INFECTION AND IMMUNITY, June 2010, p. 2356–2369 Vol. 78, No. 6
0019-9567/10/$12.00 doi:10.1128/IAI.00096-10

MINIREVIEW

Taming the Elephant: *Salmonella* Biology, Pathogenesis, and Prevention▽

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***Salmonella* infections continue to cause substantial morbidity and mortality throughout the world. However, recent discoveries and new paradigms promise to lead to novel strategies to diagnose, treat, and prevent *Salmonella* infections. This review provides an update of the *Salmonella* field based on oral presentations given at the recent 3rd ASM Conference on *Salmonella:* Biology, Pathogenesis and Prevention.**

It was six men of Indostan
To learning much inclined,
Who went to see the Elephant
(Though all of them were blind),
That each by observation
Might satisfy his mind

— J. G. Saxe (134)

The 3rd ASM Conference on *Salmonella:* Biology, Pathogenesis and Prevention took place from 5 to 9 October 2009 in Aix-en-Provence, France. For more than 325 scientists from 43 countries, the meeting provided an opportunity to learn about recent discoveries regarding the epidemiology, biology, and pathogenesis of *Salmonella* and to identify promising new approaches for the diagnosis, treatment, and prevention of *Salmonella* infections. Jeremy Farrar, from the Oxford Clinical Research Unit in Vietnam, compared the meeting to the proverbial six blind men encountering an elephant. This proved to be an apt characterization of a multifaceted meeting in which *Salmonella* was considered from diverse perspectives. The following are selected highlights from oral presentations given at the meeting, as perceived by four *Infection and Immunity* editors who were in attendance.

The First approached the Elephant,
And happening to fall
Against his broad and sturdy side,
At once began to bawl:
"God bless me! but the Elephant
is very like a wall!"

SALMONELLA EPIDEMIOLOGY

According to contemporary classification, the genus *Salmonella* contains only two species, *Salmonella bongori* and *Salmonella enterica*, but there are more than 2,500 serovars of *S. enterica*. Although no longer prevalent in the developed world, *Salmonella enterica* serovars Typhi and Paratyphi continue to cause enteric fever in many parts of the developing world, especially in Asia and northern regions of Africa (60, 138). These agents are still estimated to cause approximately 22 million cases of disease and 200,000 deaths each year, primarily in regions where sanitation is poor and clean water is inaccessible (37). In south Asia, approximately one of every four cases of enteric fever is caused by *Salmonella enterica* serovar Paratyphi (117), with the remainder caused by *S.* Typhi.

The epidemiology of *Salmonella* infections is changing. Jeremy Farrar reported a dramatic decline in the overall incidence of typhoid fever in Vietnam in recent years, suggesting that eradication of this disease might be within reach. This reduction is not the result of a specific typhoid fever control program but rather a consequence of economic development and improved sanitation, paralleling the decline in typhoid fever in the United States during the early 20th century. An important remaining challenge for the eradication of typhoid fever is the development and implementation of a rapid, accurate, and affordable diagnostic assay that can be used in areas of typhoid fever endemicity (84). Another problem is the rapidly emerging antibiotic resistance among *Salmonella* serovars responsible for typhoid fever, since initial reports in the 1970s (7). A recent survey of eight Asian countries revealed nalidixic acid resistance in 5 to 51% of *S.* Typhi isolates (29), and many nalidixic acid-resistant strains are resistant to multiple antibiotics. Isolates resistant to nalidixic acid are less responsive to fluoroquinolone antibiotics (158). Nalidixic acid-susceptible *Salmonella* isolates with reduced susceptibility to fluoroquinolones are also increasingly being recognized (38), and the presence of these isolates may require changes in current clinical microbiology practices used to detect nonsusceptible strains. The latter resistance pattern is caused by plasmid-borne *qnr* resistance determinants, which raise MICs for fluoroquinolones but not nalidixic acid (68). An unexpected recent finding is that mutations conferring antibiotic resistance

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▽ Published ahead of print on 12 April 2010.

do not necessarily appear to reduce *Salmonella* fitness in the absence of antibiotic selection (124).

A joint effort between the Wellcome Trust Sanger Institute, the Oxford University Clinical Research Unit, and Patan Hospital in Kathmandu, Nepal, is applying new genetic typing methods to *Salmonella* isolates from enteric fever patients, in combination with geospatial mapping (84). By use of this technology, hot spots for *S.* Typhi and *S.* Paratyphi infection have been identified, areas of high transmission have been localized, and factors such as elevation, water sources, and sewage disposal can be taken into account in determining transmission patterns. The linkage of genomic typing and mapping has the potential to change thinking about transmission patterns, improve epidemiologic tracking, and help abrogate transmission at the household level.

In sub-Saharan Africa, cases of nontyphoidal salmonellosis (NTS), frequently complicated by bacteremia, are now more numerous than cases of enteric fever (60). Although invasive NTS bacteremia was first documented over 20 years ago (43), the magnitude of this emerging problem has only belatedly been appreciated (107). The incidence of NTS has risen in association with predisposing infections with HIV and *Plasmodium falciparum* (24). NTS isolates are now among the most common blood culture isolates in many parts of Africa, comprising as much as 50% of cases of bacteremia (23, 60, 61). The distribution of pediatric NTS bacteremia in African children corresponds almost precisely to the prevalence of malaria (60), although the reasons for this correlation are poorly understood.

Genomic epidemiology using powerful sequence-based methods has permitted the characterization of emerging invasive NTS isolates. Melita Gordon, of the University of Liverpool, has documented that in Malawi NTS isolates are the leading cause of bacteremia in children and that 75% of these isolates are *Salmonella enterica* serovar Typhimurium (60). During relapses, bacteria are more numerous in bone marrow, suggesting a persistent intracellular reservoir of infection (62). Robert Kingsley and colleagues at the Sanger Institute have used subgenomic assays and whole-genome sequencing to characterize a specific invasive multidrug-resistant NTS clone designated ST313 (88), which is now dominant in Malawi and Kenya. ST313 clusters most closely with the host-specific *S.* Typhimurium strain ST128, which causes serious systemic disease in pigeons (8). This observation suggests that ST313 may be in the very early stages of host adaptation (88). The presence of numerous pseudogenes indicates that ST313 is in a state of genome degradation, typically observed in a pathogen or endosymbiont that has become adapted to a single host. This characteristic has been used to distinguish the genomes of generalist and specialized *Salmonella* serovars (78, 99, 100, 146, 147). It is particularly intriguing that some of the genes lost by ST313 have been implicated in *S.* Typhimurium virulence or are also missing or nonfunctional in *S.* Typhi, suggesting that ST313 may be in the process of evolving from an intestinal pathogen spread by food and water to an invasive enteric fever pathogen spread from person to person. A comparison of host-adapted and non-host-adapted strains belonging to a single serovar provides a unique window into very early events in the evolution of host adaptation.

Genome degradation, prophage repertoire, and differential transcriptional regulation are each proposed to influence the host range of individual isolates belonging to *Salmonella* serovar Typhimurium (88). Previous microarray-based studies of pigeon-adapted *S.* Typhimurium have suggested that gene loss is unlikely to be involved in the host adaptation of these strains (8). However, more recent work has demonstrated that the pigeon-adapted *S.* Typhimurium strain ST128 has 17 pseudogenes, while ST313, the invasive human NTS strain, has 77 pseudogenes (88), indicating that genome degradation is in fact occurring as these isolates undergo progressive adaptation to a particular host. The transcriptional responses to temperature exhibited by host-adapted *S.* Typhimurium strains may also be evolving as they adapt to hosts with different body temperatures. These studies will lead to an improved understanding of the specific mechanisms that determine pathogen host range.

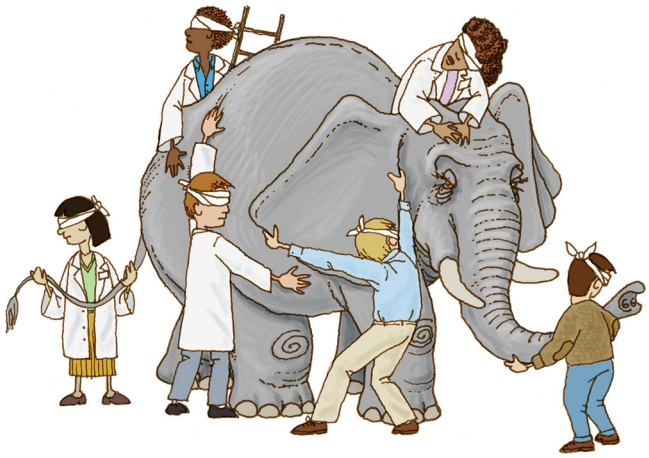

Illustration courtesy of Patrick Lane, ScEYEnce Studios.

The Second, feeling of the tusk,
Cried, "Ho! what have we here
So very round and smooth and sharp?
To me 'tis mighty clear
This wonder of an Elephant
Is very like a spear!"

MODULATION AND EXPLOITATION OF THE HOST BY *SALMONELLA*

The host-*Salmonella* interaction is dominated by the broad array of sophisticated weaponry used by *Salmonella* to overcome host defenses. Much of the current research on *Salmonella* pathogenesis focuses on understanding two important disease manifestations in immunocompetent individuals: gastroenteritis, caused by nontyphoidal *Salmonella* serovars, and enteric fever, caused by typhoidal *Salmonella* serovars.

Nontyphoidal *Salmonella* serovars, exemplified by classical *S. enterica* serovar Typhimurium strains, cause gastroenteritis by employing two type III secretion systems (T3SS) (13, 34, 149). The invasion-associated T3SS encoded by *Salmonella* pathogenicity island 1 (SPI-1) enables *S.* Typhimurium to enter the intestinal epithelium (reviewed in reference 174), while the T3SS encoded by SPI-2 is subsequently used to promote survival within macrophages (reviewed in reference 1). The SPI-1 and SPI-2 T3SS are structurally related to the archetypal

flagellar T3SS, which has provided a model for understanding the intricate process involved in the self-assembly of such complex nanomachines. Kelly Hughes, from the University of Utah, provided an update on the details of flagellar assembly, including the discovery that proton motive force, rather than ATP hydrolysis, is required for type III secretion (81, 122).

Invasion of epithelial cells *in vivo* is observed within 10 to 15 min after introduction of *S.* Typhimurium into the intestinal lumen, but by 4 h after infection the majority of bacteria are located in the lamina propria, with bacteria no longer observed within epithelial cells by electron microscopy (132). A possible mechanism for clearance of the organism from the gut epithelium has been suggested by Leigh Knodler, of the NIAID Rocky Mountain Laboratories. Upon *Salmonella* invasion of a model polarized Caco-2 C2Bb21 epithelium, expression of SPI-1 and flagellar genes is initially downregulated, but SPI-1 expression is detectable at later time points in a subset of bacteria rapidly replicating in the cytosol (89). Epithelial cells containing these flagellated bacteria are extruded from the apical surface of the monolayer in a process reminiscent of the exfoliating processes of effete enterocytes at the tips of small intestinal villi. The extrusion of infected epithelial cells may represent a novel host defense mechanism to clear invasive microbes, although this process may also reseed the intestinal lumen with organisms.

Direct interactions of *S.* Typhimurium with host cells initiate the production of proinflammatory cytokines in tissue, which drive a rapid recruitment of neutrophils, the pathological hallmark of gastroenteritis caused by nontyphoidal *Salmonella* serovars. Genetic methods have been employed to identify *S.* Typhimurium virulence factors contributing to inflammation in animal models. These include flagella and the SPI-1 T3SS, which are important during the early phase of infection (71, 137, 143, 149, 152, 164, 173), and the SPI-2 T3SS, whose contribution becomes apparent at later time points (34, 149). Inflammatory responses mediated by the SPI-2 T3SS require the presence of myeloid differentiation primary response protein 88 (MyD88) (72), a host adaptor protein required for signaling through the interleukin-1β (IL-1β) receptor (112, 167), the IL-18 receptor (3), and most Toll-like receptors (TLRs) other than TLR3 (86, 103). However, little progress in identifying host factors important for initiating SPI-1-dependent inflammatory responses *in vivo* has been made. Work by Wolf-Dietrich Hardt and colleagues in Zurich, Switzerland, suggests that the presence of multiple pathways initiating SPI-1-dependent intestinal inflammation has masked the contribution of individual factors. *S.* Typhimurium secretes several SPI-1 effector proteins involved in inducing intestinal inflammation in the streptomycin-pretreated mouse model, including SipA, SopB, SopE, and SopE2 (71). An *S.* Typhimurium mutant expressing only SopE induces intestinal inflammation by a mechanism dependent on caspase-1, an enzyme required for cleaving the proforms of IL-1β and IL-18 into their active forms. Consistent with a contribution of caspase-1 to host responses, SopE-mediated inflammation was abrogated in mice deficient for IL-18 or the IL-1β receptor. However, when streptomycin-pretreated mice were infected with an *S.* Typhimurium mutant expressing both SopE and SipA, an effector protein that induces inflammation through a different pathway, the contribution of caspase-1 to intestinal inflammation was no longer evident histopathologically (110). The use of bacterial genetics to restrict the *in vivo* inflammatory process to single SPI-1 effector proteins is a promising strategy to elucidate the contribution of redundant pathways producing intestinal inflammation. Presentations by Beth McCormick, from the University of Massachusetts, and Brett Finlay, from the University of British Columbia, underscored the involvement of common mechanisms in *Salmonella* enteritis and inflammatory bowel diseases (IBDs) (52, 101). Such work promises to have important therapeutic implications and is discussed in greater detail below.

After crossing the epithelial barrier, *S.* Typhimurium is located predominantly within mononuclear cells (macrophages and dendritic cells) and neutrophils in the underlying tissue (132). The SPI-2 T3SS plays an essential role in preventing rapid clearance from the livers and spleens of mice (74) and from the intestinal tissues of calves (149) by promoting survival within mononuclear phagocytes (118). In his keynote address, David Holden, from the Imperial College London, presented evidence to indicate contact dependence of SPI-2 T3SS function during the interaction of *Salmonella* with macrophages. It was known from previous work that secretion of SseB, which is part of the SPI-2 T3SS translocation complex in the host cell membrane, is induced by acidic pH, while other effector proteins are not efficiently secreted under these conditions (20). A series of experiments was presented to support the hypothesis that the neutral pH of the host cell cytosol is sensed through the needle complex following the acid pH-dependent formation of the translocation complex (76). This is proposed to relieve the inhibition of secretion mediated by a complex composed of SsaL, SsaM, and SpiC at the base of the SPI-2 T3SS secretion apparatus, thus allowing the translocation of effector proteins into the host cell cytosol. These observations suggest that a mechanism for sensing the pH difference between the phagosome and the cytosol through the T3SS secretion channel renders the secretion of effector proteins dependent on bacterial contact with the vacuolar membrane.

The SPI-2 effectors promote *Salmonella* replication within the *Salmonella*-containing vacuole (SCV), stabilize the vacuolar membrane, influence endocytic trafficking, and induce delayed host cell death, among other proposed functions (163). *Salmonella* interactions with mammalian cells have been shown to involve the pathogen-directed manipulation of host Rho GTPases (136), but Matthias Christen, representing the laboratory of Samuel Miller at the University of Washington, presented an example in which RhoA actually activates a bacterial virulence effector. The SPI-2 effector SseJ binds to the GTP-bound form of RhoA, stimulating its lipase activity to facilitate *Salmonella* esterification of cholesterol in the SCV membrane, an event believed to play an important role in SCV membrane dynamics (33). This observation represents the first known instance in which a bacterial virulence factor senses rather than alters the signaling state of a Rho GTPase.

S. Typhi and *S.* Typhimurium share many of the virulence factors important for gastroenteritis, including flagella and the SPI-1 and SPI-2 T3SS. Nevertheless, the clinical presentation of typhoid fever differs in several important aspects from that of gastroenteritis. First, typhoid fever has an average incubation period of 2 weeks, compared to an incubation period for gastroenteritis of only 12 to 72 h (119). This suggests that *S.*

Typhi is able to suppress and/or avoid detection by the host immune system early in the course of infection. Second, *S.* Typhi causes a systemic infection associated with the gradual development of mononuclear inflammatory infiltrates in the intestine (91, 109, 116, 142), while localized *S.* Typhimurium infection in immunocompetent individuals is accompanied by a rapid recruitment of neutrophils into the intestinal mucosa (41, 102). Again, this clinical observation illustrates that *S.* Typhi and *S.* Typhimurium differ in the ways each pathogen is viewed by the host immune system. The different disease manifestations caused by *S.* Typhi and *S.* Typhimurium in humans must be due to their genetic differences, and understanding these differences has become a focus of typhoid fever research in the postgenomic era.

One such difference is the *viaB* locus, which is present in *S.* Typhi but absent from *S.* Typhimurium. The *viaB* locus encodes genes for the biosynthesis (*tviBCDE*), export (*vexABCDE*), and regulation (*tviA*) of the *S.* Typhi Vi capsular polysaccharide (153). Andreas Bäumler, from the University of California at Davis, showed that acquisition of the TviA regulatory protein by *S.* Typhi alters expression of flagella and the SPI-1 T3SS in response to changes in osmolarity during the transition from the intestinal lumen to deeper tissues (170). Introduction of the *viaB* locus into *S.* Typhimurium reduces the inflammatory response elicited by this pathogen in streptomycin-pretreated mice; this effect is observed during the stage of infection in which inflammation is dependent on MyD88, but it appears to be independent of the SPI-1 T3SS (70). Two effects of Vi capsule that might blunt inflammatory responses are the inhibition of TLR4 recognition (168) and the repression of flagellum expression, which reduces TLR5-mediated responses in tissue culture models (169). Inactivation of flagellin genes in *S.* Typhimurium (*fliC fljB* mutant) or repression of flagellin expression by introduction of the *tviA* gene into the *S.* Typhimurium chromosome increases bacterial dissemination to the spleen in a chicken model (14). These data suggest that *viaB* provides *S.* Typhi with both a novel virulence determinant (Vi) and a novel regulatory gene (*tviA*) that alters the expression of virulence determinants highly conserved within the genus *Salmonella*, such as flagella and SPI-1.

A cluster of toxin-like genes, termed *pltA*, *cdtB*, and *pltC*, represents another genetic region that distinguishes *S.* Typhi from *S.* Typhimurium. Jorge Galán, from Yale University, demonstrated that this gene cluster encodes an A/B toxin, designated typhoid toxin, which exhibits the enzymatic activity of a cytolethal distending toxin (69, 141). The typhoid toxin is delivered from intracellular bacteria through both autocrine and paracrine pathways to neighboring host cells (54, 141). The toxin causes DNA damage, an action predicted to preferentially kill host cells undergoing rapid cell division, such as expanding B- and-T cell populations. The lack of animal models for the human pathogen *S.* Typhi represents a major obstacle for testing this hypothesis and for studying typhoid fever pathogenesis in general.

Significant progress in developing a mouse model for *S.* Typhi infection was presented by Stephen Libby and coworkers from the University of Washington, the University of Massachusetts, and the Jackson Labs. NOD-*scid*-IL2Rγ(null) mice were engrafted with human umbilical cord blood stem cells (hu-SRC-SCID mice) to develop a humanized mouse model for typhoid fever (92). Initial characterization of the model showed that in contrast to conventional or parental unengrafted NOD-*scid*-IL2Rγ(null) mice, hu-SRC-SCID mice became highly susceptible to *S.* Typhi infection and developed granulomas containing multinucleated giant cells in the spleen. The ability of *S.* Typhi to cause progressive lethal infection in hu-SRC-SCID animals indicates that human immune cells are required for *S.* Typhi replication *in vivo*. Further development of this model promises to accelerate future research on typhoid fever pathogenesis.

The ability to cause systemic infection may confer a selective advantage to *S.* Typhi by increasing the probability of colonization of the gallbladder, from which the organism can be reintroduced intermittently into the intestine. Chronic carriage is essential for pathogen persistence in small host populations and was probably a key factor in the evolution of human-adapted *S.* Typhi, particularly prior to the advent of agriculture, which supported higher population densities. Chronic *S.* Typhi gallbladder carriage is also of interest because it is an important risk factor for developing gallbladder cancer (166). John Gunn, from the Ohio State University, has performed studies of mechanisms involved in chronic gallbladder carriage of *Salmonella* (36). Since gallstones, which are composed mainly of cholesterol, are a major risk factor for developing chronic *S.* Typhi carriage, biofilm formation on this surface in the presence of bile was studied. Biofilm formation on cholesterol by *S.* Typhi and *S.* Typhimurium requires the production of an O-antigen capsule, which is distinct from the Vi capsular antigen (35). Mice fed a high-cholesterol diet develop gallstones and exhibit increased gallbladder colonization after *S.* Typhimurium infection in comparison to controls. Biofilms can be visualized on gallstones resected from chronic *S.* Typhi carriers. Collectively, these data suggest that biofilm formation on gallstones is a mechanism contributing to the pathogenesis of chronic gallbladder carriage in typhoid fever.

The Third approached the animal,
And happening to take
The squirming trunk within his hands,
Thus, boldly up and spake:
"I see," quoth he, "the Elephant
Is very like a snake!"

HOST DEFENSES AGAINST *SALMONELLA* INFECTION

The last decade has seen a rapid growth in our understanding of innate immunity, which has provided many opportunities for looking at initial host-pathogen interactions from a new perspective. Host responses elicited by *S.* Typhimurium are stereotypic, and an analysis of their induction and outcome has provided valuable general insights into bacterium-host interactions.

The interaction of *S.* Typhimurium with the host immune system is initiated by direct bacterium-host cell contact, such as occurs in SPI-1 T3SS-mediated invasion of epithelial cells. Alternatively, this interaction can be initiated by a mechanism in which CD18-positive dendritic cells reach through the epithelium to sample luminal contents, a pathway that is independent of SPI-1 (151). Isabelle Hautefort, from the Institute for Food Research, United Kingdom, presented data on dendritic cell migration in response to inoculation of ligated murine ileal loops with a SPI-1-deficient (*invA*) *S.* Typhimurium mutant

strain (9, 73). Marked migration of dendritic cells into intestinal villi and transmigration into the intestinal lumen were observed after infection with an *S.* Typhimurium *invA* mutant but not following inoculation with *Escherichia coli*. The dendritic cell migration was dependent on MyD88 and was not observed after inoculation with *Salmonella* strains that were nonmotile (*fliC fljB* mutant) or unable to translocate flagellin across polarized epithelial monolayers due to a mutation inactivating SPI-2. Collectively, this *in vivo* analysis was consistent with the hypothesis that flagellin sensed by TLR5 on the basolateral surface of the sentinel intestinal epithelial layer triggers dendritic cell migration in response to *S.* Typhimurium infection. For initiation of responses against microbes, macrophages and dendritic cells express multiple pathogen recognition receptors, including the cytosolic nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs) and TLRs located on the cell surface or within a vacuolar compartment. A subset of NLRs can activate caspase-1 and trigger pyroptosis, a form of programmed cell death that is accompanied by proteolytic activation of IL-1β and IL-18 (reviewed in reference 51). Brad Cookson, from the University of Washington, presented evidence that *S.* Typhimurium-induced pyroptosis activates immune responses through two major pathways. The first is well characterized and proceeds through the proteolytic activation of IL-1β and IL-18 by caspase-1. Experiments presented at the meeting provided evidence for the existence of a second pathway involving calcium fluxes that induce lysosomal exocytosis (19). Lysosomal exocytosis was shown to result in the release of pathogen-associated molecular patterns along with lysosomal contents, which might further enhance cytokine induction and contribute antimicrobial effector molecules.

The sequential evolution of the immune response to *Salmonella* over time was reviewed by Pietro Mastroeni, from the University of Cambridge, United Kingdom (98). Evidence for bacterial growth and NADPH phagocyte oxidase (Nox2)-mediated bacterial killing was observed within the first 6 h of infection (64). At later time points, host factors, including natural resistance-associated macrophage protein 1 (Nramp1, Slc11a1), gamma interferon (IFN-γ), tumor necrosis factor alpha (TNF-α), and inducible nitric oxide synthase (iNOS), exhibited predominantly bacteriostatic effects on *S.* Typhimurium. New insights into the role of B cells during infection have also been obtained. During transit between host cells, *S.* Typhimurium is susceptible to antibodies. B cells further contribute to immunity by producing IL-6 and IFN-γ, promoting the development of antigen-specific Th17 cells and Th1 cells, respectively. During the early phase of infection, cytokine production by B cells is driven by innate MyD88-dependent responses, while cytokine production subsequently becomes antigen dependent (12).

Two vaccines for the prevention of typhoid fever, Typhim Vi and the live oral Ty21a strain, are currently available (reviewed in reference 129). Calman MacLennan, from the University of Birmingham, United Kingdom, provided an update on the development of a new conjugate Vi vaccine that has shown in clinical trials an efficacy superior to that of the currently licensed vaccine. Clinical studies point to an important role for antibodies, complement, and phagocytes in protection against *Salmonella* infections (59), while T cells have a critical role in bacterial clearance. These insights will help to guide future vaccine development.

The Fourth reached out an eager hand,
And felt about the knee.
"What most this wondrous beast is like
Is mighty plain," quoth he;
"Tis clear enough the Elephant
Is very like a tree!"

CHALLENGE OF FOOD-BORNE NONTYPHOIDAL SALMONELLOSIS

Since national surveillance of NTS in the United States was established by the Centers for Disease Control (CDC) in 1963, the incidence of these infections has made a steady ascent, reaching a plateau at 14 to 15 cases per population of 100,000 during the last 20 years despite strong efforts to reduce these numbers (157). At the beginning of the last decade, the CDC set a national goal to reduce NTS cases by 50%, to 6.8 culture-confirmed cases per population of 100,000 by 2010 (157). Of the common food-borne pathogens, *Salmonella* is presently the furthest from its national health target. *Salmonella* serovars Typhimurium and Enteritidis are most prevalent in the United States, with each currently responsible for 16 to 17% of cases. However, several other serovars, including Newport, Javiana, and the *Salmonella* I 4,[5],12:1:− variant, are in ascendance (145, 157). In recent years, multistate outbreaks of NTS from conventional sources, such as raw meats, and unconventional food sources not previously known to transmit *Salmonella* have required increased active epidemiologic surveillance and created new challenges in tracing and controlling these outbreaks.

Robert Tauxe, of the Centers for Disease Control, discussed recent food-borne outbreaks of NTS in the United States, with the recognition of new food vectors, including peanut butter, a vegetarian snack food, dry dog food, dry puffed breakfast cereal, microwaveable pot pies, and hot peppers (145). *Salmonella* contamination of a peanut paste used as a basic ingredient in many processed foods led to the recall of 3,900 products. Factors contributing to the increasing frequency of NTS include gaps in systems to ensure food safety, a limited understanding of the ecological determinants of *Salmonella* contamination of foods in the field, and improved methods for active surveillance. In the United States, active surveillance for *Salmonella* and other food-borne pathogens is conducted by the Food-borne Active Disease Surveillance Network (FoodNet), established in 1995 as a component of the CDC's Emerging Infections Program (EIP). FoodNet is a collaborative effort of multiple federal agencies, including the CDC, the USDA, the FDA, and 10 cooperating EIP sites (http://www.cdc.gov/FoodNet/surveillance_pages/whatisfoodnet.htm), that now covers 15.1% of the U.S. population.

The investigation of large food-borne NTS outbreaks and international typhoid fever outbreaks in recent years has required improved epidemiologic, tracking, and typing methods to identify the sources. Although serotyping remains commonly in use for typing and tracking of isolates, more precise molecular methods are being employed to determine whether isolates from multiple, even widely dispersed, cases of salmonellosis are related. In the United States, pulsed-field gel electrophoresis (PFGE) data on NTS isolates is collected and made accessible via PulseNet, a nationwide system used to

subtype bacteria that cause food-borne disease, with participation from a network of state and local health departments and federal agencies. PulseNet has become an essential tool for linking cases caused by single bacterial strains and following the spread of large outbreaks (145).

Additional typing methods include multilocus sequence typing (MLST) and MLST-like approaches (see the *S. enterica* MLST database at http://mlst.ucc.ie/mlst/dbs/Senterica) (87) and newer approaches that use single nucleotide polymorphisms (SNPs) to determine the haplotypes of disease isolates. MLST has been used by Gabriel Perron, Sylvain Quessy, and colleagues at McGill University and the Université de Montréal to analyze reservoirs of antibiotic-resistant bacteria in asymptomatic Canadian livestock (123). MLST-like approaches include multi-virulence-locus sequence typing (MVLST) (31, 32), a method that combines traditional MLST with typing of conserved virulence loci and has recently been used to assess the stability of structural genes encoded on SPI-1 (25).

Strains belonging to some *Salmonella* serovars, such as *S.* Typhi, are too closely related to differentiate using traditional typing methods (77, 130). For such strains, complete genome sequencing can reveal SNPs throughout the genome (77). In the case of *S.* Typhi, complete genome sequencing using both Roche 454 and Illumina Solexa sequencing technology allowed Kathryn Holt and colleagues at the Wellcome Trust Sanger Institute (Cambridge, United Kingdom) to identify 2,000 SNPs (77). Genome-wide SNP typing is now being used by these investigators to determine the haplotypes of 260 *S.* Typhi isolates collected in Vietnam over a 2-year period (79). Although 98% of these isolates consisted of a single haplotype, 40 SNPs allowed differentiation of isolates within this group. Combining genome-wide SNP typing and geospatial mapping technology allows the discrimination of isolates down to the household level, providing clues about transmission into and within a given household (79). While SNP typing is not yet used to analyze NTS outbreaks, it will potentially be very useful for this purpose as well.

Following, tracing, and controlling *Salmonella* outbreaks that result from NTS contamination of traditional and nontraditional foods are major challenges for food safety. Although 61% of U.S. *Salmonella* infections in 2008 were caused by contamination of foods that are not traditional vectors for this organism (145), knowledge of how *Salmonella* contaminates, survives, and grows on foods, including vegetables and plants, remains rudimentary. Jeri Barak and colleagues at the University of Wisconsin have begun to determine the mechanisms used by *Salmonella* to colonize plants (11). A *Salmonella enterica* serovar Newport Tn*10* mutant library was screened for defects in attachment to alfalfa sprouts. Many unique mutants were obtained, and 65% of the transposon insertions associated with reduced attachment were in genes of unknown function ("FUN genes"). Transposon insertions in genes encoding curli fimbriae, cellulose metabolism, and O-antigen synthesis were also isolated. Mutations affecting curli and cellulose were complemented with restoration of a wild-type phenotype. Mutations in two FUN genes, STM0278 and STM0650, were found to confer defects in swarming motility that are reversed in the presence of polysaccharide-rich root exudates. Further study of *Salmonella* colonization of plants, fruits, and vegetables may lead to new strategies to prevent contamination of important food sources.

Contaminated meat and poultry products, the traditional sources of NTS in humans, continue to be problematic, but knowledge of the factors required for NTS colonization of livestock is rapidly expanding. Recent efforts have identified *Salmonella* genes required for colonization of various livestock hosts, including cattle, chickens, and swine (28, 80, 90, 105). Using signature-tagged mutagenesis and other techniques, these studies have generated extensive lists of candidate genes implicated in the colonization of multiple or single hosts. Eirwen Morgan and colleagues in the United Kingdom have applied a new technique called transposon-mediated differential hybridization (TMDH) (30) to interrogate pools of transposon mutants to identify *S.* Typhimurium genes required during infection in different livestock models (106). In TMDH, transposon locations are easily mapped using a custom tiling array. This and similar new technologies should allow the comprehensive identification of *Salmonella* genes necessary for colonization of livestock hosts, which in turn may lead to improved preharvest interventions to prevent *Salmonella* transmission.

The Fifth, who chanced to touch the ear,
Said: "E'en the blindest man
Can tell what this resembles most,
Deny the fact who can
This marvel of an Elephant
Is very like a fan!"

NEW GENE REGULATORY PARADIGMS IN *SALMONELLA*

In the course of infection, *Salmonella* must adapt to diverse environments. These range from an external environment, such as a contaminated food or water source, to the acidic stomach lumen of the host, the intestinal tract (including the microenvironment of the surface epithelium), and the dynamic intracellular confines of the macrophage vacuole, as well as various extraintestinal tissues (e.g., liver and spleen). The regulation of *Salmonella* gene expression in response to environmental and stress conditions plays a critical role in the ability to cause disease. Numerous virulence genes, many of which are situated together in groups called pathogenicity islands, are required for one or more steps in the infection process.

The *Salmonella* pathogenicity islands were acquired by horizontal gene transfer. However, the mechanisms by which newly acquired genes become integrated into the regulatory networks of a recipient cell without compromising competitive fitness are poorly understood. Importing even a structurally simple plasmid can impose a fitness cost on a bacterium (reviewed in reference 46). An emerging paradigm proposes that the global nucleoid-associated regulatory protein called H-NS facilitates the acquisition of horizontally transferred DNA by binding to AT-rich sequences and silencing their expression (44, 45, 96, 114, 115). H-NS is a small, abundant protein that forms dimers with the ability to create DNA-protein-DNA bridges (39). In addition, H-NS is capable of cooperative binding interactions with high-affinity sites (22). H-NS-containing nucleoprotein structures impede the movement of RNA polymerase, thereby repressing gene transcription. It is uncertain whether DNA bridging is sufficient to account for transcriptional silencing or whether higher-order nucleoprotein complexes are required (48).

The DNA binding preference of H-NS correlates with sequences that exhibit intrinsic curvature (40, 126, 148). Recent

studies have determined that H-NS binding occurs at AT-rich regions throughout the *S*. Typhimurium genome, including major virulence genes located on the virulence plasmid or within *Salmonella* pathogenicity islands (96, 115). AT-rich regions can form nucleation sites from which the H-NS protein can spread laterally along DNA, forming nucleoprotein filaments in addition to DNA bridges. Curvature can also facilitate bridge formation and is responsive to environmental parameters, such as temperature and osmolarity (126). Transcriptional silencing of foreign DNA by H-NS, referred to as "xenogeneic silencing" (114), helps to explain why horizontally transferred DNA is AT rich relative to the resident genome, i.e., because recognition by H-NS facilitates the integration of this DNA into existing regulatory networks. A variety of mechanisms can counter transcriptional silencing by H-NS to allow gene expression under selected conditions (114, 144).

A protein related to H-NS, called Sfh, is encoded by R27 and related self-transmissible plasmids carried by some *Salmonella* strains (47). Sfh can fully substitute for H-NS (and vice versa) in *Escherichia coli* and *Shigella flexneri* and has a similar preference for binding curved AT-rich DNA sequences (16, 42). Charles Dorman, from Trinity College Dublin, described *sfh* as a "stealth gene" that enables the AT-rich pSf-R27 plasmid to enter new bacterial hosts with a minimal impact on global gene expression patterns and fitness, which maintains the competitive fitness of the new plasmid-host combination (47). This has the effect of stabilizing the horizontal transmission of genetic information within and between bacterial populations, as corroborated by the presence of *hns*-like genes on other plasmids (17, 47, 53) as well as other horizontally acquired AT-rich DNA elements, such as bacteriophages and pathogenicity islands, that are known to bind H-NS (17, 27, 94).

Although *Salmonella enterica* and *Escherichia coli* are often regarded as close relatives, Patrick Higgins, from the University of Alabama, has obtained surprising evidence of major differences in the superhelicities and hence the chromosomal dynamics of these two species (75). The higher average supercoiling density of mid-log-phase *E. coli* than of *Salmonella* can account for the toxicity of the *Salmonella* GyrB protein for *E. coli*, as well as a variety of other important biological characteristics, including a greater receptivity of *Salmonella* to foreign DNA.

Two-component regulatory systems also coordinate gene expression in response to specific environmental signals and represent the major paradigm for signal transduction in bacteria. Two-component systems conventionally contain a sensor kinase (often a membrane protein that functions in *trans*-membrane signaling) and a response regulator (typically a DNA-binding protein that initiates transcription). For example, in *S. enterica* the SsrA/SsrB two-component system regulates the expression of SPI-2 genes. Specifically, the SsrB protein binds to the promoters of all SPI-2 functional gene clusters (159) and is essential for expression of the SPI-2 T3SS and its effectors (171). Recent observations suggest that SsrB functions both by activating gene transcription and by antagonizing H-NS-mediated silencing. Indeed, the locations of SsrB binding sites, which include sites upstream of, overlapping with, or downstream of transcriptional start sites, are not consistent with a classical mechanism of transcriptional activation (159). Furthermore, it has been shown that SPI-2 expression no longer displays an absolute requirement for SsrB in an *hns* mutant background (159). Linda Kenney, from the University of Illinois at Chicago, has posed the question of how SsrB relieves H-NS silencing. Using atomic-force microscopy and single-molecule experiments, she has examined H-NS–DNA interactions and the effects of SsrB on H-NS/DNA binding (95). This study has revealed the two binding modes of H-NS. At high magnesium concentrations DNA bridging is observed, whereas at lower magnesium concentrations H-NS polymerization results in elongation and stiffening of the nucleoprotein complex. SsrB relieves H-NS binding only at the lower magnesium concentrations, suggesting that H-NS polymerization and the formation of higher-order nucleoprotein complexes are responsible for transcriptional silencing, which can be relieved by competition with a high-affinity DNA-binding protein (e.g., SsrB).

The PhoQ/PhoP two-component regulatory system is another major regulator of *Salmonella* virulence (67). The PhoP regulatory protein governs virulence and adaptation to the intraphagosomal environment, and its activity is controlled by the sensor protein PhoQ, which is responsive to antimicrobial peptides, acid pH, and low Mg^{2+} concentrations (127). In *S.* Typhimurium, PhoP affects the expression of as many as 3% of all *Salmonella* genes (85). Genes directly controlled by the PhoP protein often differ in their promoter structures, resulting in distinct expression levels and kinetics in response to the inducing signal. Such differential expression of PhoP-activated genes requires a fine adjustment in the levels of active PhoP protein as well as differences in the *cis*-acting promoters of genes directly under PhoP control. Eduardo Groisman, from Washington University in St. Louis, presented a series of studies to demonstrate that the order of PhoP-activated gene expression is not directly correlated with the RNA level or with the amount of active PhoP protein present (66). Ancestral PhoP-activated genes are transcribed before horizontally acquired genes. The sequential expression appears to be a consequence of H-NS silencing, which must be countered by the PhoP-activated regulator SlyA (93) in order for the horizontally acquired genes to be transcribed, resulting in their delayed expression.

Gene expression of virulence proteins can also be regulated posttranscriptionally. In *S.* Typhimurium, RNA-mediated regulation occurs as a consequence of small RNAs (sRNAs; noncoding RNAs) that act as posttranscriptional regulators of gene expression. Bacterial sRNAs are typically 50 to 250 nucleotides in length and are commonly untranslated and encoded within intergenic regions of bacterial chromosomes (155). The synthesis of sRNAs is tightly regulated and often induced by a specific stress- or virulence-related condition. Most sRNAs function as regulators by base paring with *trans*-encoded mRNAs, consequently repressing or activating target gene expression at a posttranscriptional level (154). The strongest evidence that sRNAs serve important functions in *Salmonella* is based on studies with Hfq (154), a protein that preferentially binds A/U-rich, single-stranded regions of RNA and is required for both intercellular stability of many regulatory rRNAs and annealing with target mRNAs (150). The numbers of phenotypes and deregulated genes observed in a *Salmonella hfq* deletion mutant surpass those reported for any other pathogen (139, 154). Recent studies have determined that that an *hfq* mutation attenuates the ability of *Salmonella* to invade epithelial cells, secrete virulence factors, infect mice, and sur-

vive inside macrophages (140). Moreover, transcriptome analysis has revealed that Hfq controls the expression of nearly 20% of *Salmonella* genes, including genes in several horizontally acquired pathogenicity islands (SPI-1, -2, -3, -4, and -5), two sigma factor regulons, and the flagellar gene cascade (139). Since Hfq acts in concert with sRNAs, it is inferred that many of the above-described phenotypes are attributable to the loss of gene regulation by Hfq-associated sRNAs. Jörg Vogel, from the Max Planck Institute in Berlin, Germany, has used deep sequencing and sRNA pulse expression coupled with global transcription profiling to determine that several hundred *Salmonella* mRNAs may be controlled directly by Hfq-dependent small RNAs. Both conserved and *Salmonella*-specific sRNAs are recruited to appropriately transmit information from the *Salmonella* core genome and virulence regions at a posttranscriptional level (156). Nine *Salmonella*-specific sRNAs that bind to Hfq have been identified thus far, and the *sgrS* sRNA (induced by glucose phosphate stress) has been found to contain a conserved antisense domain that targets both *ptsG* and *sopD* mRNA.

Yet another regulatory paradigm is provided by small hydrophobic peptides that interact with protein partners at the inner membrane to modulate protein activity and/or stability (6). The control of protein stability allows a bacterial cell to adjust to changing conditions by adjusting the rate of protein turnover. Regulated proteolysis has been well characterized for a few proteins, including proteins involved in stress responses (63). Anne-Béatrice Blanc-Potard and Eric Alix, at CNRS in Montpellier, France, have recently identified a regulatory hydrophobic peptide called MgtR, which is encoded by a nonannotated gene in the *mgtCB* operon (5). MgtR interacts with MgtC *in vivo* and promotes the degradation of MgtC by the FtsH protease, which belongs to a family of ATP-dependent AAA^+ proteases whose substrate recognition is regulated by adaptor proteins (130). The *mgtR* gene is cotranscribed with *mgtC*, which encodes a virulence factor important for intramacrophage survival (4). The transmembrane segment of MgtR interacts with MgtC in a bacterial two-hybrid system (83), suggesting that this interaction might unfold MgtC to render the protein susceptible to FtsH-mediated degradation. This provides the first example of an alpha-helical hydrophobic peptide that modulates degradation of a membrane protein by an AAA^+ protease. A genome-wide analysis has recently identified 14 new putative membrane peptides, including peptides with homologs in *E. coli* and peptides specific to *Salmonella*, like MgtR (21). It is envisaged that the discovery of this novel class of molecules will lead to new insight regarding the interactions between alpha-helices within the biological membrane.

The Sixth no sooner had begun
About the beast to grope,
Than, seizing on the swinging tail
That fell within his scope,
"I see," quoth he, "the Elephant
Is very like a rope!"

BROAD BIOLOGICAL IMPLICATIONS OF *SALMONELLA* RESEARCH

Studies of *Salmonella* genetics and physiology have helped to form the foundation of modern molecular biology. Similarly, investigation of the molecular and cellular mechanisms that underlie *S.* Typhimurium pathogenesis has provided new insights and practical applications that are broadly relevant to infectious diseases and even to a variety of noninfectious conditions, such as inflammatory bowel disease, hemochromatosis, and atherosclerosis.

Inflammatory bowel disease. The IBDs Crohn's disease (CD) and ulcerative colitis (UC) are lifelong, relapsing illnesses that affect the gastrointestinal tract primarily in young adults. Such conditions are characterized by chronic inflammation, mucosal damage, and epithelial cell destruction resulting from a complex interplay of genetic, immunologic, and microbial factors. The active phase of IBD is histologically characterized by a pronounced infiltration of neutrophils (polymorphonuclear leukocytes [PMNs]) into and across the epithelial lining of the intestine, accompanied by epithelial cell necrosis and ulceration (120, 121, 172). Disease activity and symptomatology correlate with the presence of these findings (120, 172). Remarkably, a similar massive transepithelial migration of PMNs occurs in the acute phase of gastroenteritis induced by *S.* Typhimurium (41, 102, 131). Thus, insight into pathogen-elicited acute inflammation of the intestine may serve as a model for the biological events that evoke active inflammation in IBD. Recently, it was discovered that the eicosanoid hepoxilin A_3 (HXA_3) is responsible for directing the transepithelial migration of neutrophils associated with intestinal inflammation (108). Beth McCormick, from the University of Massachusetts Medical School, has used *Salmonella*-infected polarized intestinal cell monolayers to demonstrate a novel mechanism for the vectored secretion of HXA_3 from the apical surfaces of epithelial cells, involving the ATP binding cassette (ABC) transporter multidrug resistance-associated protein 2 (MRP2). Multiple *in vitro* and *in vivo* models of *S.* Typhimurium infection have demonstrated that induction of intestinal inflammation profoundly upregulates apical expression of MRP2 and that interference with HXA_3 synthesis and/or MRP2 function markedly reduces inflammation and the severity of disease. Inflamed intestinal epithelia in human biopsy specimens also exhibit upregulation of MRP2. These findings not only shed new light on the contribution of ABC transporters to the pathogenesis of *S.* Typhimurium enteritis but also identify novel targets for the treatment of epithelium-associated inflammatory conditions, such as IBD.

Although inflammatory changes in intestinal physiology cause many of the symptoms associated with CD, significant morbidity also results from the irreversible tissue injury and fibrosis that frequently occur as a complication (2, 15). Although more than one-third of patients with CD develop a distinct fibrostenosing phenotype that results in recurrent intestinal stricture formation, good models that mimic the pathology of intestinal fibrosis have been lacking (26). Fibrosis in CD is believed to result from an overzealous healing response to injury (128). For reasons that remain unclear, the reparative process associated with CD progresses uncontrollably, leading to the proliferation of mesenchymal cells and the unrestrained deposition of the extracellular matrix (ECM) (57). Abnormal contraction of the ECM leads to scar formation and tissue distortion. Ultimately, this fibrotic process thickens the wall of the gut, reducing flexibility and narrowing the bowel lumen, resulting in obstructive strictures (10, 57).

Brett Finlay, from the University of British Columbia, has developed a mouse model of chronic colitis and intestinal

fibrosis that mimics many of the features of CD-induced fibrosis (52). This model is unique in that the intestinal fibrosis is initiated by *S.* Typhimurium infection. In this model, mice are pretreated with streptomycin prior to oral infection with *S.* Typhimurium, and the resulting enteric phase of infection leads to heavy colonization of the cecum and colon, with the development of significant colitis (65). Initial characterization of the model demonstrated that factors contributing to fibrosis are similar to those implicated in cecal inflammation in the streptomycin-pretreated mouse model, including the flagellar, SPI-1, and SPI-2 T3SS on the bacterial side (13, 34, 143) and Th1 cytokines, Th17 cytokines, and T cells on the host side (58). This model highlights two important advances in the study of intestinal fibrosis: (i) infection with *S.* Typhimurium leads to chronic infection and colitis in association with extensive transmural ECM deposition within the cecum and colon, and (ii) fibrosis and extensive transmural inflammation occur along the entire length of the colon, with the most severe and extensive fibrosis found in the cecum. With such consistent localization of fibrotic areas, it is hoped that this model may serve to aid the future investigation of mechanisms underlying the fibrotic response.

Hemochromatosis. Iron plays important roles in both pathogen virulence and host innate immunity (82, 135). Alterations of iron homeostasis in humans affect susceptibility to infectious disease. For example, iron overload from dietary sources, hemolysis, or inherited metabolic disorders enhances susceptibility to salmonellosis, tuberculosis, and other infections (55, 97, 111, 160). Infection and other inflammatory stimuli induce an "iron-withholding response" in the host that reduces the availability of iron within the host environment and constitutes an important component of innate immunity (56). Hereditary hemochromatosis (HH) is a group of genetic disorders characterized by an abnormal accumulation of iron in tissues (125). The most common form of the disease (type I) is caused by variations in HFE, the hemochromatosis gene, which encodes a nonclassical major histocompatibility complex class I-like protein (50). The HFE protein forms a complex with the transferrin receptor and regulates multiple aspects of cellular iron homeostasis (50, 125, 165, 175). Two missense mutations in HFE (C282Y and H63D) account for most cases of HH.

Recent studies with *S.* Typhimurium have revealed a novel role for iron in the regulation of the inflammatory response (161). The mouse model of type I hemochromatosis is associated with an attenuated inflammatory response to *Salmonella* infection, both *in vivo* and in cultured macrophages. HFE mutations also confer increased resistance against intracellular pathogens that require iron, and Manfred Nairz, of the Medical University in Innsbruck, Austria, presented data to suggest a mechanistic basis for this observation (113). He showed that mice lacking one or both HFE alleles are not only protected from *S.* Typhimurium septicemia but also exhibit increased survival, suggesting that HFE-deficient mice are more resistant to infection. This finding was associated with increased production of the enterochelin-binding peptide lipocalin-2 (Lcn2), which promotes iron efflux and reduces the availability of iron for *Salmonella* within HFE-deficient macrophages (113). In contrast, $Hfe^{-/-}$ $Lcn2^{-/-}$ macrophages are unable to withhold iron from intracellular *Salmonella*, and as a consequence bacterial proliferation is unrestrained. Thus, although individuals with hereditary hemochromatosis suffer consequences from iron overload in tissues, the iron content of their macrophages is actually reduced, limiting the growth of intracellular *Salmonella*. The evolutionary benefit provided by reduced inflammatory responses and enhanced resistance to intracellular pathogens may account for the high prevalence of hemochromatosis as a genetic disorder; this idea has been used to explain the unusually high frequency of the HFE gene variants in European populations (104).

Atherosclerosis and other inflammatory disorders. Diverse conditions, including atherosclerosis, cerebral ischemia, inflammatory bowel disease, and neurodegenerative disorders, exhibit the common denominators of caspase-1 activation, inflammation, and cell death (reviewed in references 18 and 51). Caspase-1-dependent programmed cell death, referred to as "pyroptosis," can be stimulated by a range of microbial pathogens, including *Salmonella*, *Francisella*, and *Legionella* (18). Pyroptosis is morphologically and mechanistically distinct from other forms of cell death, and caspase-1 dependence is a defining feature of pyroptosis. Specifically, pyroptosis features rapid plasma membrane rupture and the activation and release of the proinflammatory mediators IL-1β and IL-18 (18). Pyroptosis protects the host against infection but can also result in pathological inflammation. Brad Cookson, from the University of Washington, suggests that a fine balance must be achieved to utilize pyroptosis as a protective host response to infection while avoiding detrimental consequences of caspase-1 activation (19). For example, mutations in Nod-like receptor (NLR) proteins lead to aberrant caspase-1 activation, which is associated with hereditary autoinflammatory syndromes (18). Caspase-1 deficiency or pharmacological inhibition may provide protection against inflammation, cell death, and subsequent organ dysfunction, making caspase-1 an attractive therapeutic target in both infectious and noninfectious inflammatory conditions. Notably, the protection afforded by caspase-1 deficiency against sepsis and renal failure is not mimicked by neutralization of the cytokines IL-1β and IL-18 (49, 133, 162), indicating that caspase-1 has important roles in inflammation in addition to cytokine processing. The conserved proinflammatory programmed cell death pathway of pyroptosis, elucidated by studies with *Salmonella*, is clearly of broad biological significance.

And so these men of Indostan
Disputed loud and long,
Each in his own opinion
Exceeding stiff and strong,
Though each was partly in the right,
And all were in the wrong!
So oft in theologic wars,
The disputants, I ween,
Rail on in utter ignorance
Of what each other mean,
And prate about an Elephant
Not one of them has seen

Despite many advances in *Salmonella* research, *Salmonella* infections continue to cause substantial morbidity and mortality throughout the world. Food-borne outbreaks occur with regularity, enteric fever continues as a major public health problem in many parts of the world, multiple *Salmonella* serovars are responsible for major economic losses in livestock, and nontyphoid *Salmonella* has emerged as a highly invasive pathogen in sub-Saharan Africa. The challenge is to apply the ever-

increasing understanding of *Salmonella* to reduce its burden on human society. Recent discoveries have not only moved the *Salmonella* field closer to this goal but have also led to the creation of novel biological paradigms and therapeutic approaches with far-reaching applications. *Salmonella* researchers may no longer be working blind, but much work remains before this elephant can be tamed.

ACKNOWLEDGMENTS

We gratefully acknowledge support from the National Institutes of Health (AI83646, AI83964, and AI77645 to H.L.A.-P.; RR00169, AI40124, AI44170, AI76246, AI73120, and AI79173 to A.J.B.; DK56754 to B.A.M.; and AI39557, AI44486, and AI82785 to F.C.F.) and from the Crohn's and Colitis Foundation of America (to B.A.M.).

F.C.F. also thanks his colleagues on the Conference Organizing Committee, Olivia Steele-Mortimer, Richard Strugnell, Duncan Maskell, and Stéphane Méresse, for their dedication and good humor.

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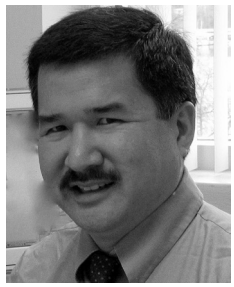

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