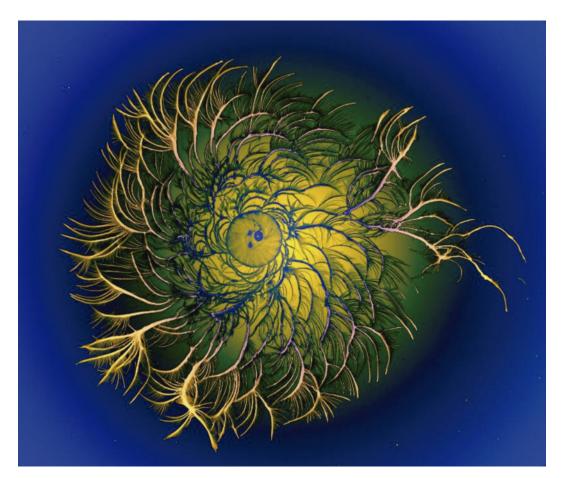


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**Enlightenment.** An image produced by Eshel Ben Jacob from his work studying the behaviour of bacterial colonies under stress. Author: Eshel Ben Jacob. http://star.tau.ac.il/~eshel/pics/images/Enlightenment.jpg. Reproduced with his kind permission.



Microbes and Metaphors: A dialogue between scientists, artists and activists

Part of the Reimagining Resistance Series

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This publication is for educational purposes only and for use by participants in the Reimagining Resistance initiative. Subsequent publications in this series will develop the themes taken up in this report further.

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# INTRODUCTION

seven decades ago public health measures, together with the advent of antibiotics, had made a major impact on spread of infection. However now, bacterial resistance to all known classes of antibiotics threatens to take the world back to the pre-antibiotic age with all the dire consequences involved.

In particular such resistance threatens to undermine various modern medical procedures that are both life saving and life-prolonging, such as heart surgery and organ transplantation besides posing a grave threat to our ability to treat even common bacterial infections.

There have been several responses to this looming crisis, chief among them the quest to discover new antibiotics or find new ways of keeping the old ones going for a longer time. Attention has also been focused on the need for prudent use of antibiotics, regulating their sale in pharmacies and prescription by clinicians. Policies relating to public health, the administration of hospitals, sanitation and hygiene issues and consumer awareness have also come under much scrutiny.

All this effort has achieved some improvements in certain places in moderating overuse and abuse of antibiotics through change in government policies, improved regulation of their sales, better procedures adopted in hospitals and so on.

However none of this has been adequate to stem the spread of resistant bacteria or address the problem on the scale that it really demands. Instead, it is becoming clear that the crisis in medicine due to the emergence of antibiotic resistance requires a close examination of the philosophy and assumptions behind the very

idea of antibiotics or for that matter the continued use of the term 'resistance' with all its negative connotations.

One of the main reasons for this lack of progress in dealing with the phenomenon of 'resistance' seems to be the flawed 'war metaphor' which shapes the way antibiotics are used against pathogenic bacteria. Experience in tackling infectious diseases is showing that antibiotics are no longer the 'magic bullets'; they were once conceived to be while bacteria are also not the 'enemy' to be eliminated through any means whatsoever.

Recent developments in microbiology also cast doubt about the wisdom of the 'us versus them' mind set that dominates traditional approaches to microbial ecology. Chief among the insights that new research is providing is the extent to which human life is closely intertwined with that of the microbial world and the complex mechanisms by which the latter operates. Mechanisms, one may add, that are still poorly understood and which hold the key to finding ways by which the human species can peacefully co-exist with the great diversity and volume of microorganisms that populate our planet.

It is a crisis in the world of medicine that can also be converted into an opportunity to ask new questions, often very basic and simple ones, that delve into not just the science but also the history, culture and politics of medicine, microbial ecology and human activity. Some of the questions that need to be asked now for example are as to what exactly is the prevailing notion of 'health' in modern societies; what is the dominant idea of the 'human being' in biological terms; what is the relation of the human species with the microbial world; and even beyond all this what exactly is the long term evolutionary role of microbes on our planet?

Also when and how did 'pathogenic' bacteria first emerge? While today it may appear that 'there is no alternative' to antibiotics or some other equivalent medicine to tackle harmful bacteria we also need to enquire into the possible role of human societies in turning harmless bacteria into pathogenic ones.

The urban civilizations we have constructed over time are at their core a by-product of the human search for security and certainty against the unpredictable forces of nature. Much of this security, whether through stable agriculture or the construction of permanent habitations has been done through invading the ecological niches of other species.

There is some evidence to believe that the process of urbanization, poor living conditions, changing lifestyles and the concurrent lowering of natural human immune systems have driven at least some of the large-scale epidemics in human history. Could antibiotics be a mere quick fix – and now an increasingly 'slow-fix' solution to problems that arise from human modification of the globe's ecology? A des-



Replication Malfunction I. Michelle Day



perate, last-ditch attempt to correct in a very short time what has gone wrong over several millennia?

Furthermore, are we using the appropriate language required to understand what is really happening or are we blindly following the social and political terminology we have inherited from our recent history or the accidentally forged traditions of modern science. Can artists, sensitive to the ecological processes that govern all life forms, help us frame our questions in a better manner or gather new insights where our stale words fail us?

In the same vein, can we also consider human societies- despite the obvious differences in scale, as being analogous in some ways to microbial colonies? Can sociological studies of how human beings operate in different contexts provide us clues to why microbes behave the way they do and with what motivations?

Even more fundamentally we need to ask whether it is productive at all to constantly frame questions about the microbial world in an anthropocentric manner without considering the breathtaking diversity and even aesthetic beauty of the microbial world? Given the fact that microbes are the oldest living organisms on Earth and every other form of life-including ours- has evolved from them is it possible we can actually learn something from them or even simply, sit back, relax and admire them?

It was in an attempt to initiate an open and multi-disciplinary discussion around these and other such questions that ReAct organised a gathering of microbiologists, artists and social activists at Wee Jasper, Australia from 5 to 9 December 2008.

Meeting at the Cooradigbee Homestead set amidst open green pastures over spectacular undulating terrain and home to some of the globe's oldest fossil finds, the participants attempted to pull together ideas from a wide range of human endeavours and evolve new images and metaphors of the dynamic relationship between microbes, human beings and other species.

The number of participants present at Cooradigbee was ten, while seven contributed through presentations on Skype or by sending documents over e-mail. In the group five were scientists, six were artists and three both scientists and artists. Three participants were in the category of opinion-builders/journalists. In addition, a number of leading and prestigious scientists expressed strong support for the dialogue and also contributed rich background material.

The meeting was of course only a modest step, in what is likely to be a long process, towards finding the answers being sought but through this effort many of us have gained the confidence to say we may indeed be asking the right questions after all.





# AN INFECTIOUS DISEASE AND ANTIMICROBIAL TIMELINE

## **TABLE 1**

## 1300s

1346 Black Death begins spreading in Europe. Ancient notions of contagion and scapegoating (of foreigners, witches and Jews for example) were predominant concepts of cause and effect.

## 1400s

**1492** Christopher Columbus initiates European-American contact, which leads to transmission of European diseases to the Americas and vice versa.

## 1500s

**1530** Girolamo Fracastoro puts forward an early version of the germ theory of disease including that syphilis was spread by 'seeds', through intimate contact.

#### 1600s

- **1627** Cinchona bark (quinine) is brought to Europe from Peru to treat malaria.
- **1683** Anton van Leeuwenhoek uses his microscopes to observe tiny animalcules (later known as bacteria) in tooth plaque.

## 1700s

**1796** Edward Jenner develops technique of vaccination, at first against smallpox, based on empirical observation.

#### 1800s

- 1848 Ignaz Semmelweis introduces antiseptic methods.
- **1854** John Snow recognises link between the spread of cholera and drinking water.
- **1860s** Louis Pasteur concludes that living organisms called "germs" cause infectious diseases. An early practical consequence was Joseph Lister's development of antisepsis by using carbolic acid to disinfect wounds.
- **1876** Robert Koch validates germ theory of disease and helps initiate the science of bacteriology with a paper pinpointing a bacterium as the cause of anthrax.
- **1880-1940s** Microbe hunting era begins with golden age of microbiology; but bacteriology became isolated from conceptual revolutions in genetic and evolutionary theory, and biologists ignored microbes.
- 1880 Louis Pasteur develops method of attenuating a virulent pathogen (for chicken cholera) so that it immunizes but does not infect; devises an anthrax vaccine in 1881 and a rabies vaccine in 1885. Charles Laveran finds malarial parasites in erythrocytes of infected people & shows that the parasite replicates in the host.
- **1890** Emil von Behring and Shibasaburo Kitasato discover diphtheria antitoxin serum, the first rational approach to therapy for infectious disease.
- 1891 Paul Ehrlich proposes that antibodies are responsible for immunity.
- **1892** The field of virology begins when Dmitri Ivanowski discovers exquisitely small pathogenic agents, later known as viruses, while searching for the cause of tobacco mosaic disease.

## 1900s

**1900** Based on work by Walter Reed, researchers show that yellow fever is caused by a virus from mosquitoes; mosquito-eradication programs are begun.

- **1905** Fritz Schaudinn and Erich Hoffmann discover bacterial cause of syphilis—Treponema pallidum.
- **1911** Francis Rous reports on a viral etiology of a cancer (Rous sarcoma virus, a rotavirus to which family HIV belongs).
- 1918-1919 Epidemic of "Spanish" flu causes at least 25 million deaths.
- **1928** Frederick Griffith discovers genetic transformation phenomenon in pneumococci, and thereby a foundation of molecular genetics and the hunt for the transforming factor that turns a harmless strain into a pathogenic one.
- 1929 Alexander Fleming reports discovering penicillin in mould.
- 1930s Electron microscopy enables visualization of internal microbial anatomy
- **1935** Gerhard Domagk synthesizes the antimetabolite Prontosil, which kills Streptococcus in mice.
- 1937 Ernst Ruska uses an electron microscope to obtain first pictures of a virus.
- **1930-1940** Florey and Chain purify penicillin and conduct successful clinical trials.
- 1941 Selman Waksman suggests the word "antibiotic" for compounds/preparations that have antimicrobial properties; 2 years later, he and colleagues discover streptomycin, the first antibiotic effective against TB, in a soil fungus.
- **1944** Oswald Avery, Colin MacLeod, and Maclyn McCarty identify DNA as the genetically active material in the pneumococcus transformation.
- **1945** Rene Dubos publishes 'The Bacterial Cell' even at this time considered audacious to biologists in proposing bacteria as cellular organisms.
- **1946** Edward Tatum & Joshua Lederberg discover 'sexual' conjugation in bacteria.



- 1900 -1950 Decline in US mortality of infectious diseases accounted for almost all the improvement in life expectancy through public health measures such as protection of food and water supplies, segregation of coughing patients, personal hygiene, childhood immunization and other science-based medical interventions. Economic growth helped by contributing to less crowded housing, improved working conditions with sick leave and better nutrition.
- **1950s** Cascade of 'Wonder drugs' such as penicillin, streptomycin, choramphenicol, teracyclines, macrolides, aminoglycosides begin a wave of confidence that by mid 1960s led to the claim that infectious microbes were conquered.
- 1952 Renato Dulbecco shows that a single virus particle can produce plaques.
- 1953 James Watson and Francis Crick reveal the double helical structure of DNA.
- Late '50s Frank Burnet enunciates clonal selection theory of the immune response.
- 1960s Methicillin and nalidixic acid synthesized; first generation cephalosporins
- 1960 Arthur Kornberg demonstrates DNA synthesis in cell-free bacterial extract. F. Jacob & J. Monod report work on genetic control of enzyme virus synthesis.
- 1970 Howard Temin and David Baltimore independently discover that certain RNA viruses use reverse transcription (RNA to reconstitute DNA) as part of their replication cycle.
- **1974 onwards** Development of second generation cephalosporins wide spectrum against gram positive and gram negative organisms
- **1975** Asilomar conference sets standards for the containment of possible biohazards from recombinant DNA experiments with microbes.
- **1979** Smallpox eradication program of WHO is completed; the world is declared free of smallpox.
- **1980 onwards** Development of third generation cephalosporins with higher activity against some gram-negative infections; carbapenem, monobactam & new quinolones.

#### 1981 onwards

A series of wake up calls begin to shatter over optimism and complacency of 1960s and 1970s: AIDS first identified as a new infectious disease by U.S. Centers for Disease Control and Prevention; increasing antibiotic resistance; new viral infections, hospital-acquired infection. US infection mortality rate doubles from steady rate of 30/100,000 from 1950s to 1982 to 60/1000,000.

- 1984 Barry Marshall shows that isolates from ulcer patients contain the bacterium later known as Helicobacter pylori, leading to a new pathogen-based etiology of ulcers.
- 1995 J. Craig Venter, Hamilton Smith, Claire Fraser & others elucidate the first complete genome sequence of a microorganism: Haemophilus influenzae.

# **2000**s

- **c. 2000** Antibiotic-resistant pathogens are spreading in many environments.
- c. 2005 Research agenda begins more seriously to look at host-parasite relations from an ecological and evolutionary perspective

**Table 1:** Adapted from Lederberg Infectious History Science 288(5464):287-293, 2000, which was reproduced in IOM (Institute of Medicine). 2009. Microbial Evolution and Co-adaptation: A tribute to the life and Scientific legacies of Joshua Lederberg, pp 58-61; with additional material from Saga, T. and Yamaguchi, K. (2009) Journal of the Medical Association of Japan (JMAJ), March/April, Vol. 52, NO.2, 103 – 108.



•••

# CHAPTER ONE

Antibiotic resistance essentially involves the ability of pathogenic bacteria to adapt or mutate in order to beat the mechanisms by which antibiotics seek to neutralise them. There are many reasons for the rise of such resistance, chief among them being the widespread use and abuse of antibiotics, in both the human and animal sectors.

Professor Otto Cars, former Director, ReAct and a leading Swedish infectious diseases specialist describes the way antibiotic resistance has emerged around the world and the global failure to contain its spread. His conclusion: Completely new strategies are needed and it is certainly time to stop treating microbes as enemies!

# A BRIEF HISTORY OF ANTIBIOTIC RESISTANCE

**Dr Otto Cars** 

problem of antibiotic resistance is something that has been around ever since the mass production of penicillin in 1942.

In his speech while accepting the Nobel Prize in 1945 Alexander Fleming himself had warned, "The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."

Even earlier, clever researchers and visionaries understood what was going to happen if anti-biotics were misused. Microbiologist René Dubos predicted that bacterial resistance to antibiotics should be expected as a consequence of bacterial adaptation.

It is difficult for us today to understand the medical revolution that followed penicillin,

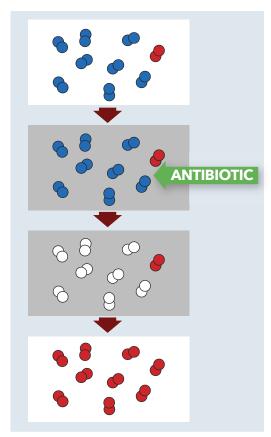
when it came into use after World War 2. The use of penicillin for example increased the chance of survival from 10% to 90%.

Antibiotics were doing so well – and many hoped that infectious diseases were cured. William Steward, the US Surgeon General in fact told the US Congress in 1969 "the time has come to close the book on infectious diseases".

And yet four decades later pneumonia remains one of the major killers in the world, especially among children. As a consequence of antibiotic resistance about 70 % of the bacteria causing neonatal sepsis in the developing world cannot be treated with the antibiotics recommended by WHO.

43.5% of children with gram-negative bloodstream infection died in a Tanzanian study as effective second line treatment was not avai-





**Image 1.1**: How resistance spreads. *Source: Otto Cars.* 

lable due to high costs. In South Asia alone one child is dying every second minute because the antibiotics given has lost their power.

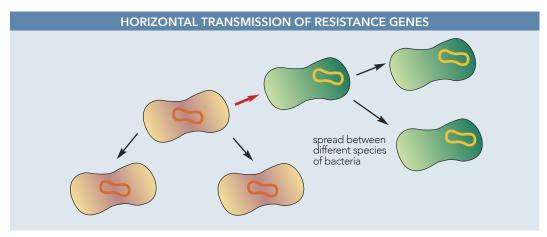
Many of the achievements of modern medicines have been brought forward under the protection of effective antibiotics. If we cannot guarantee effective control and prevention of infections, especially in vulnerable populations, many medical interventions that we take for granted today will be threatened.

## How resistance spreads

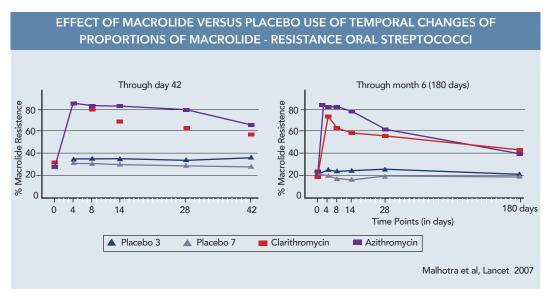
Under the pressure of antibiotics, resistant bacteria (red) will outcompete the susceptible bacteria (blue) (Image 1.1).

Not only will the resistance genes in bacteria be spread to the daughter cells during cell division, but these genes can also be spread between bacteria, i.e. in the normal gut flora, which will speed up and increase the dynamics of spread (Image 1.2).

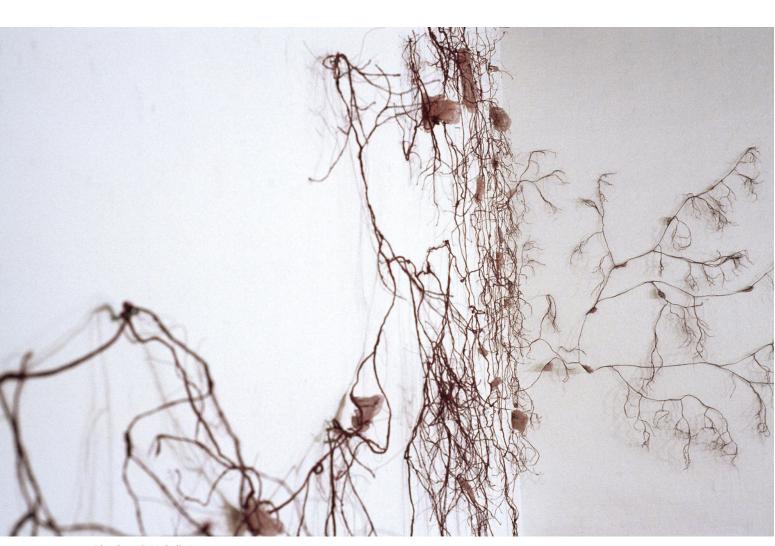
One example of the influence of antibiotics on the normal commensal flora is this study, which shows the increasing level of resistance in oral streptococci following treatment of two macrolide antibiotics (upper curves). Resistance levels rapidly increased and stayed on this high level even after 6 months. Thus, antibiotic treatment will build up a resistance gene pool in the normal flora (Image 1.3).



**Image 1.2:** Horizontal transmission of resistance genes. Source: Otto Cars.



**Image 1.3:** Effect of Macrolide versus Placebo Use on Temporal Changes of Proportion of Macrolide-Resistant Oral Streptococi.



Bloodvine 3. Michelle Day.

## Global failure to contain resistance

Despite increasing scientific literature on the threat to modern medical procedures due to antibacterial resistance the problem has still not left the conference rooms. In 2002, the WHO published a global strategy to contain antibiotic resistance, but so far the implementation of this strategy has been very weak. Although the essential components of control of antibiotic resistance have long been well known, success has been limited in changing policies and efficiently responding to the problem.

The problem is compounded by the fact that since the 1970's only two new classes of antibiotics have been brought to market. There were 16 new antibiotics created by the drug companies between 1983 and 1987 but in only 7 new ones from 1998 to 2002 and currently antibacterial drugs constitute only 1.6 per cent of all the drugs being developed. There is an urgent need for new antibiotics for major bacterial diseases.

At ReAct we are striving to bring all stakeholders together, including scientists, health professionals and civil society. The core action areas of ReAct include:

- Advocacy and communication, which makes the impact of antibiotic resistance and the need for new drugs more visible to policy makers and the public;
- Innovation to explore ways to stimulate needs-driven research and development of new anti-bacterials;
- Gap analysis to identify antibacterial compounds in the pipeline versus resistance trends;
- Networking and collaboration to stimulate, organize and support political, professional and community action to combat antibiotic resistance around the world;
- Promoting new ways of approaching the problem of antibiotic resistance including emphasis on the balance between microbes and man and changing the war metaphor.

Ultimately we need to change the current paradigm in medicine, which looks upon bacteria as our enemies. A small proportion of the bacteria is causing harm, most of them protect us. The time has come for us to be friends.



# CHAPTER TWO

Not many people realize the sheer scale and diversity of microbial life on our planet. Not only are there anywhere from 5 to 10 million species of bacteria alone but micro-organisms make up something like 80 per cent of all the biomass on Earth. Further, in 1997, a study calculated that their economic contribution annually amounts to US\$35 trillion every year. Indeed no other species would exist at all if not for the beneficial activities of microbes.

Mary Murray and Satya Sivaraman talk to Professor Michael Gillings, an evolutionary biologist at Macquarie University in Sydney, Australia, about the fascinating world of microbes where he argues for the need to take a fresh look at current approaches to the phenomenon of antibiotic resistance.

# MOVING TOWARDS MICROBIAL DETENTE

Q: How useful do you perceive the war metaphor as a way of understanding our relationships with bacteria?

**Prof Gillings:** We have the common perception that bacteria are the enemy. In fact, there are only some bacteria, in fact very, very few bacteria that are dangerous to humans. The vast, overwhelming majority of bacteria are actually good for us. If bacteria were to disappear from human environments, everything would close down - everything would stop. Our health is dependent on the bacteria in us and on us. Our food production is dependent on bacteria: in fermentation, to make bread, coffee, chocolate and beer etc. Almost everything we eat has bacterial or fungal action on it before we eat it. All the food crops in the ground rely on fungi that are what we call symbionts with the plants. So, to me, the war metaphor is not a good one because it casts microorganisms as the enemy when they are extremely beneficial for humans and the rest of the organisms on the planet.

Q: What are the new ways of seeing microbes that are emerging to understand what they are doing and how they are working?

**Prof Gillings:** Firstly, it is only in the last fifteen years that we have realized exactly how many microorganisms there are around. To give you an example, we have named 5000 bacterial species but we now suspect that there could be anything from 5 million to 100 million bacterial species. We also have begun to realise that bacteria can do anything. They can live at 120 degrees Celsius, they can grow in frozen snow, they can live in solid rock three kilometers down underneath our feet, they can live in cooling pipes of nuclear power plants, and they can survive for tens of millions of years in salt crystals.

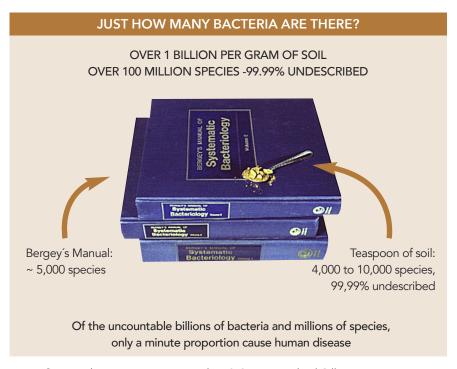


Image 2.1: Just how many Bacteria are there?. Source: Michael Gillings.

One of the things we need to bear in mind is that the planet as a whole is driven by cycling of nutrients -like sulphur, phosphorous, nitrogen and carbon. Microorganisms supply most of these services such as the oxygen we breathe; the recycling of cellulose into usable forms of carbon; the cycling of sulphur; the production of nitrogen for plant growth and fertilization. These things are done by microorganisms. If you take all these services – called eco-system services – and add up the value of these to humans, it will add up to something like US\$35 trillion a year. This is three times the gross domestic product of all the countries in the whole world. And, surprisingly, that estimate was first made only in 1997. Microorganisms are the good guys.

## MICROORGANISMS PROVIDE FREE ECOSYSTEM SERVICES THAT RUN THE PLANET'S ATMOSPHERIC AND BIOGEOCHEMICAL CYCLES Ecosystem service \$ billion/year Erosion control 576 Soil formation 53 Biological control 417 Food production 1386 1341 Regulation of atmospheric gases Wate treatment 2277 Nutrient eyeling 17075 Microbial contributions to each of these services are a major proportion of the total activity (After Constanza et al. Nature 387:253-260)

**Image 2.2:** Microorganisms perform essential ecosystem processes. Source: Michael Gillings.

# Q: What kind of 'agreements' with microorganisms do we need to move towards?

**Prof Gillings:** One of the first things we need to realise is that anyone launching a war on microbes is going to lose. There is just no way around that. There are so many of them, they are so diverse, they have such high population numbers and rapid generation times that whatever we do to try and control them, or force our will on microorganisms, it is not going to work. What we have to do is to learn to get along with microorganisms, in particular, to try to understand their biology, their ecology and their evolution. In some ways, it is similar to warring countries. If two countries go to war, essentially both of them lose.

I am not suggesting that we should ignore the fact that microorganisms sometimes kill people. But what we need to do is to understand how the process



proceeds and understand the ecological and evolutionary pressures on those microorganisms so as to come to a more mutually agreeable détente. I think detente is a good word for it.

Q: You were telling us about the natural immunity of human beings to pathogenic bacteria. What happened to that? Why has that changed?

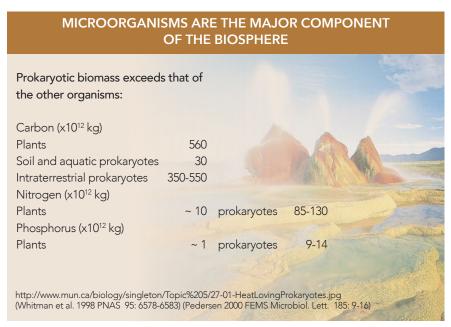
Prof Gillings: Okay. That is another interesting question. Humans have diversity in their DNA, which means, more or less, that some humans are susceptible to some infections and parasites and some are not. There is usually enough diversity in human population such that if there is a pandemic that wiped out hundreds of millions of people there would always be people left over who were partly resistant or completely resistant to that disease. However, there is innate immunity and there is acquired immunity. Acquired immunity develops when you have actually been exposed to diseases and your immune system recognises these diseases as foreign bodies and then mounts a defence against them. It is an extraordinarily complex, beautifully tuned and changing system that evolved along with the vertebrates.

One of the problems we have is that we are actually not dirty enough. Growing up in too clean an environment means that the immune system, one could say, is searching for things to react to. It has not had enough exercise to

mount the immune responses it is supposed to. So, it mounts inappropriate responses instead. So, allergies, asthma, and so on, are the result. The immune system is reacting to things it shouldn't. It may be that, like peanut hypersensitivity, and sensitivity to shellfish, to nickel, milk and so on, our immune systems are not sufficiently trained early enough. So when babies are eating snails and shovelling dirt into their mouth, it is probably a good thing.

Q: This takes us to an interesting paradox. On the one hand, we come emphasise cleanliness too much and in other places the fact remains that people are exposed to infectious diseases. In what way can we reduce infections?

Prof Gillings: We have to find a balance between being incredibly sterile in our lives and understanding enough about the transmission of disease to prevent transmission from obvious sources. And one of the ways of looking at this is to look at the difference between the developed and the less developed world. It is true that cholera, dysentery, typhoid, diarrhoea and cryptosporidium can sweep through communities, but mainly because of poor water quality. In fact, this is something that we are going to have to address very soon because with global climate change, the rise in human population and the exploitation of groundwater, the sources of clean water are already shrinking and are probably below what is sustainable for humans.



**Image 2.3:** Microorganisms are the major component of the biosphere. Source: Michael Gillings.

# Q: Imagining that they can think, what do you think that the microorganisms will be thinking about us?

**Prof Gillings:** There is no doubt that humans have provided new niches for the microorganisms to colonise. There are six and a half billion humans on the planet, which makes for a lot of human-associated microorganisms. And also our manipulation of the environment creates ideal conditions for some microorganisms and lowers concentration of others. For instance, there is a big difference in the composition of microbial communities of farmlands in contrast to adjacent forestland. We have done quite a lot of things to the planet that change the way the microorganisms work. One is actually the industrial fixation

of nitrogen, called the Haber process, which takes atmospheric nitrogen and makes fertilizer. Humans now contribute a very large amount of fixed nitrogen in the form nitrates and things like that to the world's ecosystems and, as a result, I imagine that the bacteria that used to do that job are being undercut. That would have a knock-on effect.

I find it hard to answer your question about how bacteria would think about something that is being done. I prefer to think in terms of evolution. What new evolutionary opportunities do the human manipulations of the earth offer the bacteria? We offer lots and lots. Because we create thousands, if not hundreds of thousands, of new chemicals that have never been seen on our planet before. Wherever we have done that, we find that there are bacteria that eventually figure out a way to utilize those chemicals. We have created nutrient-rich environments of all sorts, simply by washing our cars and by putting detergents down the sinks and by spilling oil and by creating piles of trash and plastics. These are new niches for bacteria.

Q: You work on the elements that bacteria use to share resistance to antibiotics. Can you make this come alive for us? How does it really work?

**Prof Gillings:**Let us start with outlining the differences between how we reproduce and how the bacteria reproduce and the way the genes move between the two. In humans, you get

all your genes from your mother and father. Whatever genes they have, you take half of your genes from your mother and half from the father. That is called vertical inheritance. Bacteria do it differently. To start with, when the bacterium divides, it divides into two identical cells, exactly the same as the parent. Those two identical cells can also do something else. They can sample genes from the general environment. So they can capture bits of DNA from members of their own species, from members of different species, from plant DNA, or animal DNA, or virus DNA. They take these pieces of DNA and they put them into their own chromosomes - into their own DNA. And if it turns out that the new species' DNA actually brings some kind of advantage, then this bacteria does well. It helps them do something else it couldn't do before.

But knowing this does not really help understand the real impact of this. So we have to think about the scale of this. In every teaspoon of soil there are a billion bacteria, there are ten thousand different species and they are all exchanging DNA. So it is a fluid situation. Every single cell in that billion is probably different in some way. Imagine one of those cells has a gene that allows it to survive toluene or xylene or some such nasty chemical. All other bacteria die and that particular bacterium survives and fills that gram of soil. Somewhere else in this soil something similar is going on. In this way, the agents of destruction that we come across in the environment help 'select' the bacteria that can survive them.

So that is how antibiotic resistance arises. Somewhere there is a gene in a bacterium that is capable of degrading the antibiotic, or pumping it out of the cell or chopping it in two or making a cell membrane that doesn't absorb the antibiotic. All these would cause resistance to an antibiotic. So we use an antibiotic and it so happens that a human pathogen has picked up that particular gene, then it becomes an antibiotic resistant pathogen and it continues to infect the poor individual who is sick and the antibiotic makes no difference. It doesn't kill the pathogen at all.

Now, imagine there is a lot of that particular pathogen. Say it is in a hospital where there are a lot of sick people and there are a lot of people running between sick people. The bacteria get spread around. It is highly likely that resistant genes are going to spread around among different people. They may not cause disease. People need not necessarily become sick but people carry the genes around. Now imagine that the gene is there in the hospital and that it has quite a high frequency - because there is a lot of that particular bacterium around. So, now it is capable of transmitting the same gene to unrelated bacteria. New pathogens. So, the antibiotic resistance spreads from Pseudomonas, say, to golden staph to Acinetobacter, to something else, and so on. We get many resistant strains appearing. Where does the resistance come from? It comes from somewhere in the general environment, somewhere from the vast hyper diverse pool of bacteria and their genes that are capable of doing all these strange things. You know if there are a billion bacteria in a gram of soil, then there are a billion cells that all have genes that are interesting. Now take ten tones of soil. How many genes are there, now? Now take all the soil on the planet. How many genes are there now? Uncountable billions of different genes doing different things. So, it is almost certain that every time we invent something to kill a bacterium, there is already going to be some bacterium somewhere that can do something about it.

And what we are doing while we are using an antibiotic or a disinfectant is actually promoting the selection of those rare events such that we now have organisms that are resistant to five, six, ten antibiotics all at once. The resistance to each one was picked up from different genes from different places.

# Q: Is it ever possible to block antibiotic resistance forever?

Prof Gillings: There are a couple of things we can do. Firstly, we can realise that any individual antibiotic or disinfectant has a shelf life. It will only work so long. Gradually, more and more things will become resistant to it. And, eventually, it will cease to work. So, we need to use those items really carefully. We need to think about how to use them in a way that minimises the appearance of resistance. In order to do that, we need to understand how resistance arises. Where the genes are coming from and where they are going? How we are using it?

How long we are using it? In what context? And for what disease? And that is the highest priority: to preserve what we have got while we are to discover new agents and then preserve them. We can stretch this period out and move carefully from one compound to another and buy time for the difficult task of discovering new compounds before the others have worn out.

The other thing we could do is to think about the ways of controlling bacteria by using other organisms that evolve faster than the bacteria. Using viruses that kill bacteria is one way of doing that. Viruses have a faster rate of evolution than bacteria. The virus changes quicker than the bacteria, and so you can use what is called phage therapy.

We could also just accept that we are going to have tragedies. People are going to die of infectious diseases and in some ways we can do nothing about it.

Q: It seems difficult for people to see that by always choosing an antibiotic as the option, we are limiting our options. What about the search for new antibiotics? We see this as our main priority -is this wise?

**Prof Gillings:** I would say, instead, that the use of antibiotics should be the last resort. There are a couple of important points to make here. One is that we use antibiotics frivolously. We use them for conditions that are actually not bacterial at all. We use them in our domestic animals and plants. We used to spray our apple trees with antibiotics to control bacterial diseases. That is just a disaster waiting to happen. Take the use of antibiotics in aquaculture for instance, where you grow prawns or fish. It is one thing to feed antibiotic to an individual fish to make it better. It is quite another thing to recklessly put antibiotic into the waters. You are going to get resistance straightaway. It is inevitable. The appropriate use of antibiotics is essential.

The other point that I would like to make is a social one. Antibiotic resistance is a global problem. It will be one of the major obstacles facing human medicine and disease control over the next 20 years. So everyone has to do something about it. But at the individual level, would you choose not to use an antibiotic because of the small chance that, in you, it might develop drug resistance, which



is going to cause more global problems? You are probably going to choose to use it. This distinction between private and public good is an important one.

Q: Can you inspire us? How will we go about developing that public consciousness, vision even? Is quorum-sensing a good metaphor for this? How could this be a metaphor?

Prof Gillings: Quorum-sensing is about bacterial communication. People always thought that bacteria were single independent cells just by themselves and that you could understand everything about bacteria by understanding a single cell. That is analogous to trying to understand everything about human communities from understanding the actions of one single person. People don't think that bacteria talk to each other. But it turns out that they can. They produce small signalling molecules that tell other bacteria, "Hey, we are here. I belong to the same group as you". But they can mix with other types also. So, they know the other bacteria of different types are there as well. This allows a certain amount of cohesion between bacterial cells, there is a certain amount of cooperation as well. It is also used for antagonism. But often it is used to coordinate the activities of individuals that belong to a single species and to coordinate groups of species into things such as bio-films, which are complex communities of different types of microorganisms, such as slime on rocks etc. Most people would know bio-films as plaque on teeth. The fuzzy stuff on teeth is actually bacterial bio-films made up of huge number of organisms interacting in particular ways. Some 300 different species may be there, building upon each other and attached to each other in different ways, and in the process they are communicating. If you ask me what we can learn from bacteria, about generating public good and private good at the same time, it is simply communication. It is simply educating people and talking about issues and exchanging information about different points of view. Communication is the way forward.

Q: If you were an artist and if you were to look at the world of microbes, what would you see? Is theirs a world beyond utility?

Prof Gillings: Microbes are organisms and absolutely beautiful. The problem is that we can't see them. So we don't necessarily appreciate their beauty. If you just get a microscope or, if you are lucky, a scanning electron microscope, you can see fantastic scenes beautiful, giant, blue amoeba and amazing diatoms. One of the best examples are diatoms. Before television was invented, people used to do a lot of interesting things to socialize, one of which was to collect diatoms. Diatoms are single celled marine plants, essentially, that have beautiful, highly complex silicon jewel-like structures. In Victorian times people collected diatoms like microscopic flowers and arranged them beautifully on microscope slides. They would visit each other to compare the beauty. They look like stained glass windows in baroque cathedrals. There



**Image 2.4:** Microorganisms are essential for food production. Source: Michael Gillings.

are millions of beautiful and tiny cell structures in microscopic images. It is a sad commentary on modern humans that our use for diatoms is mainly as diatomaceous earth filters in swimming pools and as kitty litter. So, every time you empty the cat litter you should imagine that there are thousands and millions of microscopic jewels in there, tiny cell structures of dead diatoms as beautiful as any stained glass window.

# Q: Even if we can't ordinarily see that beauty, do you think that we could learn to feel their beauty?

**Prof Gillings:** That is an interesting idea. I would say that we can see beautiful microorganisms all the time. It is just we don't know that. For instance, a good example is lichens which are examples of cooperation between a fungus and a photosynthetic green algae or cyanobacterium - two microorganisms cooperating to produce one organism. We see lichens everywhere. Anytime you walk on any rock you are actually walking on a living surface of microorganisms. Here at Macquarie University in Sydney we are on Hawkesbury sandstone. Unless you physically break a piece of sandstone off, you don't actually see rock. What you see is a coating of lichens and microorganisms. Even the surface of soil is held together by microbial mats. Most people don't like slime but I think there is a certain beauty in green tendrils of cyanobacteria in streams. And, people have photographed and drawn the fruiting bodies of fungi and mushrooms for hundreds of years if not thousands.

Q: Perhaps now is a moment in our social history for scientists and artists to cooperate together to throw more light on the microbial world.

**Prof Gillings:** Well, I never thought there was a difference between art and science!

# CHAPTER THREE

Most microbes (bacteria, archaea and eukarya) are single celled organisms. (For simplicity of discussion here, we will include viruses in this group, although they are not cellular) From the origin of life on Earth, perhaps 3.5 billion years ago, until about 900 million years ago when the first multicellular organisms arose, all life was microbial. It stands to reason therefore, that if one wants to piece together what happened in those first 2.5 billion years of evolution—many of the most interesting chapters of the story—one must study microbes. And microbes still rule the planet: the vast majority of the diversity of life on Earth today is microbial. Microbes occupy every possible niche, from the high atmosphere to the deep ocean and the Earth's crust, including many regions that cannot yet be accessed for study. Biologists have known these facts for a long time, but very recently they have come to realize that their previous estimate of microbial diversity has been far, far too low.

Why the gross underestimate? Traditional (i.e. twentieth century) analytical techniques required that microbes first be grown in pure culture (i.e. cultured) in the laboratory. Organisms that could not be readily cultured were therefore not studied at all unless they posed some significant known threat to human health or commerce. Now however, thanks to the recent advent of industrial-strength molecular sequencing and analysis technologies, it is possible to collect samples from the environment and survey their diversity directly without having to culture them. This new branch of science is known as metagenomics. Metagenomic surveys have revealed that traditional culture-based methods have overlooked more than 99% of the microbes that inhabit the Earth today.

# MICROBES: COOPERATION AND COMMUNICATION

#### **Linda Blackall**

Australian Institute of Marine Science Marine Microbes and Symbioses

MICROBES were the first species on earth and the only original life forms. As the atmosphere changed due to production of oxygen from photosynthesis by cyanobacteria, the more complex eukaryotic species began to evolve.

This diagram shows the evolutionary pathways. The progenitor or origin of life on earth is difficult to be confident of, but the lineages presented in blue (bacteria) and red (archaea) are comprised solely of microbes. Organisms represented in green are the eukaryotic organisms, which account for most generally known life forms on earth. The macroscopic organisms, bracketed, are visible as life forms = plants, animals and fungi. However the microorganisms are hugely more abundant and metabolically more relevant - but as we can't see them we rarely think about them. Microorganisms (sometimes referred to as "prokaryotes" = bacteria and archaea), due to their abundance, ubiquity and panoramic biochemical transformation capacities impact the ENTIRE biosphere. They are present in virtually all of Earth's environments, including some of the most extreme, from acidic lakes to the deepest oceans, and from frozen environments to hydrothermal vents. Prokaryotes represent more than 90% of the biomass in the marine environment. They actively engage in many marine symbioses. They are tremendously important – THEY EXIST WHEREEVER LIFE EXISTS.

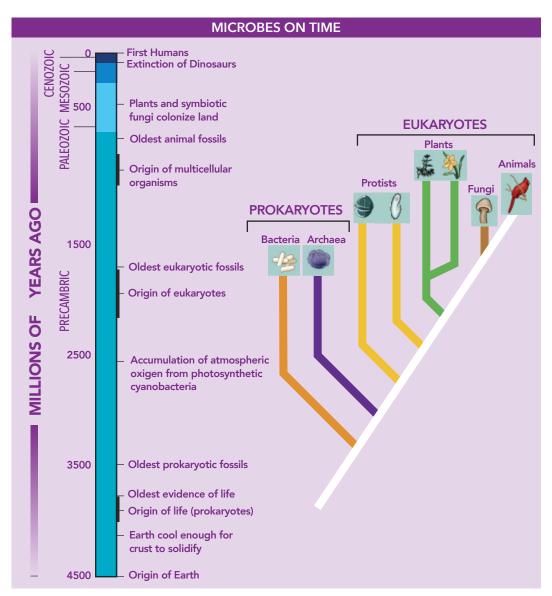
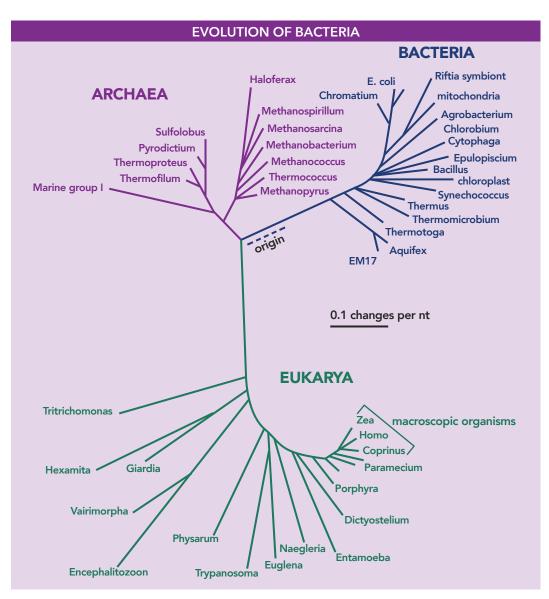
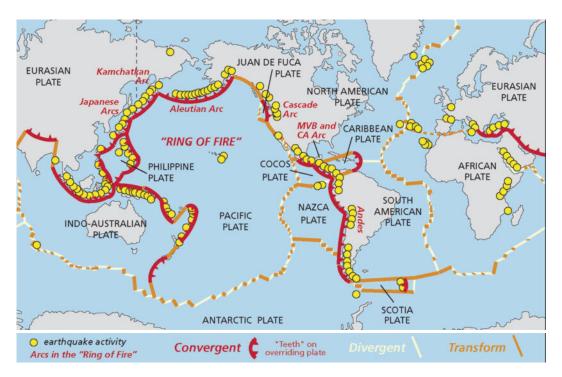


Image 3.1: Microbes were the first species on Earth. Source: Based on Books/Cole. Cengage learning. Biodiversity and Evolution. Accessed Sept. 3, 2011 via teachers.redclay.k12.de.us/william.baker/.../biodiv.../chapter4%20pp.ppt



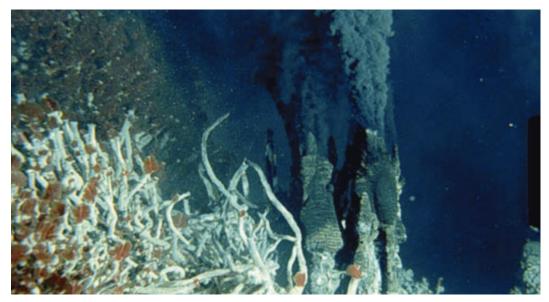
**Image 3.2:** Evolution of micro and macroscopic organisms. Source: Linda Blackall based on Pace, N.R. (1997), A Molecular View of Microbial Diversity and the Biosphere, Science: 276 734-740.



Microorganisms are active around tectonic plates – in hydrothermal vents called 'black smokers' (below)– where there is no light – but there is evidence of life.

The world's hottest animal is the Pompeii worm (Alvinella pompejana) - a deep-sea polychaete worm. It tolerates extremely high temps and sulfur levels.

Giant tube worms (Riftia pachyptila) live over 2 km deep on the floor of the Pacific Ocean near black smokers and can tolerate extremely high temperatures and sulfur levels. They can grow up to 2.4 metres.



**Image 3.4:** Hydrothermal vents at the bottom of the sea. Source: Linda Blackall internet reference accessed September 3, 2011 http://www.google.com.au/imgres?imgurl=http://www.dailygalaxy.com/photos/uncategorized/2008/08/04/black\_smoker.jpg&imgrefurl=http://www.dailygalaxy.com/my\_weblog/2008/08/extreme



**Image 3.5:** The Pompeii worm. Source: Linda Blackall. http://www.ceoe.udel.edu/ex treme2002/creatures/pompeiiworm/



**Image 3.6:** Giant tube worms. Source: Linda Blackall http://www.expeditions.udel.edu/extreme08/creature/tube-worms/

How do cells know what they should do?

Animal and plant cells have hormones, which are the communicating agents. Bacteria have these also. Bacteria communicate between species, across genera and with their hosts in a sophisticated manner using chemical signalling.

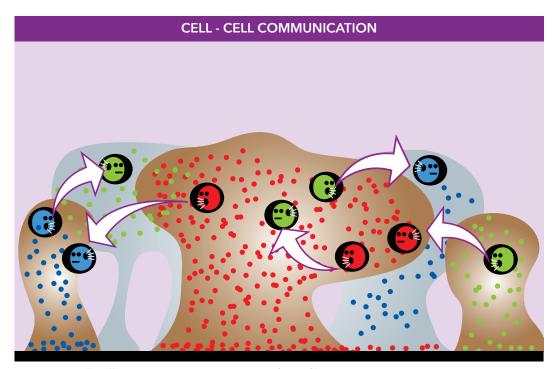


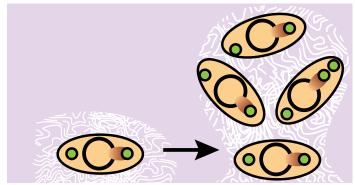
Image 3.7: Cell-Cell Communication. Source: Center for Biofilm Engineering, Montana

Quorum-sensing, or cell-to-cell signalling, in bacteria is done through the regulation of their gene expression in response to fluctuations in cell-population density.





**Image 3.8:** Bacteria produce shiny material to enable communication Source: Linda Blackall from Center for Biofilm Engineering, Montana.



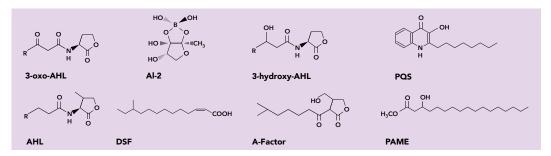
**Image 3.9:** Shiny material helps bacteria stick to surfaces, communicate ... Source: Linda Blackall from Center for Biofilm Engineering, Montana

Bacteria can't communicate by quorum sensing if there are not enough of them present together. They induce their genes to produce a shiny material that sticks on the cell surface that enables them to communicate.

As the abundance of bacteria increases, the amount of shiny 'stuff' increases to help them stick to surfaces. This communication helps them to stick to a surface and leave when needed



**Image 3.10:** : ... and leave when needed. Source: Linda Blackall from Center for Biofilm Engineering, Montana. There are many chemicals involved in bacterial signalling and some of their chemical structures have been identified.



**Image 3.11:** Structures of some quorum sensing signalling molecules. Source: Linda Blackall from Williams et al. Phil Trans R Soc B 2007

There are many chemicals involved in bacterial signalling and some of their chemical structures have been identified.

There are three sorts of quorum sensing communications known. The first language is called Autoinducer-1 (Al-1). It is genetic and was discovered in 1990. It is active in intra-species communication. These molecules are acyl homoserine lactones and are species specific. They are responsible for functions such as biofilm formation, motility, virulence, antibiotic production, bioluminescence, root nodulation, symbiosis and pigment production.

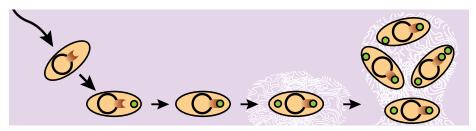
The second language, Autoinducer-2 (AI-2), is involved in interspecies communication and responsible for functions such as bioluminescence and virulence. At least two chemicals have been identified. Vibrio harveyi uses a borate diester and Salmonella typhimurium uses one without borate (Williams et al., (2007), Bacterial conversations: talking, listening and eavesdropping. An introduction. Phil Trans R Soc B, 362, 1115-1117; Shiner et al. FEMS Microbiol Rev 2005.)

The third language, Autoinducer-3 (Al-3), has been identified but the chemical composition is not known. It is responsible for inter-kingdom communication – from bacteria to eukarya. There is an aromatic signalling system that cross-signals with the eukaryotic hormones epinephrine and/or norepinephrine. (Hughes & Sperandio Nature Rev Microbiol 2008)

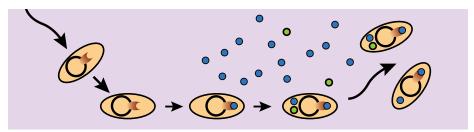
Importantly, molecules have been found which 'mimic' the inducer molecules and so confuse normal 'quorum sensing' mechanisms of bacteria. This was discovered in some marine algae, which do not grow biofilms.

The molecules, which mimic autoinducers are of three types. AHL is a halogenated furanone found in the red alga Delisea pulchra. AI-2 inducers are like epinephrine and AI-3 inducers like norepinephrine.

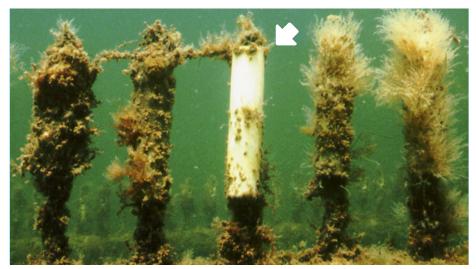
The effect of AHL as an inhibitor of biofilm growth by Delisea pulchra is clearly seen in an experiment on extruded polymer pipes underwater.



**Image 3.12:** Normal "Quorum Sensing". Source: Linda Blackall from Center for Biofilm Engineering, Montana



**Image 3.13:** Molecular mimics (blue) of the inducers (green) confuse the bacteria. Source: Linda Blackall from Center for Biofilm Engineering, Montana



**Image 3.14:** Effect of AHL as an inhibitor of biofilm growth. Source: Linda Blackall from Givskov et al. J Bacteriol 1996

The key point here is that there is no killing attempted – only confusion. Therefore there is no motivation for mutation by the bacteria to avoid this strategy. If one does not attempt to kill them, they do not feel the need to resist.

The phenotype of bacteria in biofilm format is more resistant to antibiotics than bacteria in the blood. The future of prosthesis surgery is under threat from resistant bacteria. Therefore one possibility is to put new compounds into the prosthesis to confuse growth in the biofilm.

There is no mechanism by which the bacteria resist confusion to their communication. This research is already being applied in contact lens - a non- invasive application. Because prostheses applications are internal to the blood, the requirements are more rigorous and it takes much longer to demonstrate efficacy.

There are many symbioses in nature – either horizontal or vertical.

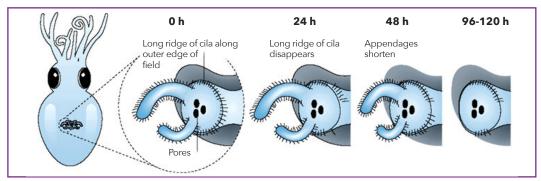
Horizontal symbioses operate between organisms in the environment. Vertical symbioses

HOST	SYMBIONT	TRANSMISSION*
Porifera		
Various sponges	Cyanobacteria (bacteriocytes)	Vertical
Aplysina cavernicola (mesohyl)	Bacteria	Horizontal
Cnidaria		
Corals (gastrodermis)	Symbiodinium spp.	Horizontal/vertical
Vestimentifera		
Riftia Pachyptila (trophosome)	Sulphide-oxidizing bacteria	Horizontal
Mollusca		
Vesycomid clams (gills)	Sulphide-oxidizing bacteria	Vertical
Bathymodiolus spp. (gills)	Sulphide-oxidizing bacteria	Horizontal
Eupryma scolopes (ligth organ)	Vibrio fischeri	Horizontal
Squids (accessory nidamental gland)	Bacteria	Horizontal
Arthropoda		
Aphids (bacteriome)	Buchnera spp.	Vertical
Insects (reproductive tissues	Wlbachia spp.	Vertical
Termites (hindgut)	Bacteria/protist	Horizontal
Chordata		
Mus musculus (alimentary canal)	Bacteria/protist	Horizontal
Bos spp. (cow rumen)	Bacteria/protist	Horizontal
Homo sapiens (alimentary canal; skin)	Bacteria/protist	Horizontal

**Image 3.15:** Examples of horizontal and vertical symbioses in nature. Source: Linda Blackall (from Hughes & Sperandio, 2008)



**Image 3.16:** The Hawaiian bob-tail squid lives in symbiosis with the bacteria Vibrio fischeri which makes light in the squid's sight organ to prevent it casting a shadow on full moonlight nights. Source: Monterey Bay Aquarium http://www.montereybayaquarium.org/animal-guide/octopus-and-kin/hawaiian-bobtail-squid



**Image 3.17:** The appendage on the squid alters in shape to allow the bacteria, v.fischeri, to colonise it over a 128 hour period. Source: Linda Blackall from Nyholm, McFall-Ngai, Ruby

are transferred in ova or sperm from one generation to another.

One of the most fascinating horizontal symboses is the case of the squid (Euprymna scolopes) and the bacterium Vibrio fischeri. This tiny Hawaiian bob-tail squid eats shrimp at night and buries itself in the sand during the day.

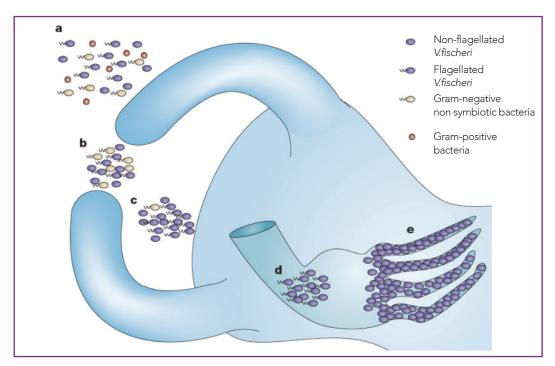
There is a light organ about 5cm in the sight organ of this squid. A bacterium, V. fischeri, lives there and makes light so that on full moonlit nights, the squid does not cast a shadow. The light organ evolved for this function.

Colonisation by the bacteria occurs over a 128 hour period.

First the appendage on the squid alters in shape and loses its cilia. Then the flagellated V. fischeri, along with flagellated gram-negative non-symbiotic bacteria are 'sorted' out somehow as they approach the appendage of the squid.

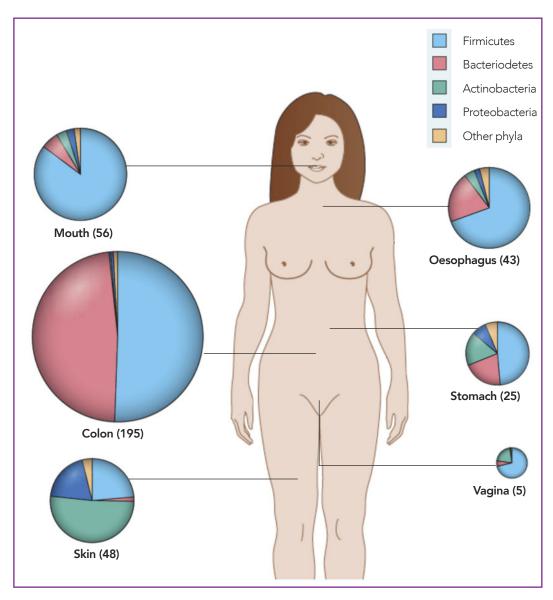
Only V fischeri can enter the opening and then they lose their tails and colonisation and reproduction occurs in the light organ. It is a complex communication between the two organisms and the mechanisms are unsolved.

The induction of symbiont growth is harmonized to the day night cycle.



**Image 3.18:** : Only the bacteria V.fischeri can enter the squid opening by a complex communication process whose mechanism is unknown. Source: Linda Blackall from Nyholm, McFall-Ngai, Ruby

The human body would not survive without bacteria – there are large numbers of bacteria in and on the body.



**Image 3.19:** Image 3.19: The human body is colonised by many types of bacteria and would not survive without them. Source: Linda Blackall from Dethlefson et al. Nature 2007

Examples of inter-kingdom signalling include:

- AHLs (furnanone structure) which promote cell death in mammalian cells and some also suppress the immune system;
- Furanaones produced by algae;
- Bacteria with adrenergic receptors;
- Zoospores of the marine alga Ulva intestinalis which respond to bacterial quorum-sensing autoinducers;
- Rhyzobium-legume association is driven by AHLs.
- The large ecosystem the Coral Holobiont is made up of coral animals, photosynthetic plants AND bacteria, archea, funguses and viruses.



Image 3.20: Image 3.20: The Coral Holobiant.Source: Linda Blackall

I am a passionate believer in alternatives.

Microbes are the smartest things on earth. They are everywhere. There are other ways to control infection using the normal microbiota of the gut. But there is only partial knowledge of the gut's microbiome. For example obese people have a different species relationship to lean people. The natural microbiota is important in maintaining balances to reduce infection, the need for antibiotics and antibiotic resistance.



#### CHAPTER FOUR

The use of antibiotics is not the only option when it comes to tackling infectious diseases. Long before the advent of these 'magic pills' measures to improve sanitation and public health systems helped to dramatically lower the impact of epidemics on human populations.

Professor Robert Clancy, in his presentation here, outlines the way scientists and policy makers worked together in the early part of the twentieth century to tackle the plague and helped save lives, costs and prevent social disruption.

An immunologist by profession and passion Prof. Clancy also argues for the need to improve host immunity in order to keep infectious diseases in check. This, he says, calls for paying closer attention to the processes by which the human immune system works and what all it takes to maintain the balance between our defences and pressure on it from pathogenic microbes.

#### 4.1

### WAR, DEMOCRACY, CIVIL DISOBEDIENCE OF INFECTIOUS DISEASE

#### **Robert Clancy**

Professor of Pathology, Newcastle University and Director, Hunter Immunology, Newcastle Australia.

has always been the nemesis of mankind. In Sydney, Australia, in 1900 the top four causes of death were tuberculosis, pneumonia, typhoid fever and violence (the only non-infectious cause). It is only in the 'window' of the last 50 years that public health measures, immunisation and antibiotics have combined to reduce the burden of infection in the western world. It is salutatory for us to remember that within the space of one generation, antibiotics as armament against infection have come and have begun to go with resistance now appearing in some instances against every known antibiotic.

It is a long time since a new antibiotic class has been identified and the numerous potential strategies available to minimise the use of antibiotics and thus delay the ultimate limitations of their use, must be aggressively identified and used.

#### **PROCESSES OF INFECTION**

Clinical infection is a particular outcome of a relationship that involves two opposing pressures – the pressure of microbes versus the pressure of host resistance. In the scenario of antibiotic resistance, so often this simple concept of clinical infection is forgotten and certainly in practice most appear to push their own ideas without considering the whole.

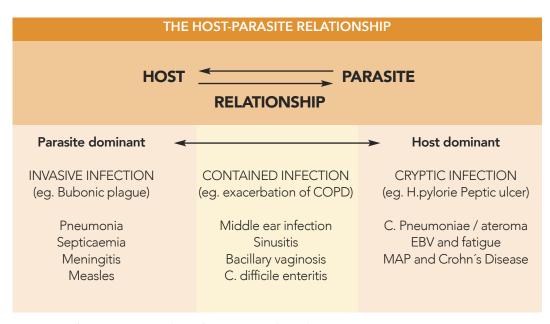


Image 4.1: The Host-Parasite Relationship. Source: Robert Clancy



This slide above outlines the relationship between the host and the parasite (or infecting microbe) and indicates a spectrum of clinical conditions determined by the relative strengths of these two pressures. When a highly invasive vigorous bacteria infects at a time when there is little or no host reaction, overwhelming invasive infection occurs. This is the classic infection of epidemics that has

dominated man's history. Systemic infections can rapidly overwhelm the host leading to early death. This is the case, for example, when bacteria multiply within the blood system causing septicaemia. Usually the invading organism is a single microbial species.

Infection has become a subtler foe over time. Many infections seen today are complex infections where there is no simple association between easily grown bacteria and a clinical disease with 'normal' host protection. Some examples are surface or mucosal infections, which I call contained infections where abnormal mucosal colonisation by bacteria occurs secondary to damaged mucosa. Examples are the respiratory tract, (acute exacerbations of Chronic Obstructive Airways Disease (COPD), the gut (hospital and community acquired super C.difficile). These non-invasive infections differ from systemic infections in both the nature of the organism and the mechanism of host protection. The classic rules of antibiotic therapy don't apply, as bacteria are not eradicated. The underlying damage remains and repeated antibiotic used selects out the resistant bacteria, which then colonise the damaged mucosa.

At the other end of the spectrum, infection can contribute to disease in ways not previously thought of as 'infectious'. The host response can be so complicated and so overwhelming that the parasite may not be easy to find. I have called this cryptic infection where the host plays a complex role. How long did it take to recognise that peptic ulcer disease was in fact a cryptic infection by Helicobacter pylori? Still we argue about the role of Chlamydia infection in the generation of atheroma and coronary artery disease, and few really understand the role of the glandular fever (Epstein Bar Virus) virus infection in individuals with impaired performance or relapsing fatigue. The list goes on.

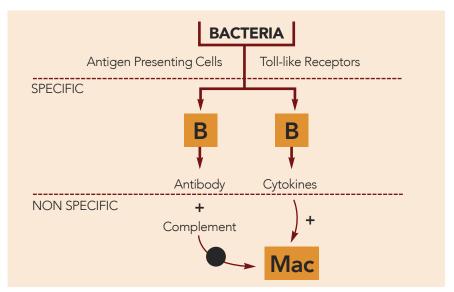
# HOW DOES THE HOST RESPOND TO PROTECT ITSELF?

The protective host response must be assembled and activated very quickly. The mechanisms differ slightly for the different types of infection mentioned above. But in general there is a specific response, which activates a nonspecific response. Why? Because antibodies are specific and sensitive but few in number, So for every different bacteria, the 'few' relevant specific antibodies activate or recruit a series of non-specific factors and cells to ensure rapid and adequate destruction of bacteria. The way this works is that bacteria have specific markers on their surface called antigens. These antigens stimulate the production of protective antibodies (called IgG antibodies), which immediately activate the bacterial destruction process (through phagocytes and other mechanisms). So the process is begun when the IgG antibodies bind to the antigens on the bacterial surface and begin the guick delivery of mechanisms to destroy the bacteria.

# WHAT DOES THIS LOOK LIKE INSIDE THE CELLS?

This diagram above in a simplistic fashion summarises the way in which the body specifically responds to a potentially invading organism. It emphasises the role of antigen presenting cells (APC) and receptors on the surface of the

APC's, called Toll-like receptors. The antigen presenting cells process the bacteria into a palatable antigenic form. These palatable bacteria, together with self-communicating molecules on the surface of the APC, can then be presented to specific receptors on B lymphocytes which will go on to produce antibody. They are also presented to T lymphocytes, which will produce mediators called cyto-kines (that in turn will activate phagocytic macrophages (MAC) which ingest and destroy bacteria). Antibodies produced from the B cells facilitate this uptake of bacteria but also activate further cascading non-specific systems such as the complement system<sup>(1)</sup>, which can also lead to direct destruction of bacteria. This is a highly integrated collaborative process. Many structural components of bacteria will specifically combine with certain TOLL like receptors to facilitate and augment this process. Probiotics for example seem to work by activating Toll-like receptors, making antigen-processing more efficient.



**Image 4.2:** How the body responds immunologically to a potentially invading microorganism. Source: Robert Clancy

<sup>1.</sup> The 'complement system' was functionally defined soon after specific antibodies were described, and it was shown that soluble proteins in blood were needed to allow the antibody to 'kill' bacteria. These non-specific proteins actually 'complemented' antibodies.

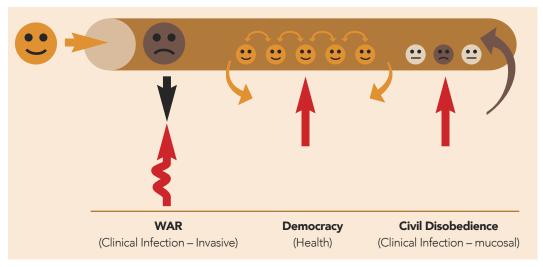
In mucosal infections, control of colonising bacteria involves a local compartment antibody known as IgA, which binds to organisms before they enter the body, thus preventing them from attaching to the mucosal surface. It also involves activating phagocytic cells (especially neutrophils), which reduce the density of colonising bacteria by phagocytosis. The mechanism of this latter activity depends on generation of specific T cells in lymphoid aggregates lining the small bowel, known as Peyer's patches. Thus there is a common mucosal system, dependent upon T cells in Peyer's patches.

When an infection occurs, the antigens on the bacteria stimulate the immune system to give a protective response. This can be done 'artificially' to achieve protection without suffering

the disease first. This is called immunisation and is the basis of controlling many infectious diseases such as the childhood infections. To provide systemic immunity (to protect against invasive infection such as meningitis etc.) it is necessary to inject the antigen, while immunisation against mucosal infections is best achieved with antigen delivered by mouth to eventually access the Peyer's patches in the small bowel.

# HOW DOES THIS RELATE TO THE WAR METAPHOR?

This diagram presents this same concept of balance and outcome between host and microbe (parasite) in a slightly different way. It fo-



**Image 4.3:** Two ways in which infection can occur and the possible responses: War, Democracy and Civil Disobedience!. Source: Robert Clancy

cuses again on the two ways in which infection can occur. All infecting organisms enter the body via the skin or the mucosal surfaces. Those organisms that can quickly penetrate these barriers, avoid the host response, spread effectively and secret toxins are immediately life threatening, the more so if the host has no prior immunity or there is major breakdown in the host defence. Hence the host requires a rapid acting immune system to engage the enemy. This is where injected or systemic vaccines play a critical role by preparing the host for the occasion when such a bacteria appears. WAR is a good metaphor for this.

Of course what works best for both the parasite and the host is a situation of DEMOCRACY where there is a balance between the organism and the host so that everybody is a winner. Here the bacteria 'talk' to each other and 'talk' to the host. Within the host there is a balance between infection pressure and host protection. Promote this!

At the other end of the spectrum the host dominates bacteria, where the bacteria may now be difficult to see, and the non specific outcomes of the host response actually damage the host as well as the bacteria – this I have called 'Civil Disobedience'. Subtle defects in host resistance allow the bacteria to persist. The strategy to prevent/control this type of disease is to specifically (vaccine) or non-specifically (e.g. Probiotics) enhance host protection, to control it in such a way that the host response does not become excessive and inappropriate.

It is only when normal balance is disturbed that you get inappropriate host response and so called civil disobedience. Most infections fall into the latter class. Thus infections in the upper and lower airways, be they middle ear infection, exacerbations of chronic airways disease, sinusitis, various gut infections and reproductive tract infections, all fit the model of disturbed colonisation and civil disobedience.

So in summary, it is important to visualise infection as an outcome of a relationship between the 'vigour of microbes' on one hand and the 'effectivity of host protection' on the other. We must see management of infection as focused on the microbe or focused on enhancement (or repair) of host defences. It is a war like any other.

Most 'parasites' (be they virus, bacteria, fungus, etc.) 'win' by coming to terms with the host and co-existing. Often the organisms actually are good for the host (e.g. bacteria living in the gut make vitamins essential for the host). Thus it is the exception for the host-parasite relationship (H-PR) to result in 'clinical infection'. Clinical infection in the host is a 'bad' outcome for the microbe (as well as the host) as the microbe wants its species to survive and that requires a healthy host!

Clinical infection occurs when there is a particularly vigorous organism (such as Ebola fever, Black Death, etc.) or there is a defect in host protection. The defect may be physical (e.g. extensive burns removing skin protection, diabetes with a high sugar level, blocked ducts

or blood vessels, etc.) or immunological (e.g. low antibody level). With any clinical infection defective host factors must be considered – but often are not! Antibiotics attack the microbe and their use needs to be carefully considered as they address only one factor in the H-PR equation – and that factor may not be the main problem. Using antibiotics is often like using a 'band aid'. Antibiotic use will always apply pressure to the organism to select out resistant forms. Half a century of antibiotic use has created an outcome where, for the first time, we see organisms resistant to every

known antibiotic. There have been very limited advances in recent years in creating 'new antibiotic platforms'. Most if not all new antibiotics are variants of 'old' precursors.

Awareness of this is everyone's responsibility. Clinical infections should be anticipated and prevented or reduced. We need to target infection and treat it optimally and show how it can be done.

My immediate views include a three-pronged attack.

Education, Prevention, Adapted Public Health	Non Antibiotic Treatment Strategies	Antibiotics
Include a number of clinical studies and consider regional factors.	Develop new non-antibiotic strategies to control infection; focus therapy on enhancing host protection.	Reduce use of antibiotics; specifically target antibiotics
Epidemiological review of antibiotic usage including reasons for use;	Vaccines (not considered further here as obvious. But need to monitor downside as we use more)	Need for new 'classes' of antibiotics;
Assess value of routine cultures pre-antibiotic in more circumstances (e.g. throat infection; nasal swabs pre-operation etc)	Control Surface Colonisation. Important and great opportunity. Aim is control not elimination of bacteria as damaged surface simply becomes re-colonised with resistant bacteria:  (a) re-colonise with non pathogens (Probiotics – which also 'switch' host response);  (b) Stimulate mucosal protection (especially oral 'vaccines' e.g. NTHi and COPD and non-specific stimulation – often complementary medicines)  (c) Phage (specific for various bacteria)  (d) 'Egg Vaccines' (e.g. C. difficile)	Monitored guidelines for usage

#### 4.2

### 'ANTIBIOTIC RESISTANCE IS DUE TO A BREAKDOWN IN COMMUNICATION'

#### **Interview with Prof. Robert Clancy**

Q: As an immunologist working on this whole issue for so many years and having so much experience, how do you look at the human body? If you had a third eye, which could look at microbes not just with a microscope but with the naked eye, what would the human body look like?

**Prof. Clancy:** Yes, a very interesting question. The body would look like a very active-interactive organism. As a very large organism with lots of smaller organisms and we happen to call these smaller ones the microbes. And, there is a very active communication process between all the parties. In reality, the creation of antibiotic resistance and infections that are not responding to antibiotics are an outcome of the breakdown of this communication process.

Q: In that sense, it would look like an eco-system altogether?

**Prof. Clancy:** Absolutely, absolutely. It is an eco-system. And, it is the perturbation or disturbance of the status of this eco-system that allows the unwanted outcomes.

Q: And do you think that the visualisation of the human body in ecosystem terms and not like what it is/as it is visible to the naked eye...would that make a difference in how people perceive microbes and perceive antibiotics, would that bring about a change in behaviour?

**Prof. Clancy:** Yes, I think so. Most people, not just the people having antibiotics given to them but also the people who prescribe antibiotics, see antibiotics in a very narrow stage. They don't see the use of antibiotics as really a small part

of the management of the host-parasite relationship. I have spoken about the incredible importance of public health measures, and the incredible importance of immunisation strategies. And it has been those great breakthroughs in the latter part of the nineteenth century and in the early part of the twentieth century that have changed the face of infectious disease in our society.

Antibiotics changed in time and, of course, that made fantastic differences to individual infections. If you look at infections in terms of society, the number of infections occurring is much less and we must give credit to all these other interventions, and quite often, to non-medical changes, in creating a good outcome. And, I think that we have created part of the antibiotic resistance problem for ourselves. Part of handling it is to go back and learn lessons from the past and add to those lessons the importance of maintaining the host capacity, to do the job itself.

And, if you put public health issues together with the immunisation issues and maintaining of the capacity of the body's own mucosal surfaces to control the bacterial colonising processes, we can go an enormously long way to require much less by way of antibiotics and, as a result, much less of the emergence of antibiotic resistant strains of bacteria.

Q: In other words, do you think there are a large number of cases in which antibiotic use can be eliminated?

Prof. Clancy: Absolutely. I am certain that many if not most of the situations that we see can be eliminated. But, in saying this, the process should be a generic approach from all of us. It is hard to look at an individual case where a particular person has a particular infection, may be, an artificial knee joint or when they are about to lose a leg. It is very hard to look and dissect these mechanisms in that particular case. But if you are to look at the bigger picture, in all those cases, you very often find a breakdown in terms of management strategies and you would know that they have not been properly adhered to.

Q: Could you please very briefly tell us about your specific area of work, on mucosal surfaces, and how that played a role in understanding this?

Prof. Clancy: My interest over many years has been in understanding the control mechanisms of protection at the mucosal surfaces. I was part of a team some years back that described the communication systems between different mucosal systems of the body. My contribution is to look at the ways of manipulating that system for the benefit of the host and we found that by a very simple procedure of presenting killed bacteria to the 'factory' that makes the cells which go to various surfaces for protection purposes, those bacteria can stimulate a level of immunity that causes a vast reduction in the need to use antibiotics. So essentially we have adjusted this host-parasite relationship that I was talking about, to the benefit of the host by maximising the protective mechanisms at those mucosal surfaces in a very safe, simple and effective manner. So that has been my passion.

#### Q: Thank you so much. Is there anything else you want to say?

**Prof. Clancy:** One more thing. What I was talking about was specific activation of these protective mechanisms. Another area I have been interested in – and I think it is very underutilised – is the non-specific enhancement of these protective mechanisms. In my own case, we have been using normal bacteria that are harmless but in fact can provide help. These bacteria are called probiotics. These probiotics can be very effective in certain circumstances. But, unfortunately, there has not been a lot of interesting new research, and it is very hard to get a patent in probiotics. I think the interest of this non-specific enhancement of mucosal protection, relates to many of the natural therapies produced in Ayurvedic medicine in India, the traditional Chinese medicines, the traditional aboriginal medicines in Australia, and aboriginal medicines in many of the developing nations around the world. These practices have been given scant attention and yet at times are the very essence of the active principles that we prepare and purify and synthesise in our own life and society. These traditional practices have been tested over many thousands of years sometimes and, I think, they provide very effective enhanced barriers for protection. And, it is very important for us to start rediscovering some of these important medication works.



### 4.3 MANAGING THE PLAGUE

The bubonic plague or Black Death is a classic systemic invasive infection in an unprepared host. There were three plague epidemics. We know most about the second and third. The second epidemic began in Europe in 1347 and lasted four hundred years. It came to Europe via the Silk trade route via the seaports and to the mainland. About one third of people in Europe died (60-90% mortality). The epidemic paralleled the movement from Europe as a feudal society through the Renaisance. The third pandemic began in 1894 and lasted less than 50 years. It affected Asia, Africa and the New World.

A historic overview of infection using the plague as an example, indicates how it was not until the 17th century, when even the first attempt to clinically classify infection was noted.

Prior to this and even at that time all infective disease was seen as a miasmic outcome and disturbance of the four humours. It was not until the 19th century that Breteneau studying



**Image 4.4:** Image 4.4: The image of Black Death . Source: Robert Clancy

diphtheria and typhoid fever used anatomical correlations to bring together more specific infections and to suggest that maybe a morbid seed was responsible for disease.

Pasteur in 1878 with his classical germ theory following his work on putrefaction, fermentation and infection identified the germ theory with one bacteria causing one disease, and it was soon consolidated by the work of Robert Koch. Both identified a body response or host response in terms of soluble factors in the blood, which were called antibodies, and the idea that one could stimulate these antibodies by using bacteria or bacteria products, called toxoids, i.e. killed bacteria or attenuated bacteria.

The third plague pandemic that started in 1894 came at a time when there was an intersection of the sanitary movement and germ theory. Various sanitary measures had already been legislated upon Europe and other parts of the world and this helped improve gut infection even before the advent of germ theory. The latter however provided the insight that specific organisms led to a specific disease and required specific treatment and this combined with the sanitation movement helped contain the pandemic in some ways. Let's take Australia as an example.

As background, the health patterns in 19th century Sydney were related to waves of immigration-related epidemics. There was a background of debilitating health problems from dysentery, TB, sexually transmitted diseases, skin and eye disease. In the late 19th century there were epidemics of typhoid, influenza and smallpox. Infectious disease (TB, pneumonia, typhoid) and violence were the main causes of death.

The bubonic plague arrived in Australia in waves between 1900 and 1922. Around 1360 were infected of whom 535 died. Sydney accounted for 50% of all cases. The epidemic was restricted to trading ports and did not spread inland.

The plague outbreak however created hysteria and panic out of proportion to the numbers actually affected. Large sections of Sydney, the capital city of the State of New South Wales, were closed and punitive health teams patrolled the streets. Over 2000 people were quarantined, business was disrupted and trade with New South Wales was avoided by the rest of Australia. Press reports on the epidemic were inflammatory; the medical profession was confused about how to respond and quacks flourished.

However sound medical advice on how to manage the epidemic has its positive impact too. Experts like Ashburton Thompson, the father of public health in Australia, carried out the microbiology and epidemiology studies on 15,000 rats needed to confirm the rat/flea/man transmission and the time relationships of infection. He recommended, among other measures, the isolation of rats from human living spaces, management of the sick in hospitals,

contacts were not to be quarantined and affected areas were cleaned but not isolated.

All these measures resulted in saving of both lives and costs involved in the waves of plague that followed the initial outbreaks, and prevented spread of the infection into the hinterland. Thus the plague can be looked upon historically, even form 1347, as a 'pressure' on an unstable society needing change as finally as a showcase of progress in infectious disease and a validation of scientific medicine. Its containment in Australia also accelerated changes in Australian society and public health concepts.

#### BOX1

# JOSHUA LEDERBERG AND THE US INSTITUTE OF MEDICINE FORUM ON MICROBIAL THREATS— 'CALLING FOR AN END TO THE WAR METAPHOR'

Joshua Lederberg influenced thinking about microbes for much of the last 50 years. He embodied the ideal of science – curiosity and innovation. As a medical student at Colombia University in 1946, he took a year off and with his intense fascination with bacterial genetics, went to work on Escherichia coli with Edward Tatum, at Yale University. He showed that certain strains of bacteria could undergo a sexual stage, and that they mate and exchange genes. "This was ground-breaking, highly imaginative work on the nature of microorganisms, especially their mechanisms of inheritance," said one of his colleagues "It opened up bacterial genetics, including the momentous discovery of genetic recombination," a line of inquiry that resulted in Lederberg's being awarded the Nobel Prize in Physiology or Medicine in 1958, along with Tatum and George Beadle for "discoveries concerning genetic recombination and the organization of the genetic material of bacteria."

In 1996, the US Institute of Medicine (IOM) launched the Forum on Emerging Infections (now the Forum on Microbial Threats). Joshua Lederberg chaired the Forum for its first five years and was an avid participant in its workshops and discussions until his health began to fail. The Forum continues 'to be inspired by Lederberg's expansive vision: a command of science that forged connections between microbiology and a broad range of disciplines, that was profoundly informed by history and literature, and that embraced the fullness of human imagination and possibility'<sup>(2)</sup>.

In 2005, the Forum on Microbial Threats held a workshop called Ending the War Metaphor: The Changing Agenda for Unraveling the Host-Microbe Relationship. This workshop represented an expansion of its focus to recognize the breadth and diversity of host-microbe relationships beyond 'those relative few that result in overt disease'<sup>(3)</sup>. The central theme of this workshop was influenced by an essay Lederberg published in 2000, called Infectious History.

In this essay, Joshua Lederberg envisioned the future of humanity and microbes as 'episodes of a suspense thriller that could be entitled, Our Wits Versus Their Genes' (Lederberg, 2000). Driven by one of many questions he wanted to know, 'how much more can the natural history of disease teach us about fundamental biological and evolutionary mecha-

nisms,' he saw the key starting point as recognizing the ecological fact that humans, animal, plants and microbes live together on the planet. Thinking of this as a collective living system, raises questions about the origins and dynamics of instabilities within this system. He saw two main sources for instabilities - ecological and evolutionary.

Ecological instabilities follow our alterations of the physical and biological environment, the microbial and animal members of the system (including us) and our interactions with the parasites (including how we use hygiene and therapeutic interventions).

Although 'germs' have long been known to be living organisms, he pointed out that it took a long time to accept that they evolve and change and that evolutionary processes elicit changes in the genotypes of germs and of their hosts. There are now a handful of examples of the connections between infection and evolution mostly connected to malaria, tuberculosis and now a genetic alteration that affords some protection against AIDS. He concluded that

One lesson to be gleaned from this co-evolutionary dynamic is how fitful and sporadic human evolution is when our slow and plodding genetic change is pitted against the far more rapidly changing genomes of microbial pathogens<sup>(4)</sup>.

<sup>2.</sup> Microbial evolution, IOM, p 6.

<sup>3.</sup> Ending the War Metaphor: The Changing Agenda for Unraveling the Host-Microbe Relationship, pxii.

<sup>4.</sup> Infectious History reproduced in Microbial Evolution and Adaptation. P 65-66.



Bloodvine detail. Michelle Day.

He ended the essay with a call to evolve metaphors of infection and 'Teach War no More'. He argued that we should think of the host and its parasites as a super organism - a kind of chimera – an organism with different sorts of genetic makeup. This led to the concept of the microbiome, a term Lederberg used to mean the collective genome of an indigenous microbial community, which became a forefront of scientific enquiry.

After his death in 2008, the Forum on Microbial Threats dedicated a Workshop to his memory. It was called Microbial Evolution and Co-adaptation: A tribute to the life and scientific legacies of Joshua Lederberg. The agenda for the workshop reflects the perspective of Lederberg that every eukaryotic organism, and indeed cell, participates in a partnership with microbes and communities of microbes. Hosts and microbes depend on each other for survival. Thus building on the conceptual and technological advances that enable us to understand these interactions, the workshop explored a number of topics related to microbial evolution and co-adaption: methods for characterizing microbial diversity; model systems for investigating the ecology of host-microbe interactions and microbial communities at the molecular level: microbial evolution and the emergence of virulence; the phenomenon of antibiotic resistance and opportunities for mitigating its public health impact; and an exploration of current trends in infectious disease

emergence as a means to anticipate the appearance of future novel pathogens.

Results of the discussion provided insights on patterns of emergence of infectious disease emergence. Of the 1,400 pathogens capable of infecting humans only 500 are capable of being transmitted to another human and 150 have the potential to cause epidemic or endemic diseases. For novel pathogens to emerge, the most commonly cited drivers are related to economic development and land use, human demographics and behaviour, international travel and commerce, changing ecosystems, human susceptibility and hospitals.

Viruses are the main novel pathogens and evolve fastest of all and proximity is the main reason for jumping from one host to another. We share!

Our Wits versus Their Genes<sup>(5)</sup>: To predict the next emerging disease to be passed from animals to humans requires fusing the disciplines of evolution, ecology, virology and microbiology to truly understand comprehensively the relationships between and among microbes and host species and how to anticipate, detect and respond to emerging disease.

Breaking down a complacent attitude to surveillance will require altering the political and social climate which lives within the old war

<sup>5.</sup> Workshop Over view pages 46 -53.

metaphor and somehow believes that the technology and knowledge we have is sufficient and superior to microbes. Developing a global surveillance system that can provide some insights into immensely rich and fast evolutionary world of microbes is needed. We need to focus collaboratively on the ecological niches that are hotspots for emergence of new diseases.

The evolutionary context for the spectrum of resistance mechanisms from their original function in antibiotic-free environments to their potential to transmit and re-assort with other resistance elements in human-created environments such as wastewater treatment systems was explored. From the perspective of the history of antibiotic resistance, Julian Davies proposed a different approach to dealing with microbial pathogens: by interfering with the cooperative relationship many of them have with their hosts. Host cells provide many of the genes and gene products necessary for pathogen propagation and transmission. Key questions relate to the nature of community robustness and the genetic attributes of invading microorgnasims that permit them to overcome a robust community<sup>(6)</sup>.

Finally the vast majority of microbial species are yet to be identified. One participant sug-

gested the development of a field guide to microbes that describes, not only their taxonomy but their behaviour, ecology and distribution patterns. New techniques to enable the obtaining and applying detailed knowledge of intraspecies diversity could help move to investigate associations between specific mutations in a pathogen strain and its phenotype as shown in the characteristics of ability to transmit and its virulence. This would address another of Lederberg's insights – to gain wiser insight into the ground rules of pathogenic evolution.

Letting him have the last word, he might say...

Perhaps one of the most important changes we can make is to supersede the 20th-century metaphor of war for describing the relationship between people and infectious agents. A more ecologically informed metaphor, which includes the germs'-eye view of infection, might be more fruitful. Consider that microbes occupy all of our body surfaces. Besides the disease-engendering colonizers of our skin, gut, and mucous membranes, we are host to a poorly catalogued ensemble of symbionts to which we pay scant attention. Yet they are equally part of the super organism genome with which we engage the rest of the biosphere.

<sup>6.</sup> Antibiotic Resistance: Origins and Countermeasures. Overview, p 158 -160, Microbial Evolution and Co-Adaptation.

#### CHAPTER FIVE

Artists help us to see, feel and think differently and sometimes to see for the first time. But it takes time, courage and small repetitive steps. Artists can thus change our focus and help us increasingly penetrate into the new focus. This chapter opens up insights into the process of looking differently, using other senses to challenge the dominant sense and ask questions. Thus could we embody both a process of creation and disturbance and relate to the paradoxical phenomena that surround us. Janet DeBoos, one of Australia's best know potters and ceramic artist was asked to speak about the body-mind connection and how paradigms change in her world. She has always been interested in germ theory and she made connections between her work, her teaching and the challenge of infection and antibiotic resistance.

## A HAND IN BEAUTIFUL AND USEFUL THINGS

#### **Janet DeBoos**

Potter, Head of the Ceramics Studio, School of Art, Australian National University

the same way that any craft practice springs from an understanding of process and material as an extension of body, it might be helpful to view disease and microbes as an integrated part of human life, rather than 'the other'.

I have spoken a lot over the past twenty years or so about skill and its importance in craft practice, and the way in which with long practice skill moves from 'outside' one's body where it is a conscious act to an internalised position, which allows the maker to 'become' the work. To draw an analogy here with disease requires an act of imagination that allows us to 'get inside' the way disease and microbes work.

This takes time.

#### **ANECDOTE**

A friend who served in the Vietnam War described the difference between the American and Australian ways of taking a hill...the US would do it immediately and directly-front-on so to speak, use massive strike power and occupy it, often with considerable loss of life. Inevitably, this method became less and less effective against the dispersed attack by the North Vietnamese. The Australians however would just watch the hill for maybe a week, come to 'know' it, internalise it. When they felt they understood the hill, they would only then occupy it, usually with no loss of life.

We can look at disease in this way- we can attack with antibiotics up front, or we can take the time to integrate it into our understanding of self.

Skilled artists do this- they look, and they 'wonder' about things- often for a long time without finding an answer. Drawing on internalised skills allows them to express this 'wonderment' in a way that talks to other people and which (in the case of pottery) creates a continuous thread between the solitary act of making and the act of use.

There is no fast way to acquire skill- it requires uncomfortable, boring, repetitive work until you reach that state of grace where magically the boredom stops because the body has taken over from the mind. For this reason a very skilled maker is often the worst person to explain how they make something because the process has become so embodied that words fail. Showing/doing is necessary- rather than explaining. It is not dissimilar to meditation in this respect.

#### **MY PRACTICE**

I have long been interested in what constitutes our idea of 'the handmade'. And is there really any difference between the industrially produced 'handmade-looking', and the actual studio piece? When works made in these two ways look identical- how do we test our vision of them? We do it by touch. When we 'can't believe our eyes', we use our hands. This 'looking with our hands' challenges the occular-centrism of our world. Other paradigmatic shifts occur when we use other of our less dominant senses (see The Eyes of the Skin-Architecture and the Senses-Juhani Pallasmaa).

The way in which different people view the same subject is also a window into shifts of this kind.

#### **ANECDOTE**

Some time ago I had been asked with a colleague to talk at a ceramics conference entitled 'Working the Surface'. It was ostensibly about surface decoration and enrichment-but I didn't decorate my work. We decided to do a joint presentation and couldn't really agree about what was actually 'surface'. Could my manipulation of the clay itself on the potter's wheel be regarded as 'working the surface'?

We decided to ask people from widely varied professional backgrounds what surface meant to them. We videoed these interviews of botanists, artists, furniture makers, psychologists, anthropologists etc and presented them, interspersed with images of ceramic ware illustrating their understandings of 'surface'.

The views ranged from the digital artist who said there is no fixed thing (surface)- only an in-

terface between areas or volumes to the botanist who saw the surface as a active site of exchange (feeding/breathing /byproducts of living) and the anthropologist who described the flexible, unfixed and diffuse nature of the 'surface' between trance-like disembodied states and full consciousness in indigenous all night dancing.

So stepping outside one's field is always informative and useful in providing new insights.

There are a number of artists that deal with the idea of disease/microbes and or 'new' models for life, and I will show some images.

1.Katherine Ross (USA) is a ceramic artist, who is worried about the US preoccupation with hygiene. She makes multiple part installations that are concerned with selfcare, sickness and a changed relationship between the body and microbes using a reversed scale (large microbes/ small cleaning agents/ big pills)



**Image 5.1:** (The Nurse): Katherine Ross, USA - Hygiene series.Reproduced with kind permission of the artist.



**Image 5.2:** Katherine Ross. USA - Hygiene series. Reproduced with kind permission of the artist



**Image 5.3:** Katherine Ross, USA - Hygiene series. Reproduced with kind permission of the artist

2. Walter McConnell (USA) is a ceramic artist who embraces the use of microbes- fungi and bacteria - which he grows on moist, unfired clay inside large plastic environments. These are juxtaposed with more conventional 'exhibits' that are really just amusements when compared to the seriousness of the living artwork.



**Image 5.4:** Walter McConnell, USA – living clay (nature) vs artefact (culture). Source: Walter McConnell with kind permission to publish.



**Image 5.5:** Walter Mc Connell, USA - living clay (nature) vs artefact (culture) - detail. Source: Walter McConnell with kind permission to publish.



3. Marek Cecula (US/Polish) is a ceramic artist who also embraces the idea of infection. In his 'Scatology' series, he makes exquisite porcelain surgical and hospital objects that confront the unmentionable with the beautiful. This work was exhibited at the height of the AIDS epidemic when there was an extremely high level of anxiety about body waste. His suggestion was that fear is not the answer- maybe getting to know (and therefore see the beauty in) the 'enemy' was the way to go.



**Image 5.6:** Marek Cecula, USA/Poland - Scatology/Hygiene series. Reproduced with kind permission of the artist.

4. Michelle Day (Australia) is a textile artist whose mother died of cancer. She needed to 'come to terms with, and understand the disease'. She did this by creating 'Blood Vine'a beautiful hand worked red textile construction that colonised the exhibition space.



**Image 5.7:** Michelle Day Blood Vine, 2007.Materials: Thread, wire, organza, disperse dye, human hair, animal teeth and modelling clay. Dimensions: Variable.Photographer: Stuart Hay. Reproduced with kind permission of the artist





**Image 5.8:** Michelle Day Blood Vine detail. Reproduced with kind permission of the artist

#### Michelle Day - Artists Statement

Growth has many positives and negatives, but there is also a tension in the grey area in between. In our society the word growth is often considered positive before negative, almost viewed as a symbol of life. However, tension is apparent in the fact that a beauty spot or birthmark is technically a form of benign tumour (nevus) and a beautiful foetus can be a parasite to the body. My mother died as a result of a form of growth; a bone cancer developed in her ankle and migrated around her body.

I felt that I had to understand her cancer better, so I tried to put myself in the position of the cancer. This created an internal conflict for me around these ideas of growth and its positives and negatives. I realized that growth is often neither, but somewhere in between. The beautiful Giant Fig is also an example of this grey area, as it lives symbiotically off other trees and when fully grown engulfs the other tree, which rots away within the centre of the giant fig. There is also such irony in the belief that if 2 people kiss under abnormal growth caused by a disease (mistletoe), their love will flourish and grow.

To work through my conflict I researched into many forms of growth. These included: strangling and symbiotic vines and other plants of this nature, abnormal growth on plants, fungus, warts, foetal rejection, teratomas – abnormal growth of teeth and hair in different parts of the body, moles, birthmarks, cancer and tumours and the difference between the two.

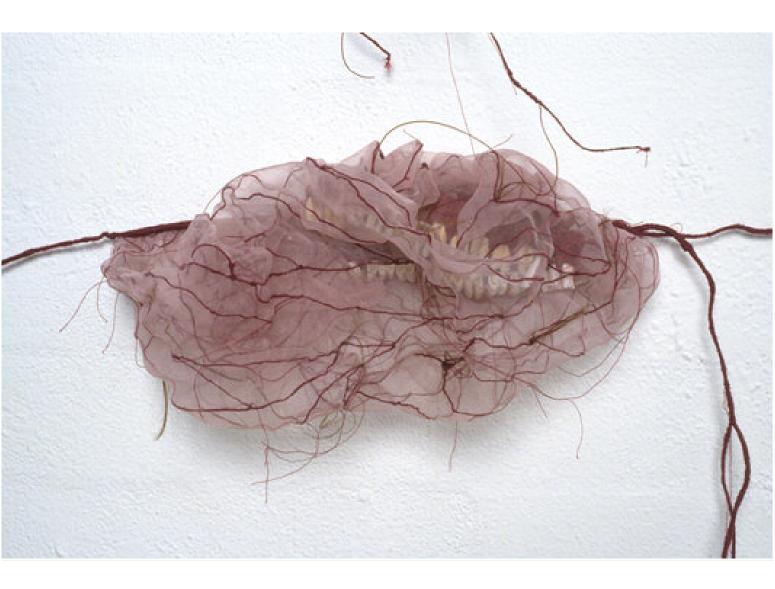
I physically studied organs, which I dissected, sketched and photographed. I found many similarities between the physical nature of the body and the physical nature of plants. The overlap between the different forms of growth became very important in my work for discussing the tension created by the context of growth.

I studied many artists who related to my work, such as soft sculpture artists Annette Messager and Alice Lang. I was also inspired by Kate Campbell Popes methods of binding and weaving organs. H.R Giger's work was often in the back of my mind while drawing, which reflected his overlap of organ, machine and plant. And Gunther Von Hagen's macabre plasticized and sliced-bodies have also been a point of fascination.

The works I have arrived at convey this overlap of growth type and context. The overlap creates new plant and organs, which as a result become dysfunctional, as a tumour causes an organ to become dysfunctional. The work has also been a healing process for me; I have essentially recreated my mother's dysfunctional organs and removed them from her body.

At this point I have just as much inner conflict about the tension surrounding ideas of growth. However it is not my idea to separate growth into categories because I am aware that all growth is either or both negative and positive depending on context. I have merely highlighted this tension and raised questions surrounding societies unconscious view of growth as a symbol of life.

**Image 5.9:** Michelle Day - artist's statement. Reproduced with kind permission of the artist



**Image 5.10:** Michelle Day Blood Vine, 2007. Materials: Thread, wire, organza, disperse dye, human hair, animal teeth and modelling clay. Dimensions: Variable. Photographer: Stuart Hay. Reproduced with kind permission of the artist.

Another work- 'Replication Malfunction' was comprised of indeterminate cell-like modules of red felt that morphed from regular looking forms to uncontrolled cell division.



**Image 5.11:** Michelle Day Replication Malfunction I, 2007. Materials: Velvet, Remazol dyes, stocking, thread. Dimensions: Variable. Reproduced with kind permission of the artist.



Image 5.12: Michelle Day Replication Malfunction II has the same details. Photographer: Stuart Hay. Reproduced with kind permission of the artist

5. Marcel Wanders (Netherlands) is a designer who used new technologies of 3-D image capture to get a picture of the shape of a sneeze. This image was then turned into a real object used as a model for his 'Snotty Vase'. The vase is used for flowers, and in this context the shape of a sneeze, and all the mucous attendant on that is subsumed in a thing of beauty.



**Image 5.13:** Marcel Wanders Airborne Snotty Vases. Source: www.marcelwanders.com. Also see: http://www.marcelwanders.nl/wanders/pages/pe-snotty-vase.shtml; www.marcelwanders.nl/wanders/.../airborne-snotty-vase.html

6. **Theo Jansen (Netherlands)** is an artist who has created from the lowly materials of our society (old lemonade bottles/ plastic tubing/ plywood) a 'new nature'- wind-driven animals that wander the beaches of the North Sea. These animals do not need food, or water, and have sensitive systems that allow them to back off from danger such as 'drowning' in the sea. See interview at: http://www.ted.com/index.php/talks/theo\_jansen\_creates\_new\_creatures.html

Theo Jansen's work is an example of how an image can engage people to alter their way of thinking about the world about us. His 'strandbeest' can be viewed at www.strandbeest.com

Image 5.14: Theo Jansen constructing Strandbeest photographed by Loek van der Klis. Source: Loek van der Klis with permission to publish.





**Image 5.15:** Theo Jansen Zeeschuim 2 Animaris Percipiere. Photograph by Loek van der Klis. Source: Loek van der Klis with permission to publish



Image 5.16: Loek ven der Klis PPdrie luik 02. Source: Loek van de Klis with permission to publish. Further information www.loekvanderklis.nl

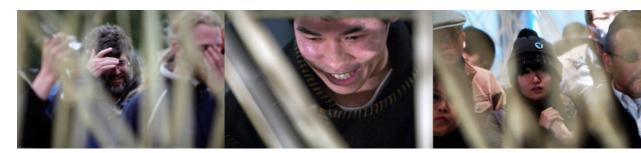


Image 5.17: Loek van der Klis. PP drie luik 12 Source: Loek van der Klis with permission to publish.



Image 5.18: Loek van der Klis PP drie luik 04. Source Loek van de klis with permission to publish.

Portraits below show viewers fascinated by the phenomenon of the Strandbeest. As photographer Loek van der Klis says,

As people have their first confrontation with the Strandbeesten. It is in the expressions of these people, young and old, you can see a surprise, unbelief, and a fascination for this evolutionary artwork. It is as if it gives them the opportunity to get a new kind of energy as well as an inspiration to new thoughts and so new perspectives!

#### LOOKING DIFFERENTLY

These artists are not offering answers- they are looking, and making propositions. In the end, that is what art practice is – looking, and asking questions. We all need to learn to look and art can help open our eyes.

# HOW DOES THIS CONVERGE WITH ANTIBACTERIAL RESISTANCE?

Perhaps the first issue is time. Big problems need to be allowed 'big time' to be solved. By 'big' time, I don't necessarily mean 'long' time, but untrammelled time. A sense of physical urgency often gets in the way of creative thinking. When the body is occupied in some kind of repetitive, time-consuming action, that is when free wheeling thinking most often occurs. Composer John Cage understood this when he exhorted composers to play a 'boring' phrase twice, then if still boring, four times, then eight- still boring? Try sixteen times- now, you're getting somewhere! An idea will emerge out of the space that repetition allows.

Acceptance and risk. Because the problem can't be resolved overnight, this means people will die. More will die if we 'take time'. It is very hard, but we have to accept this – people are dying now anyway because of improper use of antibiotics. They also die because we did not understand the extent of pathogencaused disease and treated 'lifestyle' and 'genes in the past. (See Paul Ewald's writing on the New Germ Theory<sup>(7)</sup>.

<sup>7.</sup> http://www.amazon.com/exec/obidos/tg/detail/0385721846/ref=ord\_cart\_shr?%5Fencoding=UTF8-&m=ATVPDKIKX0DER&v=glance

It is a risky business, but we must accept the risk inherent in taking time if we are to get anywhere.

Change focus of effort. Accepting that we live in -and have living in us - a bacterial 'soup', it becomes an impossible task to target ALL possible pathogens. So we need to focus away from the microbes and on to the people and the environment. Ewald refers to the different strains of Cholera present in Peru, the USA, and Central America, and how their virulence seems to be directly related to water quality in these regions. The better the water quality, the less virulent the organism. Thus it seems logical to target effort into non-germ areas such as improved water quality. In time, improved water quality may mean less virulent microbes. (See the water filter project run by Potters for Peace, using colloidal silver lined ceramic water filters made using low tech methods. A small project, but one that is well targeted- it is local and involves the education of the populations at risk<sup>(8)</sup>).

Small bites and trust. The problem sometimes seems so overwhelming, that small steps seem impossibly slow and ineffective. There needs to be a certain amount of trust that small projects will combine with others, and the net effect will be substantial. There is sometimes for art students the same sense of being over-

whelmed and not knowing where to start. The evidence time and time again, is that JUST STARTING on something is the key. There may be failure (risk) but it has been said that artists start working when the pain of not making exceeds the pain of making. Perhaps just starting (like this current seminar) is as important for living with microbes as it is for artists?

**Education.** Populations at risk need education so that there is increased understanding of the importance of completing full antibiotic courses when they have to be used. This would slow the rate of development of resistance.

We also need to educate ourselves about living with microbes and accept that they are part of our ecosystem. In my own practice area, 'design & industry' and 'studio handmaking' were regarded as enemies of each other and design was seen as antithetical to studio work. 'Bring the enemy within your own camp' my mother used to say, and 'maybe you won't have a war...'. I have done this and have found rather than a conflict, an extremely fruitful way of working between the two disciplines emerged- a way of working that has sustained my practice for almost twenty years.

Maybe we need to bring the microbes more into our own camp to see if we can stop the war...

### CHAPTER SIX

Anna Dumitriu's work blurs the boundaries between art and science. Her installations, interventions and performances use a range of digital, biological and traditional media including video, mobile phones and textiles. Her work has a strong international exhibition profile and is held in several major public collections. She was a member of the e-MobiLArt project (the European Mobile Lab for Interactive Art) and Artist in Residence at The Centre for Computational Neuroscience and Robotics at Sussex University. She is known for her work with bacterial communication and as director of "The Institute of Unnecessary Research". Currently 9 she is working on a Wellcome Trust funded art project entitled "Communicating" Bacteria", as Leverhulme Trust artist in residence on the Modernising Medical Microbiology project and with the Adaptive Systems research group at The University of Hertfordshire.

Jasper meeting over the Internet and an edited transcription of her talk can be found on the next pages.

## NOT "HOW CLEAN IS YOUR HOUSE" - BUT HOW SUBLIME IS YOUR ECO-SYSTEM?

#### **Anna Dumitriu**

what could be called a 'Double geek'. I am fascinated by both bacteria and computers. I even have my own collection of bacteria (stored at -80 degrees Celcius in a lab).

Most people believe that bacteria are bad. They are synonymous with "dirt". It has come to the point today where people even expect food to be sterile, but of course it can't be. But that does not mean the microbes on there are harmful. People have forgotten the role of bacteria in producing our foods (for example cheese or yoghurt).

## MICROBIOLOGICAL SAMPLES OF BACTERIA AND MOULDS CULTURED FROM FOOD

The popularity of antibacterial hand gels is astonishing. Someone is making a lot of money marketing these to people's fear and ignorance of bacteria, they may be useful in clinical settings but are unlikely to be necessary in everyday life. I set out to change people's ideas of bacteria and create a more balanced understanding of their role within our complex eco-system. I began by culturing bacteria from the ubiquitous everyday places of our lives.

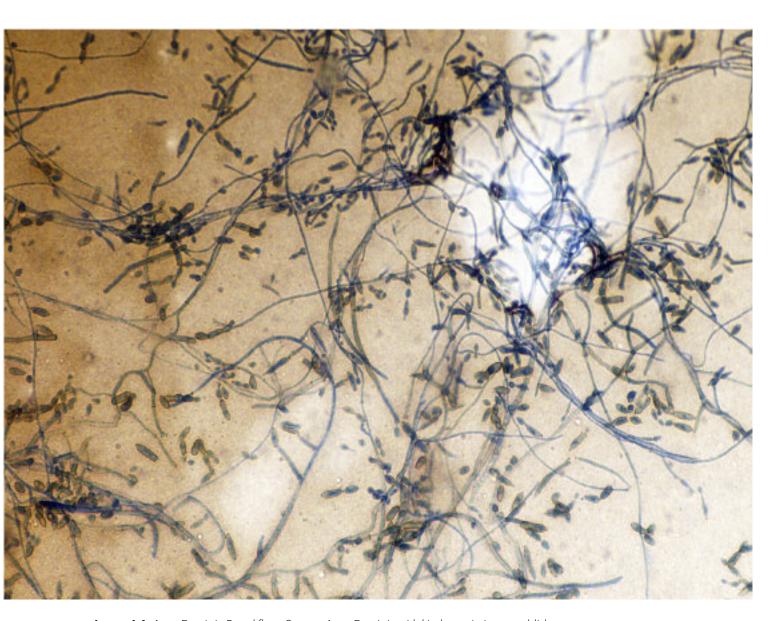


Image 6.1: Anna Dumitriu Bread flora. Source: Anna Dumitriu with kind permission to publish.

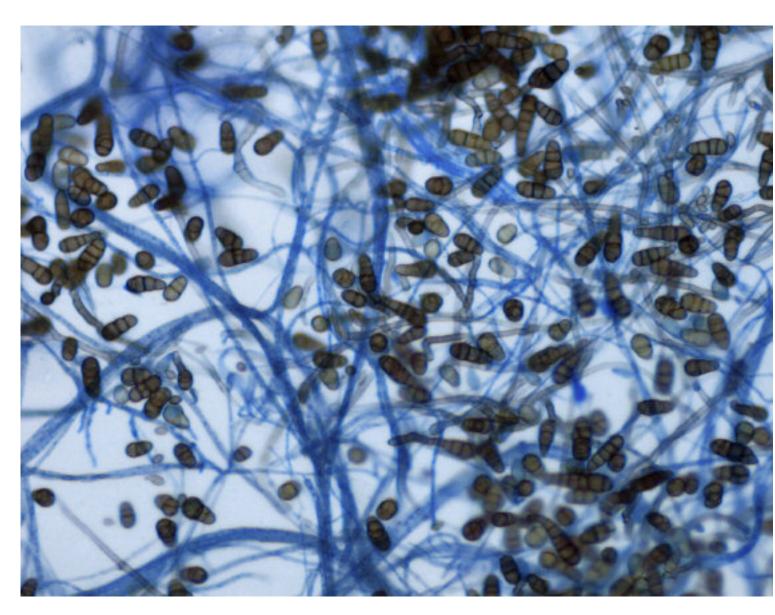
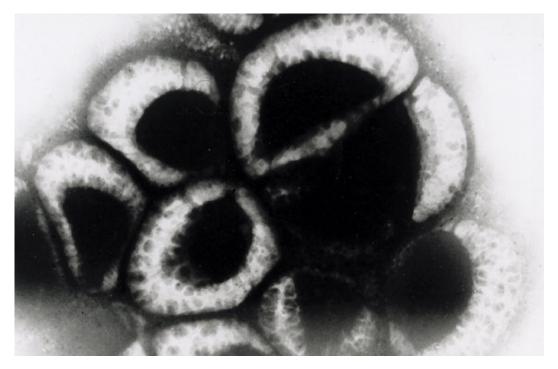


Image 6.2: Anna Dumitriu Chocolate Flora. Source: Anna Dumitriu with kind permission to publish.

Using the antithesis of the idea of the UK TV show, 'How Clean is Your House' I worked with microbiologists and hospital cleaning staff at Eastbourne Hospital to enable them to gain a greater understanding of each other's work and their microbial ecosystems (to look at the wider picture of ubiquitous bacteria). The cleaning staff undertook all the microbiological processing and sampling themselves.



**Image 6.3:** Anna Dumitriu Bed flora - Transmission Electron Microscope Image. Source: Anna Dumitriu with kind permission to publish.

I then set out to find a way to chat with people about normal flora. I began to crochet the pattern made by the bed flora I had cultured. I crocheted this pattern while chatting to people in the foyer- waiting area of the hospital, and others joined in.



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**Image 6.4:** Anna Dumitriu Bed Flora Crocheting - Eastbourne Hospital Foyer. Source: Anna Dumitriu with kind permission to publish.

I also cultured bugs growing on an ordinary chair and carved and needlepointed the image back on to it, the crocheted bed flora piece was exhibited in London and is shown below placed over the chair and the 'growing' spilling over onto the floor.



**Image 6.5:** Anna Dumitriu Chair and Bed Flora: Objects inspired by normal flora microbiology cultured from a chair and a bed in the artist's home. Installation view (at Shunt Lounge - London). Source: Anna Dumitriu with kind permission to publish



**Image 6.6:** Anna Dumitriu Chair and bed flora detail. Source: Anna Dumitriu with kind permission to publish.

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I have also cultured the bacteria growing on my lab coat and then embroidered the pattern all over the lab coat. A traditional white work embroidery technique was used which makes reference to the changing role of women in science.



**Image 6.7:** Anna Dumitriu A lab coat - hand stitched white work embroidered with the normal flora bacteria and moulds cultured from it. Source: Anna Dumitriu with kind permission to publish.



**Image 6.8:** Anna Dumitriu Performance Bacterial Crochet: Dumitriu crochets the bacteria from her own bed and invites others to do so, wearing a hand stitched white work embroidered lab coat (embroidered with the microbiology cultured from it). Source: Anna Dumitriu with kind permission to publish.

I have also worked with gifted and talented science students to develop artistic installations and interventions throughout a school.

My work is both fun and serious. I have experimented with Gram's staining and drawing. The process of Gram's Staining is similar to the artistic process of etching.



**Image 6.9:** Anna Dumitriu The Normal Flora Project (School Flora): An investigation of the sublime world of ubiquitous bacteria and moulds in a school - collecting samples. Source: Anna Dumitriu with kind permission to publish.



**Image 6.10:** Anna Dumitriu School Flora: Ubiquitous skin flora is an integral part of our immune system. Source: Anna Dumitriu with kind permission to publish



**Image 6.11:** Anna Dumitriu: School Flora: Gram's Stains, Drawings and Digital Prints. Source: Anna Dumitriu with kind permission to publish.

#### TALKING TO BACTERIA

I created an art intervention and performance talk called "Cybernetic Bacteria 1". The work involves a clear plastic tube of liquid agar jelly planted straight into the earth, this allows the soil bacteria below to grow upwards and become visible to the audience. For the 'art action' 100  $\mu$ L of Homoserine Lactone, a hormone commonly used by bacteria for chemotactic signalling, is added. I'm saying, in effect "I'm here" to the bacteria below, which (in theory) pass the signal on to their neighbours, which in turn pass it on to theirs, and so on, until the signal has travelled around the globe. The issue with this work is one of Hermeneutics; the bacteria will not be able to identify the artist as human but simply as another bacterium.

This project compares bacterial communication to our own digital communications networks, looking in particular at 'packet data' and bacterial quorum sensing. The project seeks to extend the notion of the technological sublime into a kind of microbiological sublime, reflecting the far greater complexity of the communication that is taking place at a microscopic level in comparison with human communication technologies such as the Internet.

I am interested in the concept of 'Consciousness' in bacteria: can bacteria exhibit conscious/intelligent behaviour. Slime moulds, for instance, can find the quickest distance between two points.

In our culture, the idea of bacteria is considered horrifying. In the public perception there are simply "friendly" bacteria or bad bacteria. I work with ways to help people to think about this. The marketing of so-called "friendly" bacteria is also a problem; in some tests less than 1 in 4 products contain viable amounts of 'good' bacteria. We don't know the long-term effects of 'beneficial' bacteria. Everything is about commerce.



**Image 6.12:** Anna Dumitriu. Cybernetic Bacteria 1: Adding the hormone. Source: Anna Dumitriu with kind permission to publish

One always has to ask: "who is profiting from this" and why do they want you to think/feel like that?

I am attempting to convey our interconnectedness to bacteria to other people through my artworks and performances – participatory artwork seems the ideal way to do it.

### **WEBSITES**

www.unnecessaryresearch.org www.normalflora.co.uk

With thanks to: Dr Simon Park (University of Surrey, UK), Dr John Paul (RSCH, UK), Dr Minna Mannisto (METLA, Finland)

### CHAPTER SEVEN

This chapter brings forward the reflections of two artists about the landscape and the environment. In particular they are open to the power, beauty and presence of living organisms within the landscape and the many forms they take. Both have a special kind of consciousness and are concerned about respect and openness to the consciousness of other life forms.

Peter Cameron feels his way into the landscape to encounter what is there on its own terms. The unconscious encounter is as important as the conscious one. In this way, he feels that we must encounter the consciousness of the land and its inherent structures, from mountains to microbes on their own terms – not expect them to participate in this dialogue on the terms of human consciousness.

Panya Chaiyakam, with Niracha Mongolchai, is occupied by the destructive consequences of human consciousness and civilisation. He is urging us to understand the wonder of mutation of microorganisms – the changing of life into other forms – the richness that we have lost contact with. He uses traditional art forms from his Thai heritage to present wildlife, the environment to people as he believes the traditional forms of representation make it easier for people to learn – it is more direct.

Panya loves the way bacteria change themselves. We can be one in dialogue to help us to a smooth life – to lead our life – to go together with nature.

Panya suggests that we organise an exhibition on the themes of microbes for a season. We could imagine an exhibition that travels from one city hall to another all over the world. Culture organisations in each country can collaborate. This would make a connection between all people over the world and a connection with microbes.

## 7.1 LIVING LANDSCAPES

### **Peter Cameron**

Landscape artist Manly NSW, Australia

from sensations and felt perceptions in the immediate environment and try to value them all equally, so even the un-noticed (unconscious) because small have their pervasive atmospheres just like the wind. Perhaps even as building blocks of existence they have more fluid consciousness than we agglomerates can imagine! I am also attracted to the seeming sense of community without hierarchy (portrayed without subject)".

Here, for him, is the parallel to microbes and metaphors. One specific conscious being is not more important than another.

He illustrated this with a series of paintings he brought and hung on the walls at Cooradigbee, some of which are reproduced below. These were the result of looking deeply into what he saw in the landscape – into lichen, into the mud around a dam, into a stone. These phenomena appear to come to life, to move, as one looks into the painting. There is no identifiable form for any of these – just the essence of the life form itself.

He describes his creative process:

"Reflecting (reflection; to bend or fold back) upon your own senses as you paint in the environment of this land; seeing some of your own processes. Through studying the environment and through the physical operations of painting it, coming to some awareness of being in place, that place, on it's terms and conditions.

Sometimes, (while not able to be there) painting about Guthega [a place in the Southern Highlands of NSW that he has painted a lot] while reflecting it's image in your mind's sense, because you are physically absent from that land but spiritually present; thus you become close to the landscape through the act of painting. It becomes an act of realizing. This is not nostalgia but a conscious, remote sensing action and, I find, a useful tool.

Reflecting on the movements of the elements but particularly water, about the nature of water and what lies beneath it, how it continually transforms itself, works with and through all the other elements (showing as rock or mist etc.) and living organisms, as ourselves. Examples: water reflecting upon itself like a cloud over a lake (Guthega Dam). How snow is so powerful as a glacier, carving through landmasses as if it were butter, ruthless in a blizzard, and occurs in a multitude of forms, textures. As water is life, so snow stores life, as the abundance of Spring shoots and flowers give us to witness.

Building up layers of paint in order to reveal and obfuscate at the same time; much the same way as snow hides the land surface when it falls, then reveal it again as it slowly melts away. Painting in the early stages for me is an immediate, intuitive and emotional response to a situation, environ and sense; looking at the colours, forms and textures of the surrounding physical manifestations. Later, a reflective process, in the paint, begins to discern some general characteristics, develops a dialogue between the various manifestations. Sometimes it's a pulling apart, forming a void, sometimes compression; remembering examples of countless actions in Nature's rhythms.'

I have also come back to working with the earlier series at Lake George, N.S.W. [titled' Canberra District' referred to above and reproduced below]. Here this large flat plain of mineral muds collaborates with the Sun, air and water, to often produce unusual atmospheric conditions. My early responses were surrealistic with images, textures arriving automatically. What fascinates me now in this vague and often undifferentiated landscape is the sense of atmosphere itself, experienced variously, with emptiness or in brilliance, when there is water lying there, or not, etc." The following paintings are from this earlier period.

Antibiotics and the consciousness of microbes: Microbes might be a god or a kind of god – 'the generation of diversity' god. An individual image goes to make up a whole system – a thinking organism. The connections between the microbes, these forming and reforming structures, can easily be understood as a potent life force exhibiting various drives, hence consciousness. A fungus makes decisions. We should think about them on their terms – otherwise it is colonization. We may develop a similar relationship with plants.





**Image 7.1:** Canberra District 12, detail. Source: Peter Cameron with kind permission to publish.

**Image 7.2:** Peter Cameron, Australia. Canberra District 12, 200,1, oil on polyester canvas, 244x92cms Source: Peter Cameron with kind permission to publish.



**Image 7.3:** Peter Cameron Canberra District 8, 2001, oil on polyester canvas, 244x92cms. Source: Pater Cameron with kind permission to publish.

**Image 7.4:** Canberra District 8, detail. Source: Peter Cameron with kind permission to publish.

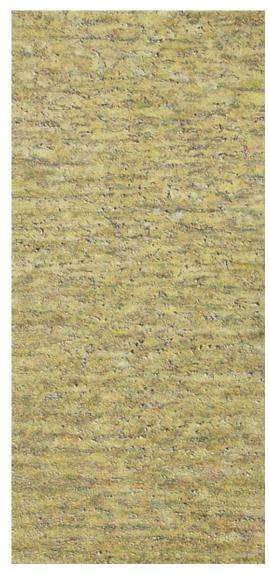






**Image 7.5:** Canberra District 9, detail. Source: Peter Cameron with kind permission to publish.

**Image 7.6:** Peter Cameron Canberra District 9, 2001, oil on polyester canvas, 244x92cms. Source: Peter Cameron with kind permission to publish.



**Image 7.7:** Peter Cameron Canberra District 3, 2001, oil on polyester canvas, 244x92cms. Source: Peter Cameron with kind permission to publish.



**Image 7.8:** Canberra District 4, 2001, oil on polyester canvas, 244x92cms. Source: Peter Cameron with kind permission to publish.







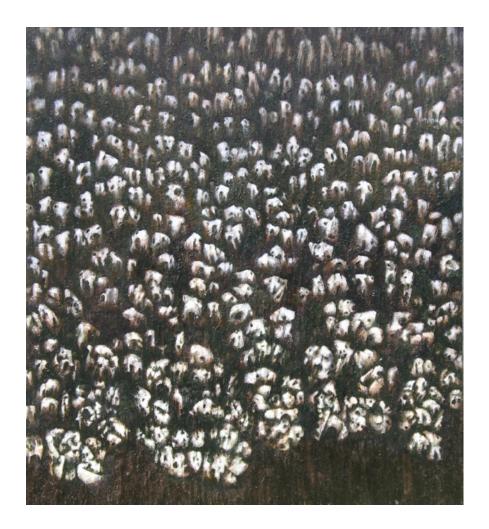
**Image 7.10:** Peter Cameron Guthega, 13, 2005, oil on linen, 137x122cms. Source: Peter Cameron with kind permission to publish.



**Image 7.11:** Peter Cameron Guthega 31, 2005. Oil on linen, 153x84cms. Source: Peter Cameron with kind permission to publish.



**Image 7.12:** Peter Cameron, Untitled no. 2, 2004, oil on , polyester canvas, 154x84cms. Source: Peter Cameron with kind permission to publish.



**Image 7.13:** Peter Cameron Untitled no. 4. Source: Peter Cameron with kind permission to publish.

# 7.2 TRACES OF LIVING

#### **Panya Chaiyakam**

Wildlife Artist, Living over Value Equity Project

### Niracha Mongolchai

Public Health Nurse, Living over Value Equity Project, Ratchaburi, Thailand

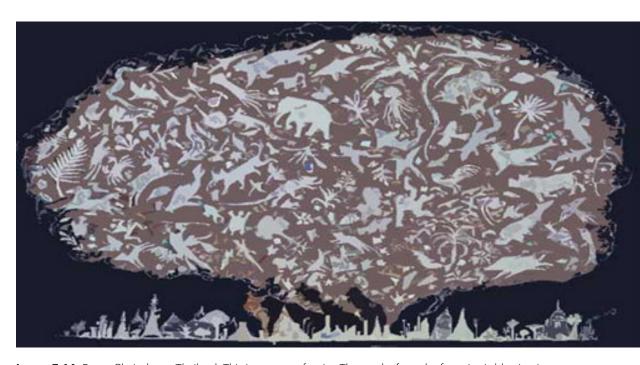
Several thousands years ago, the Old Testament described the earth's creation. The 1st day was light segregated from darkness. The ocean and land with the sky happened later after a few days. Then all creatures including man were created after the 6th day. A great mission was to empower man to rule them all. Man has taken charge of all living things since then. But man is not like god. The relation between man and animals is more like master to the slave or even worse. Man has committed destructive crimes to the environment without ceasing. These have been initiated by people of every social status, whether brave or coward or the craven, the swindler or the courtier.

There was a man around 2500 years ago, who discovered the essence of life, the reasons and motivation of living. To avoid suffering, pain, misery. Those doctrines from him are old, aged, but still up to date and used in the Buddhist adherent's daily life.

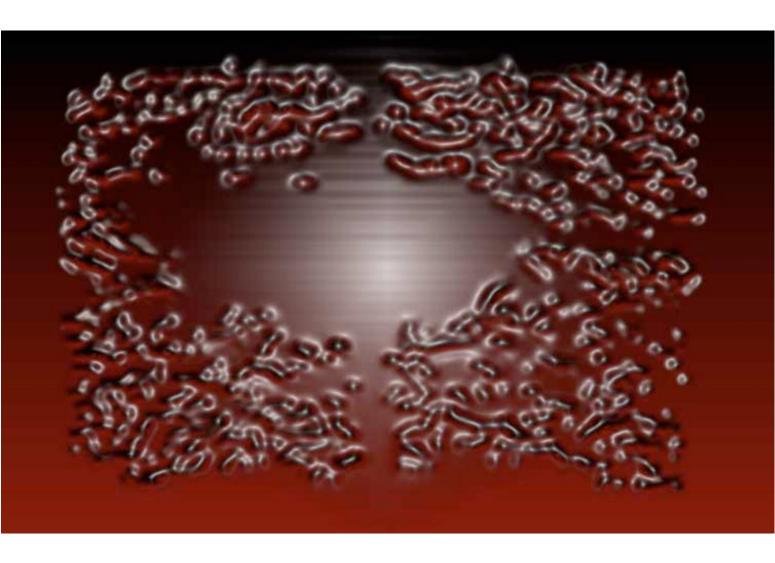
I am not a clergyman, but an environmentalist. I am really attracted to the enigma of microbes. If we could understand the mysteries of bacterial ecology and behaviour of bacteria, might it not be possible to live a complementary life with all species?

**Note:** Panya and Niracha were to have participated in person at the Wee Jasper meeting, but were unable to because of the Bangkok airport sit-in by political protestors in the first week of December 2008. They used the time to create a series of ceramic 'microbes' to reflect on the beauty and nature of real microbes.





**Image 7.14:** Panya Chaiyakam , Thailand. This is scenery of a city. The smoke from the factories is blowing in the air. There is the body of a creature burned by civilisation. We create our civilisation by destruction of natural resources. We burn them all to make our life. Source: Panya Chaiyakam, with kind permission to publish.



**Image 7.15:** Panya Chaiyakam, Thailand. These are six species of bacteria. The concept is that every life can mutate into another. Source: Panya Chaiyakam, with kind permission to publish.



TRACES OF LIVING C.PANYAENIRACHAGDEC2008



Image 7.16: Panya Chaiyakam and Niracha Mongolchai Ceramic microbes Source: Panya Chaiyakam with kind permission to publish.

# BOX2

# THE HUMAN MICROBIOME – WHAT IS THE HUMAN BODY ALL ABOUT?

Human Microbiome Project, National Institutes of Heath, US Department of Health and Human Services

Within the body of a healthy adult, microbial cells are estimated to outnumber human cells by a factor of ten to one. These communities, however, remain largely unstudied, leaving almost entirely unknown their influence upon human development, physiology, immunity, and nutrition. To take advantage of recent technological advances and to develop new ones, the NIH Roadmap has initiated the Human Microbiome Project (HMP) with the mission of generating resources enabling comprehensive characterization of the human microbiota and analysis of its role in human health and disease.

Traditional microbiology has focused on the study of individual species as isolated units. However many, if not most, have never been successfully isolated as viable specimens for analysis, presumably because their growth is dependant upon a specific microenvironment that has not been, or cannot be, reproduced experimentally. Among those species that have been isolated, analyses of genetic makeup, gene expression patterns, and metabolic physiologies have rarely extended to inter-species interactions or microbe-host interactions. Advances in DNA sequencing technologies have created a new field of research, called metagenomics, allowing comprehensive examination of microbial communities, even those comprised of uncultivable organisms. Instead of examining the genome of an individual bacterial strain that has been grown in a laboratory, the metagenomic approach allows analysis of genetic material derived from complete microbial communities harvested from natural environments. In the HMP, this method will complement genetic analyses of known isolated strains, providing unprecedented information about the complexity of human microbial communities.

By leveraging both the metagenomic and traditional approach to genomic DNA sequencing, the Human Microbiome Project will lay the foundation for

further studies of human-associated microbial communities. Broadly, the project has set the following goals:

- Determining whether individuals share a core human microbiome
- Understanding whether changes in the human microbiome can be correlated with changes in human health
- Developing the new technological and bioinformatic tools needed to support these goals
- Addressing the ethical, legal and social implications raised by human microbiome research.

Notably, however, the utility of the techniques and technologies pioneered by the HMP will not be limited to studies of human health but will be applicable to the study of microbes in a wide range of biological processes. Microbes profoundly shape this planet and all life on it, and yet the test tube of the laboratory is rarely reflective of how they actually exist in the environment. The ability to study native microbial communities represents a fundamental shift in microbiology and is one whose implications can only be imagined.

Finally, the NIH Human Microbiome Project is only one of several international efforts designed to take advantage of metagenomic analysis to study human health. The HMP expects to continue the practice established by the Human Genome Project of international collaboration to generate a rich, comprehensive, and publicly available data set. This information will be available worldwide for use by investigators and others in efforts to understand and improve human health. For more information on the Human Microbiome Project, email HMPinformation@mail.nih.gov or visit http://www.hmpdacc.org.

## CHAPTER EIGHT

As science unravels the complexity of the natural ecosystemit iscompelled to rexamine its conventional research methods and innovate new ones. In the processthere istoday new respect and open-mindedness dawning towards indigenous knowledge and ways of living. At the same time the rush to appropriate this knowledge in a utilitarian manner by pharmaceutical companies and researchersis also growing. However as Susan Semple narrates in this chapter, the journey of building real understanding of different knowledge systems across cultural differences requires a journey of adaptation and awakening in itself. Knowledge without respect and without an internal effort to adapt beyond one's social or professional conditioning limits a true ability to understand complexity and live consciously in it. The mysteries of medicinal plants, their healing and other properties are examples of knowledge that do not yield themselves to those unwilling to live and think differently. Overcoming such deeply-held prejudices may be the key to finding new ways to tackle antimicrobial resistance in old systems of knowledge.

# **ECOLOGY OF HEALTH**

### **Sue Semple**

## AFTER

studying undergraduate pharmacy (very much in the Western scientific paradigm), I was drawn to traditional ways of

thinking about health and illness. I guess what drew me to it was a much broader perspective on the way that the environment, a person's spirituality and sense of place influences their health. While Western pharmacology with its targeted approach to combating or preventing illness has certainly had some wonderful achievements I, like many others, recognise that there is much that Western science can learn from ancient knowledge systems.

My particular research focus has been on studying plant medicines used by Australian Aboriginal people for antimicrobial (antibacterial, antifungal and antiviral) and anti-inflammatory activity – focussing on plants used for what Western science would understand as symptoms or signs of microbial infection. In the work I do currently my very strong interest is in research driven locally by the Indigenous communities – research in which they are researchers as well as sharing benefits from research. They drive the research based on their local needs and research interests. The groups I work with are keen to see a much broader recognition of the role that traditional medicine can have for health and social outcomes for Indigenous people in Australia, as well as the broader Australian and global community.

Much of the work that has been done on the pharmacology and chemistry of Australian plants in the past (including some of the work I have done myself in the past) has been driven by University academics or pharmaceutical research groups. It is often based on the traditional uses of plants recorded in the literature (public domain). However, in my opinion, without the research being

driven or involving Indigenous communities this type of research only serves to further disempower Indigenous people who see this as their knowledge being taken away and exploited without incorporating their understandings of how the medicine should be used and understood. As one of the Indigenous people I work with put it "the medicine has to pass through our hands in order to work properly" (Mr David Claudie, Chairman of Chuulangun Aboriginal Corporation, Cape York, Old). Use of plants and traditional knowledge without the consent and involvement of traditional owners can cause them great stress as they see it as their responsibility to see that things are used correctly and that they can actually cause harm if they are not.

Some of the Indigenous individuals I work with talk much more about the interplay between the components in their medicines and the microbes in the environment, more about the need for a balance between all things rather than the need to "kill" or "eliminate" the causes of disease. Some of the strongest medicines are those that "protect" a person rather than treating an illness after the fact. Western medicines are often seen as too strong or "raw"(7). For Indigenous people, there is a need to use all the components of the plant medicine together, not just single chemical entities, in order to get the balance of effects without harm.

Certainly we know there is a limitation to single chemical entity antimicrobials with the emergence of microbial resistance. Perhaps the multi-component approach of traditional medicines can be one way of moving away from this. We know that plant extracts can often have several "active" components – and using them together can make it harder for the emergence of resistance. For example other components in a plant can have other effects (including how the body handles, absorbs and eliminates the "active" components) or components that prevent resistance emergence (even if they are not directly antimicrobial themselves).

Caring for the plants used as traditional medicine and the whole environment in which they are a part is also of great importance to the health of Indigenous people. Some studies are starting to recognise the role that natural resource management by Indigenous people on their traditional lands can play in the improvement of their health outcomes (for example see Burgess et al 2005<sup>(8)</sup>).

The challenge I think in the type of work I do as we go forward is also to look at better ways of understanding the activities (from a Western Scientific perspective) of traditional medicine. Testing plant extracts in standard models of antimicrobial, antiviral and anti-inflammatory activity in the laboratory has certainly showed us

<sup>7.</sup> Again, here I am using some of the words of my colleague Mr David Claudie Kaanju traditional owner from Cape York Peninsula

<sup>8.</sup> Burgess, C., F. Johnston, et al. (2005). "Healthy country: healthy people? Exploring the health benefits of Indigenous natural resource management." Australian and New Zealand Journal of Public Health 29: 117-122

some interesting effects. However for the ones that don't show effects in these tests, many of them considered very important medicines – what better ways can we develop to understand how these things work and therefore learn alternative ways of thinking about how we manage microbial infections or other illness?

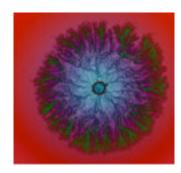
# BOX3

# A MODEL OF SOCIAL COOPERATION Eshel Ben Jacob

Bacteria, being the first form of life on Earth, had to devise ways to synthesize the complex organic molecules required for life. They are able to reverse the spontaneous course of entropy increase and convert high-entropy inorganic substances into low-entropy life-sustaining molecules. Three and a half billion years have passed, and the existence of higher organisms depends on this unique bacterial know-how. Even for us, with all our scientific knowledge and technological advances, the ways bacteria solve this fundamental requirement for life is still a mystery. We do know that this is not a solitary endeavor for the bacteria, and under natural conditions they employ chemical communication to form hierarchically structured colonies, 109-1012 bacteria each. By acting jointly, they can make use of any available source of energy and imbalances in any environments, from deep inside the Earth's crust to nuclear reactors and from freezing icebergs to sulfuric hot springs; and they can convert any available substances, from tar to metals.

Under unpredictable hostile environmental conditions, when the odds are against survival, the bacteria turn to a wide range





#### **Hexamita** Image EBJ 1: Bloody Mary - the colony cooperates to solve problems

The shape of the bacteria colony shown in this and the following photos demonstrate how members of the colony cooperate to solve problems.

(Bacteria colony images shown are in false colour; see other examples at http://star.tau.ac.il/~eshel/).

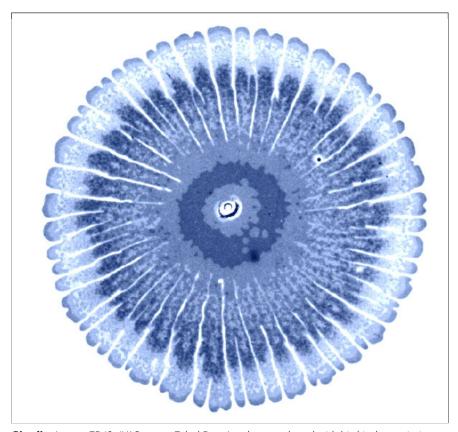
of strategies for adaptable collective responses. These cooperative modes of behavior are manifested through remarkable different patterns formed during colonial self-organization. The aesthetic beauty of these geometrical patterns is striking evidence of an ongoing cooperation that enables the bacteria to achieve a proper balance of individuality and sociality as they battle for survival, while utilizing pattern-formation mechanisms that we have only recently begun to understand.

#### **Communication**

Efficient adaptation of the colony to adverse growth conditions requires self-organization on all levels--which can only be achieved via cooperative behaviour of the individual cells. For that purpose, bacteria communicate by a broad repertoire of biochemical agents. Biochemical messages are also used in bacterial

**Electryfire Bacteria:** Image EBJ2: '-2-' .Source: Eshel Ben Jacob reproduced with his kind permission

linguistic communication for exchange of meaningful information across colonies of different species, and even with other organisms. Collectively, bacteria can glean information from the environment and from other organisms, interpret the information (assign meaning), develop common knowledge and learn from past experience. The colony behaves much like a multicellular organism, or even a social community with elevated complexity and plasticity that afford better adaptability to whatever growth conditions might be encountered.



Giardia: Image EBJ3: 'H' Source: Eshel Ben Jacob reproduced with his kind permission.

## **Social Intelligence**

In multi-colonial communities (e.g., sub-gingival plaque), bacterial social intelligence is usually used for cooperation between colonies of different species. For example, each colony develops its own expertise in performing specific tasks for the benefit of the entire community, and they all coordinate the work done. Some bacteria undertake the task of keeping valuable information, which is costly to maintain and may be hazardous for the bacteria to store. Frequently, such information is directly transferred by conjugation following

chemical courtship played by the potential partners: bacteria resistant to antibiotics emit chemical signals to announce this fact. Some fundamental aspects of social intelligence are used to handle defectors, as is reflected by



**Mitochondria:** Image EBJ4: 'The end'. Source: Eshel Ben Jacob reproduced with his kind permission.

the variety of strategies Myxobacteria can use when their social intelligence is challenged by cheaters--opportunistic individuals who take advantage of the group's cooperative effort. For example, they can single out defectors by collective alteration of their own identity into a new gene expression state. By doing so, the co-operators can generate a new "dialect" which is hard for the defectors to imitate. This everongoing intelligence clash with defectors is beneficial to the group as it helps the bacteria improve their social skills for better cooperation which can be utilized at other times.

Recent findings even indicate that the bacteria purposefully modify their colonial organization in the presence of antibiotics in ways which optimize bacterial survival, and that the bacteria have a special collective memory, which enables them to keep track of how they handled their previous encounters with antibiotics--learning from experience. Bacteria are clearly capable of developing antibiotic resistance at a higher rate than scientists develop new drugs, and we seem to be losing a crucial battle for our health. We might even discover that the last five decades of evolution in bacterial social intelligence is largely a result of their encounter with our socially irrational massive use of antibiotic materials in agriculture and human intake.

## CHAPTER NINE

What do the little people of the world do when confronted by forces far more powerful than them? History tells us that-like all resistant living organisms- they band together, maximize their collective efficiencies and adopt creative strategies to beat the Goliaths standing on their path.

This is precisely what the thousands of survivors of the Bhopal gas leak of 1984 have done over the past two and a half decades in their battle against the multinational corporations responsible for killing or maiming thousands and the indifferent Indian government that has sold out on their claims for justice and compensation.

Year after year, month after month the survivors have worked together with a large and growing network of supporters around the globe to organize medical treatment for themselves, fight long-drawn out legal battles against the corporation, force local administrators to fulfill their duties and draw global attention to their plight. Though their demands are far from being met there have been plenty of victories too, each precious one of them a testimony to their spirited refusal to give up their right to survive and live as human beings with dignity.

# LEARNING ABOUT AND FROM MICROBES

**Satinath Sarangi** 

Sadbhavana Clinic, Bhopal, India

speak first about my concern regarding microbial resistance that is related to my life as the managing trustee of a charitable clinic. I live and work in a city that was devastated by the worst industrial disaster that is ongoing even 25 years after its occurrence. The city is Bhopal in central India and the disaster was caused by the leakage of an extremely toxic chemical that leaked from a pesticide factory owned and operated by an American multinational corporation.

Over 23,000 people (an overwhelming majority of them being the poorest) have died so far and 150,000 people continue to battle with exposure induced chronic illnesses and their complications. Additionally, 25,000 people living close to the abandoned factory are sick from routine and ongoing exposure to toxic chemicals due to the leaching of recklessly dumped chemical waste into the ground water, the main source of drinking water. Children born to gas exposed and contaminated water exposed parents also carry the marks of Union Carbide's poisons. Unusually large numbers of children are born with congenital malformations and disorders of physical growth and mental development.

There is substantial documentary evidence that Union Carbide corporation was aware of the hazardous design of the factory, its unsafe location and that the management committee located in far away Danbury, Connecticut allowed if not encouraged the retrenchment of workers, the cutting down of vital safety systems and the suppression of information critical to the safety of workers and neighbourhood population with profit maximization as the principal motive. The Corporation paid a paltry sum as compensation that cost it 43 cents per share and gave about US\$ 500 to individuals with lifelong injuries. Charged with

culpable homicide and other serious offences the representatives of the corporation including its former chairman continue to abscond from Indian courts.

In 2001 Union Carbide was taken over by another American chemical corporation – Dow Chemical Company that wanted to spread its business in India. In clear violation of two principles, that of "polluter pays" and "successor liability", that are well established in USA and India, Dow Chemical continues to refuse to cleaning up the contaminated soil and ground water or pay compensation to victims of contamination. With much support (overt and covert) from the Governments of USA and India the crimes of the two corporations remain unpunished.

In the last 24 years the Indian government has consistently placed the interests of the two corporations over that of the Bhopal victims. Agreeing to a paltry settlement on behalf of the victims and downplaying exposure related deaths and injuries are the most obvious manifestation of official collusion. The industrial disaster in Bhopal was followed by a medical disaster of unprecedented proportions. Union Carbide continues to withhold information on the health impact of exposure to the leaked gases claiming that these information were trade secrets and medical research by Indian official agencies have yielded little in terms of guidelines for treatment. Substantial funds from the public exchequer have been allocated to health care and social, economic and

environmental rehabilitation but this has made little impact on the plight of the victims. So many hospitals have been built that the ratio of the number of beds per thousand people in Bhopal is higher than that in Europe and USA. However, these hospitals do not have the required specialists and doctors, equipment and quality medicines.

While official research has shown that the poisons inhaled by the victims crossed the pulmonary barrier and caused damage to almost every organ standardized treatment protocols specific to sustained amelioration of symptom complexes have never been developed. In the absence of information symptomatic treatment has been the dominant response of the doctors in Bhopal providing only temporary relief if at all. Ironically, the disaster caused by chemical corporations has led to a windfall for the pharmaceutical corporations, which are but part of most chemical giants. There is much that shows that the treatment provided to the victims is causing more harm than good. Indiscriminate prescription of antibiotics, steroids and psychotropic drugs is part of the iatrogenic injuries that have compounded those inflicted by toxic exposure.

Epidemiological and clinical studies by independent researchers have established that damage to the immune system is prominent among the exposure-induced injuries with long-term consequences. Unusually high prevalence of infectious diseases has long been documented by official research. Routine and



large scale antibiotic misuse including prescription without evidence of sensitivity of infecting organism/s, inadequate dosages and inappropriate duration are on record and continue unabated. While there has been no research directed at assessment of antibiotic resistance, data from our clinic suggests that this could well be among the world's highest. Given that a substantial proportion of the half million victims have been regular users of antibiotics there is a distinct possibility that pathogenic organisms in the city's water supply system are resistant to a range of antibiotics. Rates of multi drug resistant tuberculosis are also reported to be alarming.

At the Sambhavna clinic we have responded to this ongoing situation of rampant infection by resistant microorganisms by strictly following standardized antibiotic protocols, devising means for better compliance of recommended regimes and liberal use of microbiological investigations. The latter is not always possible in acute conditions given the time taken for results of culture/sensitivity examinations to be available. Additionally, the clinic with its facilities of concurrent treatment via Ayurveda (indigenous system of medicine based on herbs) and Yoga is uniquely positioned to design creative responses to resistant pathogens. Plant based medicines known to boost immunity and Yoga postures and Pranayama breathing exercises that lower physical and mental stress and improve lung function are incorporated in the treatment protocols designed by Sambhavna. However, these responses remain inadequate and despite these efforts morbidity and mortality among patients undergoing treatment at Sambhavna continue to be a matter of great concern.

In my other life as a campaigner for justice in Bhopal and a life of dignity for the poisoned people, one of my chief concerns has been related to the hierarchy and autocracy in the survivors' organizations. The lack of democracy in organizations campaigning for social justice is not restricted to just Bhopal, rather it is to be found in most if not all such organizations in the country. The Bhopal disaster has rightly been construed as manifestation of the crisis of the high-tech development policies pursued by the Indian government since the late 1950s. In the same vein the response of the survivors organizations to the disaster showed up the crisis within the mass movements in the country. While official apathy and corporate evasion have been the main reasons for the delay in survivors getting their demands fulfilled, the internecine feuds between organizations, the egotistical ways of the leaders and the lack of questioning by the followers have also played a significant role.

In my forty years of political activism I have associated with a large number of political organizations and have found most of them to be hierarchical, centralized, sectarian and stifling. Most organizations have a top down structure and individuals in the lower rungs are largely expected to unquestioningly follow the top leadership. I have seen several organizations.

nizations successfully challenging the powers that be but subsequently getting co-opted or crushed or broken up in to several factions primarily because of the lack of a democratic structure. In my view, organizations striving to change the world need to be organized differently, radically differently, from the way the corporations and governments are organized. The issue has been recognized the world over and one sees many attempts for ushering radical democracy within campaigning organizations and these efforts are most visible in the global campaigns against the World Bank.

However, these attempts are few and far between, are very limited in application and do not have many working models for inspiration and emulation.

As a campaigner yearning for a model for radical democratic social-political organization I am curious to know more about the organization of microbial collectives. I have gathered, from the little that I have learnt about microbial resistance, that the reason microbes can successfully deal with wide ranging attempts towards their elimination is because of the way they are organized. I think there are vital lessons to be learnt from microbial collectives for people and organizations that are confronting power and asserting their right to life and liberty. Personally, I am hopeful that these lessons can be of much significance for the ultimate victory of the survivors in Bhopal.



#### RESISTANCE A LA BHOPAL

25 years after a catastrophic gas leak from a Union Carbide pesticide plant in Bhopal, India killed nearly 10,000 people and left thousands disabled for life the survivors of the world's biggest industrial disaster are still fighting for justice.

For the past two and a half decades, the survivors have demanded:

- That Warren Anderson, the then CEO of Union Carbide Corporation, be arrested and brought to justice;
- That the toxic wastes in and around the factory premises be cleaned up immediately;
- That medical research and rehabilitation be taken up for survivors;
- That economic rehabilitation measures be initiated for all survivors.

While their unmet demands are clear evidence of the low quality of justice available both in India and internationally the continuing global campaign of the survivors also speaks volumes about their phenomenally resilient spirit. Here are some of the poorest people in the world, poisoned and horribly maimed still taking on the combined money and muscle power of large governments and corporations without ever giving up.

What's more, all this struggle without abandoning their ability to smile, laugh and have fun even in the face of severe adversity. Go to the shanty towns of Bhopal, where most of the survivors of the gas leak still live, and you will find it teeming with life, full of energy and enthusiasm for the never ending Big Fight.

Over the years, campaigners for justice to the Bhopal survivors have deployed a bewildering array of methods to book the culprits responsible for various aspects of the disaster. There have been the usual street protests, rallies and sitins of course but also powerful media campaigns, imaginative public actions aimed at waking up insensitive high government officials and even several hoaxes tinged with humor pulled on chemical industry executives.

In the late nineties, for example, when bureaucrats in the Madhya Pradesh government refused to take action on demands that clean drinking water be provided to survivor settlements protestors took on a campaign to give them 'sleepless nights'. This was done by dozens of people, standing outside the homes of the bureaucrats night after night banging pots and pans and singing loudly, giving sound to their anger.

In 2008 Bhopal campaigners carried out a hoax on international television when one of them pretended to be a Dow Chemicals executive and in a live interview with the BBC 'accepted' culpability for cleaning toxic wastes still left behind by the gas disaster of 1984! Dow officials scrambled to undo the public relations damage done by this but it was already too late to prevent their stock prices in world markets from taking a sharp dip.

The network of ordinary people who have got involved in supporting the cause of Bhopal survivors has steadily grown around the globe with everyone from university students and professors to celebrity authors and factory workers joining in. The gravity of the injustice meted out to the people of this central Indian city is one reason of course but more than that there is something contagious about the sheer enthusiasm and assertion of their right to survive that has turned their local fight into a global battle.

To anybody who has followed the struggles of Bhopal's survivors over the last two and a half decades an image that surely pops up in their heads is that of a complex ecosystem, wounded and yet bustling with life, resisting both the deadening, heavy hand of state machineries and the toxic trails of corporate greed. Almost like little microbes resisting their own demise in the face of a relentless assault by the human species and its ever-expanding industrial civilization.



know from the history of science when a particular paradigm loses the ability to convince, no amount of pottering along the same path can restore its powers of explanation. At some stage you need to pack your bags and leave on a long journey away from dead certainties and established method into the unpredictable but very alive realm of the unknown. It is only then that there can finally occur a shift in paradigms to capture the new truth about old realities.

While it may still be premature to write off the paradigm that governs the world of antibiotics, the 'miracle drug' of the 20th Century, there is no doubt it is certainly in deep crisis. The phenomenon of antibiotic resistance, that coincided with the very advent of antibiotics almost seventy years ago, continues unabated, threatening to render every new antibiotic invented in all these decades completely impotent.

Luckily, for the future of our ability to tackle infectious diseases, this crisis is also leading to a rethink of conventional approaches. In particular there is now a much needed questioning of the dominant paradigm of 'war' that has operated for long in the medical view of disease-producing bacteria, according to which 'antibiotics' are the 'magic bullets' to be used to vanquish 'enemy' microbes.

In June 2005 the Institute of Medicine (IOM) of the US National Academy of Science organized a seminar titled 'Ending the War Metaphor: The Changing Agenda for Unraveling the Host–Microbe Relationship', that called for a completely new look at how diseases develop and what is needed to tackle them. This path-breaking seminar was followed up in 2008 by a public workshop organized by the IOM's Forum on Microbial Threats to examine Dr. Joshua Lederberg's scientific and policy contributions to ideas in the life sciences, medicine, and public policy. Dr. Joshua Lederberg - scientist, Nobel laureate, visionary thinker- who died on February 2, 2008 was among the first to suggest a paradigm shift in the way we identify and think about the microbial world around us. He recommended replacing notions of aggression and conflict with a more ecologically -and evolutionarily- informed view of the dynamic relationships among and between microbes, hosts, and their environments.

In his seminal essay titled 'Infectious history' Dr Lederberg pointed out that " ... our most sophisticated leap would be to drop the Manichaean view of microbes--"We good; they evil." Microbes indeed have a knack for making us ill, killing us, and even recycling our remains to the geosphere. But in the long run microbes have a shared interest in their hosts' survival: A dead host is a dead end for most invaders too".

The IOM workshop presentations, made by many former students and colleagues of Lederberg, demonstrated the extent to which conceptual and technological developments have advanced our understanding of the microbiome, microbial genetics, microbial communities, and microbe-host-environment interactions.

Recent research in a variety of disciplines is indeed uncovering a new paradigm in microbiology, with lots of implications for understanding antibiotic resistance. Exciting new insights are emerging into how bacteria operate collectively as a colony as opposed to individual behaviour; the complex communication and decision-making processes that take place within bacterial colonies; the diverse ensemble of microbial life that inhabits the human body and their impact on our health; the critical role of bacteria in the evolution of the human body itself; and new mechanisms that confuse or contain pathogenic microbes wi-

thout necessarily 'eliminating' them thereby reducing chances of resistance.

Some microbiologists feel that studies of the human 'microbiome' could blur the line between bio-medical and environmental microbiology. While only a few major groups of the world's bacteria live in the human body, within these groups are countless bacterial species that vary greatly from person to person and within individuals too<sup>(10)</sup>.

Other research has focused on the role of microbial signalling among bacterial communities within the human body. Studies of human blood and urine show that our bodily fluids are filled with metabolites produced by our intestinal bacteria and the influence of gut microbes ranges from the ways in which we metabolize drugs and food to the subtle workings of our brain chemistry<sup>(11)</sup>.

The growing body of knowledge in microbiology is thus also throwing up a need for new metaphors with which we can understand microbial life and their complex relations with the human species and other forms of life in general.

Some of the new insights that have emerged microbiology in recent times have to do with the sheer scale and capabilities of the microbial world. As Dr Michael Gillings, an evolutionary

<sup>10.</sup> Cornell University microbiologist Ruth Ley for example has co-authored a paper arguing that human microbiome studies could bridge the divide between biomedical and environmental microbiology.

<sup>11.</sup> Nicholson

biologist at the Macquarie University in Sydney says, "It is only in the last fifteen years that we have realized exactly how many microorganisms there are around. To give you an example, we have named 5000 bacterial species but we now suspect that there could be anything from 5 million to 100 million bacterial species. We also have begun to realise that bacteria can do anything. They can live at 120 degrees Celsius, they can grow in frozen snow, they can live in solid rock three kilometers down underneath our feet, they can live in cooling pipes of nuclear power plants, and they can survive for tens of millions of years in salt crystals."

These startling facts are a good antidote to the long dominant idea that the solution to bacterial diseases lies in the complete elimination of pathogenic bacteria from our bodies and its surroundings. Antibiotics were a product of this approach and worked quite spectacularly for a while before hitting the road-block of resistance- that shows the need for other ways of conceiving of both the problem and solution involved.

In fact the new research in microbiology brings up the question of whether it makes sense to dub any but a very few sets of bacteria as being 'pathogenic' at all when their behaviour depends so much on the status of the host they live on? It may be more fruitful to understand what turns this host-microbe relationship to a pathological one? Such a nuanced approach would also help us realize that the vast,

huge majority of microbes are beneficial for our personal and eco health.

Yet another fascinating aspect of the new emerging knowledge in microbiology is also that it could help sharpen our understanding of human societies and behaviour.

Recently scientists, led by well-known Israeli theoretical bio-physicist Eshel Ben Jacob, studying how bacteria under stress collectively weigh and initiate different survival strategies said they have gained new insights into how humans make strategic decisions that affect their health, wealth and the fate of others in society.

Their study, published in the early online edition of the journal Proceedings of the National Academy of Sciences, was accomplished when the scientists applied the mathematical techniques used in physics to describe the complex interplay of genes and proteins that colonies of bacteria rely upon to initiate different survival strategies during times of environmental stress.

The authors of the new study say that how genes are turned on and off in bacteria living under conditions of stress not only shed light on how complex biological systems interact, but provide insights for economists and political scientists applying mathematical models to describe complex human decision making.

The idea that we can learn something about human behaviour by studying microbes raises

the intriguing possibility that the study of human societies can also yield valuable information about microbial activity. After all, despite the phenomenal difference in scale between microbes and humans, essentially what we are talking about is behaviour common to all living organisms- the search for nutrition, security, reproduction and comfort zones of different kinds.

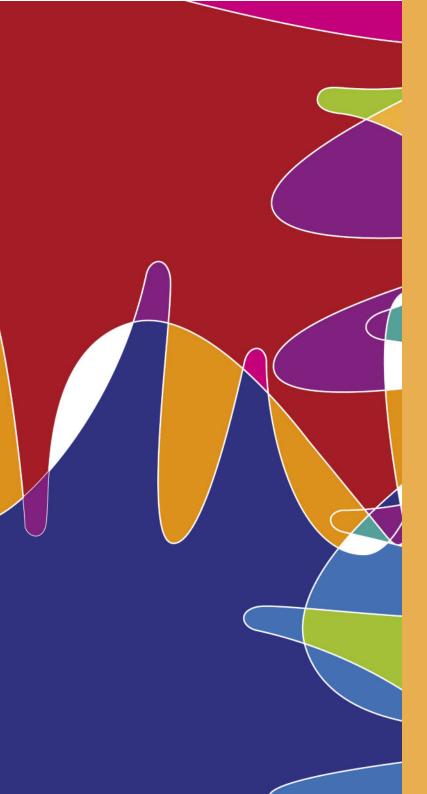
So it could very well be that the metaphors framed by human economy, art, culture and even politics of medicine and healthcare could offer new insights into how resistance develops and how it can be avoided.

Art for example, deals with new ways of understanding and describing reality. So it can perhaps help us capture some of the processes that are not adequately described by current terminology and go beyond what the 'trained' mind can visualise or imagine. Furthermore, setting aside purely utilitarian concerns, good artists can help capture the sheer beauty and mystique of microbial life on our planet- a process that could help the human species develop some more humility about its position and role on Planet Earth.

These are the kinds of questions and issues that the Microbes and Metaphors project of ReAct or Action on Antibiotic Resistance seeks to address by bringing together scientists, artists and social activists on common platforms and developing a cross-sectoral understanding of the microbial world and antibiotic resistance.

This is of course a very exciting but unknown journey, not unlike that undertaken by the early astronomers as they gazed at the skies in ancient times for answers to the various mysteries of both earth and heaven. The only difference may be that instead of 'outer space' it is the invisible 'inner space' of microscopic living organisms that will be explored. Who knows, maybe the impact of the new knowledge emerging could prove to be as profound as that wrought by the study of the stars on human societies and systems?

A dialogue berman and artists and artists and artists · ADIALOGUE BETME Adiatosie between scientists and artists



In December 2008, a group of artists, microbiologists, clinicians and health activists come together, at Wee Jasper, NSW, Australia, to discuss their view of microbes, antibiotic resistance, art and society. The Microbes and Metaphors report is an edited compilation of the presentations made and the discussions and debates that took place then.

The Wee Jasper workshop, titled 'Re-imaging bacteria, infection and the body: A dialogue between scientists and artists' was a pioneering multi-disciplinary effort to reconceptualise the perception of microbes and their relation to the human body. Subsequently, some of the ideas emerging from the workshop have shaped the 'Reimagining Resistance' initiative, which continues to explore the scientific, artistic, social and cultural dimensions of antibiotic resistance to both understand the phenomenon in itself and also our response to it.

This report, originally published as a limited edition in October 2011, is now being redesigned and reprinted for wider circulation both in hard and soft copy versions.

