Green medicine

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Fear of them accelerated in the last decade of the 20th century. They were silent, unseen and struck indiscriminately. Mere mention of their name evoked powerful images of suffering and death, and in a shrinking world they were able to sneak undetected across national borders. Eighteen months after the September 2001 destruction of the New York World Trade Center by Al Qaeda terrorists, an insurgency from the Guandong province of China slipped unnoticed across the Canadian border. With the first deaths, newspaper headlines around the world screamed 'Killer closes Canada'. By the year 2005, microbes had received an unremittingly bad press. In 2002 it was the fear of Saddam Hussein's threat to deploy anthrax, botulin and other biological weapons of mass destruction that prompted the mightiest army on earth to invade Iraq and topple the regime. Anyone who read a newspaper, listened to newscasts or surfed the internet recognized the enemy. They knew of the lethal white anthrax powder that could be sprinkled into innocent-looking envelopes and posted to intended victims. They had read of the catastrophe which could befall mankind with the evolutionary leap of the highly pathogenic avian flu virus from bird to man. Earlier, in 2001, UK television viewers had watched horrified as men from the ministry incinerated mountains of cattle to defeat an epidemic of foot and mouth disease. The offending aphthovirus had slipped across the Northumberland border in illegally imported meat, had contaminated pigswill, and had proceeded to infect the national herd. By 2005 most quiz-show contestants knew that prions caused variant Creutzfeldt–Jakob disease and that the deadly human immunodeficiency virus had travelled in the wake of the 1960s sexual revolution: the 'permissive age' had seen the reawakening of the ancient venereal diseases, syphilis and gonorrhoea. Tabloid newspapers ran stories about the superbug methicillin-resistant *Staphylococcus aureus* which struck at patients in hospital wards; and in the first

years of the new millennium the Marburg virus, cholera, TB, typhoid, measles, mumps and rubella all gained notoriety in the popular press.

The mistrust of microbes was not limited to a fearful public. For over 200 years, after the discovery of bacteria by the Dutch microscopist Antony van Leeuwenhoek, doctors watched helplessly as streptococcal puerperal sepsis killed childbearing women, and smallpox, plague, cholera and typhoid decimated populations. The battle against infection started in 1796 with Edward Jenner's observation that cowpox vaccination protected against smallpox. In 1847, infectious organisms were outmanoeuvred with a brilliant tactical move by Ignaz Semmelweis, who recognized that handwashing with chlorinated lime resulted in a major decline of puerperal and surgical sepsis.

War on microbes

Vaccination and handwashing were followed by the antibiotic arms race, beginning in 1928 with Alexander Fleming's discovery of the penicillin mould. With microbes so obviously an enemy of mankind and antibiotics such potent weapons, the second half of the 20th century saw the development of a vast and powerful arsenal of bacteriostatic, bactericidal and antiviral agents. Doctors, often goaded by their patients, adopted a policy of zero tolerance to microbes. Every sore throat, cough, sniffy nose, loose stool and stinging urine was assaulted with penicillins, macrolides, tetracyclines, cephalosporins and quinolones. In the second half of the 20th century and the first years of the 21st, the cry of mankind and its medicine men was 'a good germ is a dead germ'.

Inevitably, the unremitting assault on microbes saw a fightback with the emergence of organisms resistant to the antimicrobial arsenal. Along with *S. aureus*, resistance appeared in *Mycobacterium tuberculosis*, the gonococcus and meningococcus, *Pseudomonas*, *Haemophilus*, and even the humble streptococcus. The emergence of multidrug-resistant bacteria threatened a return to the pre-antibiotic era.

So has the time come to consider a truce with the microbe? Do bacteria need a green lobby? Do microbes deserve a better press and who will spin on their behalf? After all, only a tiny minority of microbes are pathogenic and most have evolved as our close allies and would be

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pleased to assist. Let us consider another script for our silent, unseen but close neighbours.

Symbiosis

The fetus is sterile but the newborn baby, even before taking its first breath, is bestowed with a mouthful of its mother's vulval organisms. From birth to death the skin, gut, bronchi and urogenital surfaces are colonized by a vast, complex, and dynamic consortium of gentle microorganisms that outnumber our somatic and germ cells. The adult human colon alone expresses a microbial density approaching 10^{12} organisms per gram. The relationship between mankind and microbes represents a social cohesion only dreamed of by philosophers and world religions. Over millions of years of peaceful coexistence the resident flora evoked a range of interactions with the human host, ranging through a continuum of symbiosis and commensalism, only rarely evolving renegade pathogens. The symbiotic microbes confer benefit without harm, whilst commensal partnerships refer to mutual coexistence without detriment or benefit.

The normal flora colonizing the gastrointestinal ecospace provide a basket of helpful functions.¹ They nourish the colon, synthesize vitamin K and folic acid and produce lysozymes, bacteriocins, lactoferrin and transferrin, which interfere with the reproduction of pathogenic bacteria. Furthermore, there is evidence that the non-pathogenic bacteria of the gut guard this portal from self-destruction. Biological products such as NF-KB transcription factor, synthesized by these organisms, block the immune pathway that would otherwise provoke an unhealthy inflammatory response to the millions of bacteria normally present in the intestine.² Specific strains of the healthy gut microflora induce the production of interleukin-10 and transforming growth factor-beta, both of which possess an important regulatory role in the development of allergic type immune responses. This biological anti-inflammatory activity is likely to account for the colon's capacity to tolerate and positively exploit its huge bacterial load. There is evidence that failure of this interaction might underlie the pathogenesis of inflammatory bowel disease.³ Perhaps the most striking glimpse of the important alliance between mankind and 'infectious agents' is the demonstration that the feeding of pig whipworm (*Trichuris suis*) ova to patients with Crohn's disease results in striking improvement in disease activity.⁴ The headlines in 2005 were changing as the media began to hail the whipworm with words such as 'Helminths bring hope'.

In the last years of the 20th century, as socioeconomic conditions improved in industrialized countries, a rising incidence of asthma, eczema and other allergic disorders was recognized. Evidence emerged that reduced exposure

Figure 1 Symbiosis

to childhood infections might explain this phenomenon.⁵ The 'hygiene hypothesis' suggests that lack of exposure to infections in early life and failure to establish normal gut microflora favours the development of atopy.⁶ Research into probiotics provided a further glimpse of the positive relationship between man and microbes. Probiotics are live microorganisms administered to improve microbial balance.⁷ This effect has been related to production of substances that inhibit pathogenic bacteria,^{8,9} adhesion⁸ and toxins,^{10,11} and IgA stimulation.¹² Enteric bacteria have a trophic effect on bowel mucosa.^{13,14} Paradoxically, non-pathogenic probiotics offer therapeutic potential to treat pathogenic infections including antibiotic diarrhoea, *Clostridium difficile*-associated diarrhoea and colitis, traveller's diarrhoea, acute infantile diarrhoeas, vaginal infections and urinary tract infections.¹⁵ Perhaps the billion year-old alliance between microbes and mammals should be treasured and preserved.

Dr Green

The green movement of the late 20th century raised awareness of the adverse environmental impact of recklessly burning fossil fuels and cutting down the rain forests. The stereotyping of microbes as the 'bad guys' of nature and the indiscriminate use of chemical warfare to interfere with their environmental niche could, like global warming, lead us where nature never intended. Both doctor and patient urgently need to make a peace with most microbes. They are 'good guys' and deserve our esteem. Microbes need a good press. Microbes need a spin doctor. Where is Dr Green?

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