A bacterial pathogen's view of the human condition

The bacterial view of time is very extended and we can afford to wait for our successes. Let me, as a humble bacterium, attempt to explain why the morale of the human pathogens is high.

In the beginning, there was the primeval soup and we were all in it. Peaceful co-existence was a myth from the start; the fight started as soon as life was created and the development of survival advantages was the primary order of the day. As Jacques Monod observed in *Chance and necessity*, mutations happen whether anyone decrees them or not; they are part of the game that comes with the genetic code. The fact that many chance mutations are lethal or generally disadvantageous must be a worry to Man, because humans are lumbered with a relatively long life and an extended generation time. The death of an individual human being is consiously perceived as a catastrophe in your world, although groups of humans occasionally lose their reason and kill or maim themselves in terrible numbers. Bacterial pathogens enjoy a rich harvest among battle casualties and within civilian communities at these times. Infection rather than generalisation often dictates the outcome of a campaign, as Zinsser recounted in *Rats, lice and history*. Paradoxically, your wars have brought many opportunities for medical and surgical advancement and stimulated many developments in antimicrobial concepts and practices; so your irresponsible episodes of self-destruction and aggression are a mixed blessing for us bacteria... But I digress.

As prokaryotes, we may be relatively simple, but we have many advantages to exploit. It is our nature to bide our time until opportunities to invade present themselves, then we concentrate on dividing and multiplying and not growing fat. Indeed, fatness is a sign of weakness in the strain (involution) and usually carries serious penalties. The generation time of our most versatile attackers growing in a nutritious broth at the right temperature can be as short as 20 minutes. Thus, one cell becomes at least eight in one hour, 64 in two, and more than a billion in 10. Our rapid replication frees us from the human obsession with the possibility of personal immortality, and from anxiety about the survival of our family dynasty. Each of the millions or billions of our day's progeny carries a copy of our DNA, and we can view with complacency the demise of most of them. We don't get a chance to show this potential fully when we attack man (because your various antibacterial systems tend to hold us in check), but we can show a frightening turn of reproductive speed in meningococcal septicaemia when your immune defences are down, or in gas gangrene or necrotising fasciitis when conditions allow, or in Man's food when his carelessness and ignorance about holding temperatures allow us to play havoc.

Many of us, like the anthrax bacillus and the Enteritidis salmonella, have evolved properties enabling us to infect a wide variety of animal hosts (including Man) and so enjoy the advantage that, when one kind of host is unavailable, we can colonise another. Some, like the gonococcus and the whooping cough bacillus, found it advantageous to specialise in infecting Man. Some of our specialised human colonisers developed techniques for long-term, low-profile survival in the human body to make possible transmission from grandparent to grandchild, such as typhoid and tubercle bacilli. It looks as if the prions of Creutzfeldt-Jakob disease and kuru and maybe some other agents associated with neurodegenerative diseases of Man have really taken this more than a step further, so that you may have to take back some of the unkind things your forebears said about Needham and his views on spontaneous generation. Indeed, it is time that you reviewed the postulates of Koch and Henle and your textbook dogma on sterilisation, but again I trespass beyond my terms of reference.

You and your evolutionary predecessors have been elaborating defences against us for far longer even than the five million years that hominids have been around. We have always had a hard job to keep one or two steps ahead. Real difficulties arose for the bacteria when eukaryotes evolved and developed antibacterial systems that have become more and more sophisticated over the millennia. It was difficult to contend with humoral antibodies that agglutinated and opsonised bacteria so that we were very vulnerable to phagocytosis and destruction. One apparent solution was to opt for the cover that an intracellular existence might offer. The typhoid bacillus and the brucelae and others achieved this in different ways, but they then had to cope with Man's cell-mediated immune systems. The tubercle bacillus, the gonococcus and the meningococcus found different ways of resisting intraphagocytic digestion. We had meanwhile accepted that we needed to protect our own patch from invaders and we elaborated our own antibiotics (bacteriocines) that even stopped some of our cousins moving in. We found advantages in living together in colonies on suitable surfaces of host cells and bigger things such as teeth and heart valves and the many bits of plastic that you now stick into yourselves. Nutrients are often more readily available on surfaces; even feebler members of our race, those that do not normally possess predatory instincts, find these surfaces to their liking. It took you some time to find out that bacterial fimbriae and pili, our organs of attachment to surfaces and cells, were every bit as important as flagella in this context. Our ability to secrete protective layers of slime also often helps us to maintain our hold on solid surfaces such as intravenous lines, and keeps at bay some of the noxious antibiotics that you use.

We sometimes mount particularly successful attacks on our hosts by combining forces with one or two other bacterial species to enjoy the profits of pathogenic synergy. There are those who would argue that the killing of a host in such a spectacular fashion for relatively short-term gain is not a good strategy. There is a school of thought that would hold that the highest form of parasitism is peaceful co-existence and that the life-style of the fulminating pathogens gets the bacteria a bad name. I'm not so sure. Life for bacteria of all kinds is a struggle, and we have to make the best of our chances, or perish. As commensalism is on the edge of my terms of reference, I'll not pursue this, but you will agree that the dividing line between symbiotic co-existence and opportunistic attack has virtually vanished in these difficult times for both of us.

There are numerous mechanisms of microbial pathogenicity and there is no single grand plan, but there
are some good general principles that you clearly know. If we want to start an infection with any chance of success, we need several things to go right. First, we need a source of infection from which we mount a force of sufficient numbers of our fellows to challenge a susceptible human being. Second, we need to have our challenge transmitted by an effective route; this might be via an infected needle, or a penetrating injury, or an aerosol, or by food or drink, sexual intercourse, or some other route. Third, we then have to press home the attack by expressing our virulence—either by invasiveness or toxigenicity, sometimes both. This latter concept, the expression of virulence, is complicated and many things can go wrong. Let me expand on this.

The success of the challenge depends upon the armament of the bacterium and the quality of the host’s defences (which include both non-specific natural defences and highly specific immune defences). The ability of a bacterial pathogen to evade or to counter the host defences has been improved by natural selection. Each pathogenic species has taken very many small cumulative steps to develop its armament and its defence systems. Dawkins made the point about cumulative steps and incidental consequences brilliantly in The blind watchmaker. Darwin would have loved our models of evolution. For example, bacterial pathogens with capsules that protect them from the attention of your phagocytes include the meningococcus, the pneumococcus, Haemophilus influenzae and the anthrax bacillus. Each of these can produce fulminating infections that sweep through a susceptible host’s tissues. On the other hand, some bacteria express their virulence by releasing potent toxins that home on to receptors at a vital point in the host’s system. Thus, the diphtheria bacillus and the tetanus bacillus each set up a local bridgehead of infection at their first encounter and then release deadly exotoxins. Man has learned to use toxoids to provoke protective antigenic antibodies so that, in many countries, active immunisation programmes have made diphtheria and tetanus uncommon ... but these diseases flourish in other countries only a day’s journey away. Be on guard, because we are working on ways around some of your vaccines and we thrive on your complacency! Some bacteria rely upon their remarkable invasiveness to carry them rapidly from their point of entry into and through the host tissues. They then often home on to certain organs or tissues (organotropism) and replicate there. Typhoid fever, pneumococcal (lobar) pneumonia, leptospirosis and legionnaire’s disease are good examples. In many cases, bacterial pathogens exploit both invasiveness and toxigenicity: the anthrax bacillus is capabile but produces several splendidly effective toxins; the Group A streptococcus protects itself with M protein and elaborates many toxins and aggressins. Clostridium perfringens seems to hold all of the aces; it evades the host’s phagocytes with its capsule and kills these and other host cells with a formidable range of toxins; in addition, it uses hyaluronidase to break down intercellular cement and to travel along tissue planes, while it has collagenase to liquefy muscles. When times are hard, it can produce spores to survive, and these are a key factor in its food-poisoning potential because some strains have adapted their spores to be so resistant that they survive boiling for hours.

Bacteria still have attack plays that Man does not fully understand. The pneumococcus is a deadly pathogen, yet you have no idea why it kills so effectively. You know about its aggressins, hyaluronidase and neuraminidase, but you have not identified a pneumococcal toxin. It is truly Gram-positive, so you can’t attribute its power to lipopolysaccharide endotoxin. The staphylococcus protects its bridgehead with locally elaborated coagulase and then releases toxins and aggressins; invasiveness is not its usual mode of attack, but it can use an exotoxin to produce a toxin shock or endotoxin shock or Gram-negative shock or endotoxic shock; the multiplicity of names is a fair reflection of your confusion! In fact, the Gram-negative bacteria developed their lipopolysaccharide layer millennia ago as a protective coat—and the pathogenic members of the team found it a huge bonus when it was found to be a master switch for so many cascade systems in animals and man. It will be a sad day for the bacteria if the moves to develop a therapeutically effective broad-range antibody to lipopolysaccharide endotoxin are ultimately successful.

Of course, the present century has seen many reverses for us, but we are used to challenges. Ehrlich had a dream that was very bad news for the pathogens; the subsequent development of the sulphonamides and penicillin and all the rest of the antimicrobials have seen us in some disarray, but you are mistaken if you think that you can subdue us permanently with these weapons. Clinical abuse of these powerful drugs has been on our side and we have developed many excellent pathways to destroy them or to evade their antibacterial effects. Long before that, Pasteur, Lister, Semmelweis, Pringle, and many others showed humanity how to defeat many bacterial cross-infection strategies, but Man forgets things quickly and you present lack of handwashing and toilet facilities in hospitals is a constant delight to us. Even when the sinks and basins are there, you seem to forget to use them, and the average doctor’s scant knowledge of antibacterial disinfectants and antiseptics would make our arch enemy Lister turn in his grave. The hospital staphylococci, literally waiting in the wings (of the noses of staff and patients), quickly came into their own in this scenario. They had elaborated penicillinase long before Fleming discovered penicillin. When you throw your new wonder drug around your hospitals, you selected the penicillinase-producing strains and they have made you pay dearly. When you developed bigger (but not better) antibiotic guns, you set the fuse for the explosion of multiple antibiotic resistance. So the multiple-resistant strains of Staphylococcus aureus evolved. It was a matter of sequential genetic exchanges mediated by phages and other mechanisms that brought small packets of genetic information together into individual bacteria. These then had a huge survival advantage if they colonised or infected a healthy carrier or a patient exposed to an antibiotic to which the bacteria were resistant. In such a situation, generally in hospital personnel or patients, the resistance movement flourished. Opportunities for further exchanges of resistance information were continuously provided and the hospital bacterial flora went from strength to strength. Was’n’t it Florence Nightingale who said that the first thing that a hospital should strive to ensure is that it should do the sick no harm?

Metcalf and Macfarlane Burnet, among others, opened up important lines of investigation that spelt danger for us pathogens. There was a period of relative calm while the immunologists spent so much time arguing among themselves about concepts and terminology, but the writing was on the wall. We could not expect to get a free rein with all the immunocompromised patients around in the latter half of this century and it was inevitable that immunology would come into its own. Knowledge of the many cascade systems in Man that may be on our side or his, applications of successful passive and active immunisation, the apparently limitless subject of cell sets and subsets in Man’s defensive armament, and the expanding elucidation of cytokines and other mediators involved in the
actions and reactions of systems that bring about our downfall make infinitely alarming reading. There is comfort for the bacteria in the fact that you are still far from understanding how to manipulate those systems to your own advantage rather than ours!

What else have we to console us? The bacteria have not done badly in the face of the overwhelming commitment of the biomedical scientists. We have played several very good cards. Some of the most effective must be strain and type variation, sometimes accomplished even in vivo to confuse the defences and the clinician. For example, you know that one in $10^9$–$10^{10}$ of the progeny of a tubercle bacillus may be streptomycin resistant by chance. The spontaneous resistant mutant has no advantage unless it finds itself in the presence of streptomycin, but then it has a master card and it takes over. This is why man has had to use multiple drug therapy to counter tuberculosis, because resistant mutants to your other anti-tuberculous drugs also arise spontaneously. Our various bacterial species have learned the resistance trick by many different mechanisms. The staphylococci and the coliforms and the bacterioides organisms were quite quick, greatly helped by Man's abuse of the early antibiotics (notably penicillin and tetracycline). The gonococcus took its time, and the pneumococcus and the haemolytic streptococcus are just showing their paces in this field now. It might be that the switch to a resistant mutant might carry some penalty, such as the loss of a virulence factor, or a colonisation factor, or an aggression. If this happens, the advantage for a pathogen would be compromised...but our bacterial colleagues generally get around the problem in time. It is interesting that the acquisition of resistance actually often carries an additional advantage such as enhanced virulence or improved colonisation ability or toxigenesis.

Bacterial exploitation of man's folly has always been masterly. It's Chance and necessity all over again, as evolution rolls inexorably on. Bacteria revelled in Man's overcrowding (especially in underprivileged communities), and his scant regard for basic principles of sanitation and hygiene. The sexual revolution that followed in the wake of the contraceptive pill also gave us a field day. So not only were we able to cash in with the density-dependent infections such as flu, measles, whooping cough, diphtheria, and scarlet fever in the first half of the century, but we reaped a rich harvest in the second half with sexually transmitted diseases and food-borne diseases and even tuberculosis, cholera, and plague. And we have sprung a few surprises with the campylobacters (unsuspected as gastrointestinal pathogens until just two decades ago), the helicobacters, Legionnaire's disease, Lyme disease, listeriosis, pseudomembranous colitis, and so on. It is interesting that bacteria, with such a short generation time, can demonstrate their successes over millennia whereas Man finds it difficult to look back or forward more than a generation or two.

Analogous to Man's problems with virus diseases is our own fight with bacteriophages. Man used his knowledge of phages to his advantage for the epidemiological tracing of our strains; this was done as an alternative to a direct attack upon us with phages, though some human pioneers thought that phage therapy might be feasible, and some of your workers still dream along these lines. The bacteria came to terms with many phages and settled for some of the advantages that attend the injection of exogenous nucleic acid and the added package of genetic information that is acquired. As far as sex is concerned, and the acquisition of new information, Man was slow to realise that we have been at it for many years, despite all of the textbooks' concentration on simple binary fission as our way of life. We have found that promiscuous conjugation is not such a bad thing for the family, though it seems to have been catastrophic for yours. Plus ça change.

The advent of AIDS will no doubt be discussed by a representative giving the viral view of things. Pathogenic bacteria are often indebted to the viruses for the openings that they afford. Indeed, we should coin the term sequential synergy to indicate the sequence of infection that is often evident, for example, when a haemophilus organism takes advantage of a patient's weakened resistance during or after flu. Thus, with the HIV scenario and with very many hosts compromised in so many different ways in recent decades, bacterial opportunists are happily spreading confusion and dismay throughout the world. Add to this our remarkable successes in the field of antibacterial drug resistance. By your use of antibiotics over the last half-century you selected resistant variants of traditional pathogens and these have flourished. However, you are now plagued in intensive treatment units and elsewhere with a broad range of species that you previously considered to be much less pathogenic. Many of these are inherently resistant or can readily acquire the resistance genes that you have spread around in other species to form a gene pool of trouble for mankind. Our forces in the ranks of the acinetobacters and the enterococci and the aeromonas group and many others are certainly making significant advances in this field.

A special award for distinguished service must go to the tubercle bacillus. Here was one of our most successful representatives apparently brought to its knees, at least in Western communities, by Man's therapeutic advances; now it is mobilising its resistant strains and, with its so-called atypical cousins, it is again feared across the world. The gonococcus also merits honourable mention in this context, but perhaps the prize should be shared presently by the staphylococcus and that humble organism of so-called low pathogenic potential Pseudomonas aeruginosa. Note, however, that we have infinitely more surprises in store for you.

Need I say more to make the case that we are not yet out? We have never really been down.

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Suggestions for further reading

A bacterial pathogen's view of the human condition.

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