underestimated and recurs throughout both of the manuals. Further, this concept of attention to noncombatants has been expanded to pervade other Army doctrine, including initial entry training. The common acronym summarizing battlefield intelligence has been extended to the somewhat unwieldy METT-TC (mission, enemy, terrain, troops, time, and civil considerations; FM 3-0 Operations) specifically to include 'civil considerations' – friends and allies. The potential spectrum of individuals to be encountered is broad; each needs to be fit into a complex understanding of their interrelationships. This intelligence will prove critical in later phases of the counterinsurgency.

In the clinical laboratory, counterinsurgency intelligence gathering would require new technology, a new electronic health record, and a new mindset. Various technologies for community characterization are already available – particularly high-throughput sequencing (Xu et al 2012), but also multiplexed PCR (Harris and Hartley 2003, Lindsay et al 2013), hybridization arrays (Gardner et al 2010), microfluidic culture (Ho et al 2012), flow cytometry (Jolkkonen et al 2010, Nuutila et al 2012), and novel approaches to microscopy (Foreman et al 2010, Harris et al 2013 among others). Each has limitations and none of them provide quite what would be desired to understand the function of a microbial community *de*

novo. They can provide information about structure, biochemistry or genetics, but this information does not directly translate into ecology, and simple technological fixes for this gap do not exist.

To achieve an ecological understanding from data about biochemistry and genetics is as difficult as achieving a sociological understanding from simple demographic data. Even with more sophisticated data types, such as interaction and relationship data, sociological understanding may be challenging to extract. It cannot be readily summarized in a bar chart or represented as a single critical value. Sociologists (Borgatti et al 2009), businesses (Tichy et al 1979), scientists (Borner et al 2010), public health officials (Roux and Aiello 2005, Luke and Harris 2007, Blanchet and James 2012), law enforcement (Chen et al 2004), and the military (MacGinty 2010) have each wrestled with this reality within their own spheres and have collectively turned to social network analysis (Scott and Carrington 2011). Social network analysis is one of the core analytical techniques promoted in FM 3-24. It has recently found applications in the human microbiome; but true dynamic (Kossinets and Watts 2006) and multi-level analysis (Jepperson and Meyer 2011) requires a substantial amount of data and is rarely instinctive. Though there has been some progress, particularly in relating occurrence and co-occurrence of taxa to disease presentation (Boutin et al 2013), bacterial counterinsurgency requires both new technology and qualitative shifts in the data analysis, presentation, and ecological theory enabling the interpretation of diagnostic information.

As ecological data is made available, reporting it to physicians will require changes in the strategy for reporting microbiology results from the laboratory, including the degree of interpretation available. Finally, integrating this data into clinical practice cannot occur as a single leap forward; instead, a spiral development must include physicians, regulators, technologists, educators, and microbiologists (Kirkup et al 2013). A collaborative process among the strategists and the technologists is required to discern what forms of intelligence are most useful and practical, similar to the sometimes challenging collaborations that occur in the intelligence and acquisitions communities.

Trusted networks

The purpose of identifying potential friends and allies is analogous to the surgeon determining the border of healthy tissue prior to debridement. These bacteria are the elements of a potentially healthy and healing associated community, even if some of them are behaving as pathogens at this particular time. In counterinsurgency, supportive local nationals nucleate the 'trusted network.'

The core strategic goal from FM 3-24 is to "Build Trusted Networks." To quote A-28: "This is the true main effort; everything else is secondary." After all, this trusted network will hopefully become the sinews of the new community post-insurgency. Failing to build one basically amounts to not practicing modern ('social' a la Owens 2013) counterinsurgency. FM 3-24 and FM 3-24-2 provide insight into the nature of a trusted network and the methods for developing one. The fundamental observation is that trusted networks in counterinsurgency are not intelligence networks, composed entirely of spies, a political party, formed of ideologues, or a conspiracy composed of one or another special interest group. Successful networks spread over time to encompass an increasing fraction of the community, eventually

containing those very people who may have temporarily supported the insurgency. To effectively contain this explosive diversity in functional proximity, the network itself must be very strong, have predictable emergent properties, and provide substantial benefits to membership.

Robust networks provide structured suites of social roles. In human social networks, these roles may include medical and legal professionals, primary productivity such as resource extraction or farming, resource processing or management, construction, recycling, infrastructure maintenance, security, and many other critical roles. In ecology, these include photosynthesis, breaking down minerals, recycling detritus, detoxification of waste, creation of physical structures, and various other ecological tasks. The assembly of these roles (guilds, Root 1967, Hawkins and MacMahon 1989, Simberloff and Dayan 1991) at the macro level provides 'ecosystem services.' Communities provide services as a whole; sub-communities provide ecosystem services to the larger community from within. Services are an emergent property of the interacting community. The absence of a service may arise from a number of causes and ultimately makes a particular lifestyle in the community unviable. For example, the absence of gasoline station attendants makes trucking impossible. This can have cascading effects through the community, resulting ultimately in disturbance of the overall community function.

Insurgency attracts individual community members from otherwise 'peace compatible' roles to roles as part time or full time insurgents. As anthropomorphic as this may appear, the underpinnings are mechanistic and require no ideology on the part of the bacteria. The bacteria shift from a state in which contribution to the larger community results in maintenance of integrity to one that redirects nutrients and energy into unbalanced growth and dispersal, at the cost of normally symbiotic organisms and persistent biological structures. Such growth inevitably degrades the community provision of the original role and all interdependent roles. It surges, making other peace compatible roles unviable. This may lead to displacement and possibly encourage additional membership in the insurgency. The resulting community disturbance is a complex problem, observed as cooperative pathogenesis (Raymond et al 2012, Diard et al 2013). However, the proper response described in FM 3-24 is the provision of key community services and infrastructure to sustain the trusted network while reintegrating community members into their peace compatible social roles.

Although it is still in its infancy, medical analogs are available for both the direct provision of facilities and the provision of personnel to fill key social roles. The first includes the provision of prebiotics – chemicals that are used as substrates or metabolites by the community (a generalization from the original conception of Gibson and Roberfroid 1995, Roberfroid 2007; extending the logic of Schrezenmeir and de Vrese 2001 as in Krutmann 2009). These have been explored in various medical settings, particularly the intestinal microbiome. The second involves population of the patient with introduced bacteria, typically called 'probiotics.' These may be transient (Ouwehand et al 2002) or semi-persistent (De Champs et al 2003) and have been used in the oral (Burton et al 2013, Di Pierro et al 2013), vaginal (Burton et al 2003, Stapleton et al 2011), skin (Lai et al 2010, Shu et al 2013, Wang et al 2013), and gut microbiomes (Bolla et al 2013) to prevent and treat several diseases. Probiotics can interact with both bacteria and host. One known mechanism of action is the exclusion of specific pathogens (Vincent et al 2013) or competition with pathogens (Brown et al 2009). A second is the

encouragement of other bacteria in the community (Lawley et al 2012). A third is the management of host endocrinology (Levkovich et al 2013, Poutahidis et al 2013). Fourth is the management and resolution of inflammation (Kelly et al 2003, Verdu et al 2004, Nembrini et al 2011). However great its potential, the field of probiotics is very immature. Some proposed therapies have been dangerously close to a panacea even when supported mechanistically. Given the sweep of the claims, evidence of efficacy has been expectedly uneven.

One of the key difficulties is a lack of appropriate intelligence. Medical practice is not equipped to diagnose disease in terms of missing infrastructure elements and ecological roles. Some groundbreaking research has employed an empiric strategy to determine the missing roles and a combinatorial approach to replacement therapy (Lawley et al 2012). The introduction of six different organisms led to the reconstitution of an additional ~70 dependent populations and the treatment of an otherwise fatal infection. Prebiotics are less well developed as a therapy. Prebiotics are very difficult to design rationally (den Abbeele et al 2013); most attempts have relied on intuition rather than formal models. Metabolic models required to predict the community response to any given metabolite are non-trivial and frequently paradoxical (Abubucker et al 2012, Levy and Borenstein 2013, Jiao et al 2013). For example, both *Salmonella* and *Clostridium* appear to rely on a temporary excess of sialic acid in the intestines following antibiotic administration to establish their characteristic infections (Stiemsma et al 2013, Ng et al 2013). However, these two bacteria have very different metabolisms and their shared reliance on a single nutrient for infection is counter-intuitive. Secondly, prebiotics are inherently less likely than probiotics to achieve striking results because of the dose dependence, specificity, and self-limiting nature of the intervention.

Hasty Action

The inverse of attention to gathering intelligence and constructing a trusted network is 'hasty action.' FM 3-24 specifically warns against 'hasty action' (A-25). Under the traditional 'war metaphor,' rapid response is absolutely critical (Heath et al 1996, Rivers et al 2001, Lodise et al 2003, Kang et al 2003, Vince et al 2008). Intrusions become more difficult to manage the longer the response is delayed. In traditional military doctrine, preventing initial penetration is the single best defensive strategy. If an effective defense cannot be mounted at all points, a mobile rapid-reaction force, which can bring overwhelming pressure against the initial gap, is the best alternative. Waiting is not a good strategy though the possibility of a feint alters the calculation somewhat. Given an intrusion of a potentially replicating opponent, any pause in the response is doubly counter-intuitive. In counter-insurgency, however, springing with overwhelming force on every potential insurgent results in widespread disaffection due to the false-positive rate with which insurgents are identified and the high degree of collateral damage.

Medically, some clinical guidelines approximate the insight of 'avoid hasty action.' Inappropriate antibiotic selection is already a recognized outcome from hasty action (Schweizer et al 2010, Shen et al 2012, Moehring et al 2013). Clinical management of dismounted complex blast injury (DCBI) has changed over the past several years. Military surgeons have already arrived at an interesting

approximation of 'Avoid Hasty Action;' during the process of serial debridements and irrigations, removing presumably unsalvageable tissue, they do not administer antibiotics until gross evidence of infection is available (Hospenthal et al 2011, Fleming et al 2012). This presumption of innocence avoids antibiotic prescription, sparing their intestinal flora, skin flora, nasal and dental flora, and so on. It also prevents the increased occurrence of invasive fungal infections (Radowsky et al 2011, Warkentien et al 2012) and antibiotic resistance later in patient care, something predicted by theory, measured in experiment, and observed in clinical practice. From a research perspective, the development of advanced diagnostics should certainly be a priority (Ehrlich and Post 2013).

Target the Strategy not the Forces

In FM 3-24, an emerging principle is the suppression of violence by all parties (A-31). There are four potential sources of violence (the established government, the insurgents, daily friction within the community, and the intervening forces) and the absence of violence from all these sources can be referred to as 'civil security.' The provision of security for all local nationals, whether by mood affiliated with the insurgents or not, is a counterintuitive goal for intervening counterinsurgency forces, which have a tendency to provide security for friends and allies alone. However, disparate security worsens underlying tensions in a society and prevents the inclusion of potential insurgents into the trusted network, where they will no longer be potential insurgents. Only in mutual security can trusted networks grow to include former insurgents and their supporters. Defusing tensions and preventing all kinds of violence is important for allowing the network to gain the trust of others. As a result, civil security operations are at the heart of counterinsurgency.

Bacteria, no less than humans, respond violently when faced with violence. Bacterial counterinsurgency recognizes the same four sources of violence impacting the microbiome – the human immune system, the active pathogenic bacteria, the remaining non-insurgent microbial community, and the physician. Minimizing the violence of the human immune system sounds counterintuitive, but it is actually an element of the current medical standard of care during diverse infections. Upper respiratory infections are treated with anti-inflammatory agents, i.e. antihistamines, steroids, NSAIDS, and opioids, and for the past twenty years, the role of anti-inflammatory agents in wound healing has been debated (Srinivasan et al 1981, Tarnawski et al 2003, Krischak et al 2007, Stein and Kuchler 2013). The use of anti-inflammatory agents for infection is somewhat controversial, because the agents themselves are diverse, have a spectrum of activities including antimicrobial activity, have personalized pharmacokinetics (Clayton et al 2009), and may be helpful at some stages of an infection but not others (Koh and DiPietro 2011). Typically, the intent of limiting inflammation is to prevent the human from damaging himself through high fevers, chronic inflammation, and shock, but controlling the symptoms of infection is also important because it limits the spiraling damage of violence within the microbial community. It was recently demonstrated that bacteria respond to fevers with virulence, for example (Loh et al 2013), and the cross-talk between other symptoms of inflammation and virulence have been long recognized (Schwab et al 2014, Knights et al 2013). In fact, some hypotheses about virulence suggest that inflammation is the goal of particular pathogens, which use the disturbance to their own

ends including indirect competition (Chow and Mazmanian 2010, Chow et al 2011) and nutrition (Rohmer et al 2011, Rogers et al 2013, Hajishengalliset al 2011).

Limiting the violence caused by active pathogens is termed 'anti-virulence' (Finlay and Falkow 1997, Goldschmidt et al 1997, Alksne 2002, Rasko and Sperandio 2010, Martinez et al 2011, Khodaverdian et al 2013). Virulence is not only action directed against the host, but also those insurgent activities inimical to good order and destructive to the trusted network. It can even be aimed at provoking an ill-timed, ill-directed or disproportionate immune or medical response. These activities must be controlled during counterinsurgency, but the reflex of controlling the virulence by killing the pathogen is not necessarily sparing – or effective. The main message in FM 3-24 is "Attack the enemy's strategy, not enemy forces." (A-49 and A-50) Again, "Only attack insurgents when they get in the way. Try not to be distracted into a series of reactive moves by a desire to kill or capture them." These dictates capture the tension inherent in counterinsurgency, that violence used to restrain violence is itself an offense against civil security.

The difficulty is in restraining virulence without violence. The most classic anti-virulence strategy is an antitoxin (Rous et al 1919, Lyons 1935). In this case, the specific products of the pathogen are removed from circulation without any direct attempt to kill the pathogen itself. This deprives the pathogen of any direct benefit from toxin production, limits the damage to the host, and reduces the overall level of violence in the system. This has the added benefit of reducing the fitness benefit of toxigenesis to the point that bacteria are selected for atoxigenic mutants. However, because of the ability of pathogens to produce large volumes of toxin, antitoxins can be difficult to administer in a timely fashion and at appropriate concentrations.

Some new anti-virulence strategies act directly on genetic mechanisms to reduce virulence. Preventing gene expression has the benefit of targeting a single gene instead of millions of the gene products (Lee et al 2001). However, preventing gene expression also has several weaknesses, including the requirement to hit a molecular target within the bacterial cell. Second, because toxin production is costly, rendering the toxin itself useless encourages growth of bacteria which have lost the toxin gene; interfering with toxin production permits the bacteria to continue carrying the toxin gene at relatively little cost. Clinical trials would be required to determine how specific bacterial populations respond to the introduction of such anti-virulence strategies over time.

Following from the 'war metaphor,' in which "the only good [hospital] microbiome, as far as I am concerned, is a dead one" (M. Pallen, referring to the hospital microbiome, November 20, 2013), in the medical literature anti-virulence has typically been viewed as disarming an opponent with the full intention of killing him later. This strategy would not encourage further compliance among human insurgents and should not be expected to be better received among bacteria. While bacteria do not anthropomorphically anticipate actions rationally, they readily adapt as a population to patterns of human behavior. If virulence is fundamentally required for the growth and dispersal of the organism, the assumption that resistance cannot evolve is unrealistic. Selection pressures will act to work around the anti-virulence strategy just as quickly as around any directly lethal mechanism (Maeda et al 2011,

Mellbye and Schuster 2011). To successfully pursue bacterial counterinsurgency, new anti-virulence strategies that preserve the ability of the organisms to reproduce and thrive as members of the healthy microbiome are required.

Finally, antimicrobial therapy does violence to the microbial community. Broad spectrum antibiotics target both the insurgents and the healthy microbiome for indiscriminate destruction. This is not in keeping with FM 3-24, which espouses restraint (even in the context of military casualties) and minimizes collateral damage (explored and debated in Newsinger 1992, Thronton 2004, Bennett 2007, Criddle 2011, Reis 2011). In dealing death effectively, only those community members whose contributions to violence exceed the disruption required to remove them should be targets (in some parlance, keystone pathogens; Darveau et al 2012, Hajishengallis et al 2012, Hajishengallis et al 2014). The number of viable targets, then, increases with the selectivity of the available antimicrobial strategies. This has been recognized in cancer treatment; those therapies are all judged to the degree that they are finely targeted against personalized genomes (Dias-Santagata et al 2010), tumor genomes (Wood et al 2007, Greenman et al 2007, Garnett et al 2012), and specific locations (i.e. with microsurgery, gamma knives, focused ultrasound).

By contrast, pharmaceutical companies are still investing heavily in relatively broad spectrum, systemic antibiotics (Ehrlich et al 2012). There are two factors that militate against specificity (narrow spectrum, topical or local). The first is market pressure (Hamad 2010) for each new antibiotic to address as many cases as conceivable. Naturally, a single antibiotic that could treat every infection would be attractive to the market. The second is the poor state of clinical diagnostics. It can be difficult to physically find a bacterial infection that could be localized to specific crypts in the tonsils or on one surface of a prosthetic joint (Ehrlich et al 2012). Some infections may have disseminated throughout the body. It is also often not possible to identify the organism causing the infection specifically or an infection may involve multiple organisms. Because the physician is typically working with limited information, the ability to select antibiotics is compromised, with the result that there is a limited market for highly specific antibiotics.

Unfortunately, without a market for specific antibiotics, a diagnostic that is highly informative provides no new ability to better select an antibiotic. This presents a closed loop that discourages both diagnostic and narrow-spectrum antibiotic development. Awareness of additional antibiotic side effects and growing antibiotic resistance may remove broad spectrum antibiotics as viable therapies and require alternatives. The development of a suite of diagnostics and antibiotics with a relatively low marginal development cost and collectively cover a broad range of bacterial infections would be serendipitous.

Honest communication

Many researchers are excited by the potential to interfere with bacterial communications; this mirrors military enthusiasm for information operations. However, currently, the most refined strategies apparently focus on encouraging bacteria to remove themselves from the protective cover of biofilms and persistence so that they are open to killing by antibiotics (Kalan and Wright 2011, Mansouri et al

2013, Hwang et al 2013, Schuch et al 2013). FM 3-24 (A-58) presents a counter-intuitive alternative: honesty.

The difficulty of providing credible false information to large numbers of people repeatedly over time has been noticed by the military. The challenge increases when the information is critical to the survival of the deceived people. The high stakes and the degree of difficulty have led to the guidance in FM 3-24: it is less risky to tell the truth to local leaders. Trust cannot be built in the context of persistent deception and the progressive growth of trusted networks is the stated method for counterinsurgency.

Similarly, we humans presently lack the finesse or expertise to consciously insert ourselves repeatedly into vast and complex bacterial communication networks to deceive robustly (Anand et al 2013, Zhu and Gunnar et al 2013). Just as human communities have dealt with insincerity for centuries, bacteria have also been a target for disinformation from plants (Pérez-Montaño et al 2013, Koh et al 2013), animals (Natrah et al 2011, Hartmann et al 2012) and each other (Dulla et al 2010, Wang et al 2011). As a result, the bacteria possess complex and robust communication systems (Bassler and Losick 2006, Camilli and Bassler 2006, Stacy et al 2012). Further, the bacteria have many tools at hand to modulate, educate, control, encourage, and punish each other with delicate proportionality and sophisticated distinction (Gomes et al 2013). The most complex bacterial communication mechanisms known at this time may include the transmission of informative polymers in vesicles (Ellis and Kuehn 2010, Mashburn and Whiteley 2005, Berleman et al 2013, Biller et al 2014). However, the use of nanopore arrays (Lehner et al 2013) and spatially-relevant contact dependent methods (Aoki et al 2010, Dubey and Ben-Yehuda 2011, Sanchez 2011, Schertzer and Whiteley 2011, Sherer 2013, Pathak et al 2012) seem strange because they violate our notion of bacteria as spatially undifferentiated due to diffusion processes. In addition, bacteria passively regulate many key behaviors behind a veil of phenotypic noise to prevent ready manipulation through any deterministic means (Silander et al 2012, Rainey et al 2011, Viney and Reece 2013, Sánchez-Romero 2014,). As their final defense against manipulation, if exploitation of a flaw in communication systems results in strong selection pressure on numerous bacteria, success itself will create an unambiguous selection for resistance (Jermy 2013, Kalia et al 2013, El-Halfawy et al 2013, Pena-Miller et al 2013, Yurtsev et al 2013) regardless of how clever the scientists believe themselves to be (Deforidt et al 2010, LaSarre et al 2013, Bhardwaj et al 2013).

Despite the daunting complexity of the bacterial communication systems, the communication modes that link them to the community and host are still the richest interfaces between bacterial behavior and community ecology, just as human communication provides an opportunity to adjust the behavior of those around us. On this ground, just as we have inverted Koch's postulates by first engaging with the normal microbial community and only secondarily attending to the insurgents, we may also invert our rude tendencies and instead appropriately signal to our microbiome that all is well, that the host isn't about to die, in order to reengage them in the healthful metabolism. Some relatively basic information operations, if not too discordant with the other signals the bacteria are receiving and in conjunction with other methods of intervention, may pacify the existing microbial community and restore homeostasis. When there is a healing compatible microbiome available, using information operations to reach it is an ideal intervention.

Win the Peace

The FM ends on a positive note, planning for the cessation of hostilities and the withdrawal of interventions (A-53). Nature abhors a vacuum, a power vacuum no less than any other. Traditional broad spectrum therapy may successfully remove the bacterial population from a habitat, but in traumatic wounds, a fear of invasive fungal infections (IFI) leads physicians to currently add, not subtract, from their broad-spectrum drug cocktail. Yet fungi are typically a small fraction of the skin microbiome (Park et al 2012, Cui et al 2013) and rarely invasive in the presence of diverse bacteria. In contrast to broad spectrum antibiotic therapy, following a successful bacterial counterinsurgency operation, fungi are unlikely to pose any difficulty. Ultimately, this is only one aspect of patient health that could be considered in constructing an ongoing bacterial trusted network during recovery from an insurgency. Other considerations include colonization resistance against invasive pathogens, overall metabolism, and immune modulation.

Spillover Effects

The implications of counterinsurgency operations transcend the local to regional (Zhukov 2012) and global geopolitical impacts (Salehyan 2009). Similarly, an unhealthy microbiome is a risk to other people, and the influence of a healthy microbiome may increase health in other people as well. Certainly, the observed impact of antibiotic overuse is spillover across a medical facility (Peacock et al 1980, Cosgrove 2006), a community (McGowan 1983, Archibald et al 1997), a nation (Goossens et al 2005), and the globe (O'Brien 1997). The importance of conducting careful infectious disease practices transcends patient care and impacts the entire human population.

Conclusions

Altering the underlying metaphor for the practice of infectious disease has numerous strategic implications. A relatively direct reading of FM 3-24 and FM 3-24-2 raises and subsequently addresses several rarely considered concerns that are largely counter-intuitive. Because counterinsurgency has attracted substantial and sustained strategic consideration, an opportunity exists to import insight from outside the medical community. Some of the challenges are: deepening the theoretical basis of counterinsurgency with structural and quantitative underpinnings that can be shared between the sociological and microbiological applications, exploring the discontinuities that arise in analogizing between humans and microbes, circumscribing the analogy by determining the extent that it holds true in various infectious diseases, and recreating a conceptual framework for infectious disease that can be taught convincingly to practitioners and discussed with the public.

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