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An Evening with Brian: The Disease Revolution*

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ATTITUDES TO INFECTION

Microscopists have been at the forefront of one of the greatest achievements of modern society: the conquering of infectious disease. Sometimes it has been through improvements in hygiene; sometimes it has been due to our understanding of epidemiology, often it has been based on laboratory work with the microorganisms that cause infections. We all rightly hail this great challenge as a hallmark of recent centuries and we know that it represents a triumph for science. But there is a danger in our optimism. It is too easy to assume that we have been ticking off diseases from an ever-growing list, with ever fewer targets for our attention. But that is not the whole story. There are new challenges for the future, and there are new diseases currently emerging that will preoccupy us in the years ahead. About these emergent infections much less is said, so let us take a look at what may be consuming our energies as this new millennium unravels.

Microbiology spent many years almost as a Cinderella science. Half a century ago new students were being warned off the topic; all the diseases are known, now, they were told; microbiology is wrapping up the loose ends and with antibiotics in abundance we could look forward to an end to the problem of infectious diseases. Such was the zeal of this message that people rarely stopped to point out our complete lack of any treatment for virus diseases; and to those that did raise the problem, the promise of vaccination was offered as the answer. I was told this in 1960 at Cardiff University. When I compiled the history of the Institute of Biology in London (it was published last year by the Institute under the title of *The First Fifty Years*) our outgoing President, John Norris, quoted his experience in 1950. He told me: "My professor explained . . . that we had antibiotics to control most bacterial diseases and given about five years we would be able to treat all of them; then the subject would be finished."

CURRENT CONCEPTS

As a direct result of this legacy, microbiology has been given a back seat. Isn't it curious that, although the public are familiar with such scientific concepts as the rings around Saturn, DNA, a computer chip, the lunar craters and microorganisms, it is this last example - the microbe - which the public never see. They know what all the others look like, and could probably draw them for you, but have no concept of what microorganisms are like. Little wonder there is not much attraction by microbiology to the typical school pupil. As a society, even in this most scientific era, we remain largely blind to microbes.

Microbes as organisms figure less than they should in microbiology. The organismal approach that I advocate so strongly has been largely overtaken by molecular biology. Now, nobody must imagine that this is a science of which I don't approve; some of my best friends are molecular biologists. Max Perutz, the man who invented the science, is an inspirational friend[1] and Fred Sanger, who discovered how to sequence DNA, is also a man I much admire. Both are Nobel prizewinners, and their science has revolutionized biology. Nobody could ever over-estimate the value to us all of their inspiring contributions.

The problem has been that the novelty of these new sciences made them fashionable. Young scientists jumped on the bandwagon and turned away from a fundamental requirement of modern science - to see living cells as entities in their own right. We now understand the mechanisms pretty well, but have lost sight of the whole.

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[1] Dr Perutz died of cancer on February 6, 2002

Example 1: the Legacy of Tuberculosis

There are practical consequences of all this. Let us look briefly at tuberculosis as an example. This is a disease, typically of the lung, caused by the waxy-coated rod-shaped bacterium *Mycobacterium tuberculosis*. The wax coating makes it difficult to stain; it is acid-fast on the slide, but its hydrophobic nature makes it somewhat resistant to conventional disinfectants. Tuberculosis (TB) has an old-fashioned resonance; it's not a fashionable disease. Its ancient legacy gave it a whole raft of different names over the centuries: consumption, King's evil, phthisis, scrofula, even 'white plague'. It was a disease associated with the lean and hungry artist, and with good reason. Look at some of those who died of the disease:

Frederick Chopin (died 1849 aged 39)
composer
John Keats (died 1821 aged 26)
poet
Robert Louis Stevenson (died 1894 aged 39)
author
Anton Chekhov (died 1904 aged 43)
playwright
Franz Kafka (died 1924 aged 40)
surrealist
The Brontë family:
Maria Branwell (the mother, died 1821 aged 39)
Her offspring:
Maria (died 1825 aged 12)
Elizabeth (died 1825 aged 11)
Branwell (died 1848 aged 31)
Emily (died 1848 aged 30)
wrote *Wuthering Heights*
Anne (died 1849 aged 29)
wrote *Agnes Grey*
Charlotte (died 1855 aged 39)
wrote *Jane Eyre*

Whole families were sometimes killed by the disease. It claimed the founder of Harvard University John Harvard, who died in 1638 aged 31, and took a toll among microbiologists. Rene Laennec, who discovered the acid-fast bacteria, died of the disease in 1826, as did the leading TB research worker Max Lurie who died 1966 aged 73.

The use of the BCG vaccine helped to prevent the spread of the disease, and antibiotics were of great value in treating it. Streptomycin was introduced in 1944, yet by 1947 resistance was being observed. *Para*-aminosalicylic acid (PAS) was shown to have weak anti-tubercular effects in 1946, and from 1948 PAS and streptomycin were issued together to treat the condition. In 1952 streptomycin was replaced by isoniazid, followed by pyrazinamide in 1954, cycloserine in 1955, ethambutol in 1962 and rifampicin in 1963. A range of aminoglycosides is now available, including amikacin, capreomycin, viomycin and kanamycin. They are sometimes used with quinolones such as ofloxacin and ciprofloxacin for resistant strains of the organism. There are some new macrolides waiting in the wings.

These methods of assault led to TB being seen as progressively less of a threat. An impressive building in Cardiff, Wales, known as the Temple of Peace, was conceived in the 1930s as a center for the war against TB, but by the 1970s it was felt that there was no further use for it. Tuberculosis was believed to be a vanquished disease. As a result of such attitudes, the United States does not have a routine program of BCG vaccination against TB. The United Kingdom, which has had such a program for decades, recently cut back on the program because of 'difficulties in obtaining supplies' of the vaccine. One hundred years ago, TB was the leading cause of death. Now it is widely regarded as a matter of low priority.

Tuberculosis in Today's World

Our indifference is not substantiated by the facts. One-third of the human population is infected with tubercle. There is a new case of TB somewhere in the world every second. Each undetected patient will infect roughly 20 new people in a year. Resistant strains are becoming widespread, and those infected with drug-resistant tubercle suffer a 70 percent risk of mortality.

Rates of infection in the West have increased steadily for the past twenty years. In the 1930s, there were about 175 per 100,000 of the US population. By 1965 that had fallen eighty-fold, to 2 per 100,000. By 1992 the figure had gone up more than twenty times to 52 per 100,000. Victims of HIV are particularly vulnerable. The Centers for Disease Control and Prevention (CDC) currently estimates that there are now up to 15 million people infected with TB in the United States. This is not a problem of yesterday, and it is not going away.

Programs to control the disease have been sporadic. In 1948 Seattle, Washington, introduced a TB control scheme that involved screening almost 400,000 residents. Of those, 400 TB patients were identified. They were admitted to the Firland Tuberculosis Sanatorium. In response to the high proportion of vagrants among the positive cases, Firland set up Ward 6 as a secure confinement facility. Patients could be confined indefinitely, and without due process of law. Within twenty years, poor patients were being detained for disciplinary reasons, even if they had no signs of ac-

They're everywhere

Superbugs may be more widespread than anyone had realised

MORE than 1 in 10 British children are carrying superbugs resistant to one or more antibiotics. The proportion of adult carriers could be even higher.

The superbugs are no immediate threat to those carrying them, but could cause dangerous infections after an operation, for example. Carriers can also infect other people.

The finding has serious public-health implications, warns Michael Millar of Bart's and the Royal London School of Medicine, the study's author. "This may be just the beginning of something that will take off in a because this allows these bugs to thrive while susceptible strains die.

But the researchers found that resistance to drugs such as chloramphenicol was usually linked to resistance to more commonly used antibiotics, such as ampicillin, which is often given to children. This implies that the genes that make the bacteria resistant are found on the same piece of bacterial DNA, and are passed on together. So giving people ampicillin can encourage bacteria to acquire and hang on to bits of DNA that make them resistant to other drugs as well.

1) This current report in New Scientist *(May 19, 2001) concludes that over 10 per cent of British children now carry multiple antibiotic-resistant staphylococci. MRSA is a growing hazard in American hospitals.*

How would I become infected?
The virus is spread by bacteria in microscopic droplets, which can remain airborne for hours after coughing, sneezing or speaking. Close contact with an infected person is the most common way of contracting TB,

2) The mass media regularly perpetuate misinformation, usually through ignorance. As this cutting from the Sunday Times exemplifies, bacteria (like tubercle) are often wrongly designated as a 'virus'.

NEW DISEASES

Research has shown that these are not new diseases at all. They are changed forms of old diseases. Viruses can become used to antibiotics. The antibiotics no longer work. When this happens, new antibiotics have to be developed. Some viruses can change before an antibiotic has been developed to fight them. Genetic engineering and biochemistry now play an important part in finding and fighting these viruses.

3) In this startlingly muddled textbook, we find that 'viruses become used to antibiotics' irrespective of the fact that they are unaffected by them; and we then read that they can mutate before antibiotics are even ready'. Extract from Fiona Reynoldson's Medicine Through Time*: 93, London, Heinemann 1996.*

nstructions as to

CHOLERA.

1832.

Observe the strictest cleanliness both in person and dwellings. Avoid all chances of being *chilled*, and keep the body warm, particularly the stomach, bowels, and feet.

Avoid placing the feet upon the cold floor.

Abstain from sleeping on the ground, or with windows open.

Avoid the cold and damp of the night air.

Avoid excessive fatigue.

Whatever may be the weather or season, do not go too lightly clad.

Sobriety cannot be too strongly recommended.

Abstain from *undressed* food of every description, and especially unripe fruit.

All *cold* drinks, when a person is heated, are very dangerous. Instead of drinking pure water, mix with two teaspoonsful of Brandy to a pint.

Excessive use of strong liquors is highly dangerous, and taking unmixed Brandy, *when fasting*, is equally so.

All Beer or Cider of bad quality, ought to be avoided.

Every person who feels himself suddenly affected by dull pains in the limbs, heaviness, or giddiness in the head—a feeling of oppression, uneasiness about the chest, heartburn, or cholic, should *immediately* apply to a Physician.

4) This handbill giving advice on avoiding cholera was circulated in London in 1832. It contains advice we would now consider appropriate, notably an avoidance of cold drinks and unwashed fruit.

5) The author with Nobel-winner Professor Fred Sanger (left) at the Royal Society in London. Gene sequencing, developed by Dr Sanger, now allows us rapidly to identify pathogens.

tive TB. After widespread protests, legal hearings began. In 1973 Firland was shut down permanently.

It was not the end of the practice, however. During the 1990s there was an upsurge in cases in New York City, and the New York City Health Code of 1994 permits the forcible treatment of patients. Particularly noteworthy is Section 11.47(d), which allows the authorities to issue 'any order deemed necessary to protect the public health.' Persons who may be detained include those refusing treatment, and even people who may have been in contact with a victim. Patients who leave the hospital early, or whom are regarded as 'unreliable' over taking their medication, can be detained. Between 1993 and 1995, over three hundred people were detained; the median length of forcible detention was 28 weeks for noninfectious patients. Legal review is due each 90 days.

Even if this seems draconian, new measures of this sort are still being introduced. Lousisana State is introducing a similar scheme this year, sanctifying the detention of recalcitrant patients against their will. The Lousiana measures have more built-in safeguards (the patient's own examining physician is the certifying doctor preferred by the authorities, for example), but these new measures illustrate how seriously the authorities are taking the recent upsurge in cases of TB.

The paradox is that these outbreaks are facilitated by a national failure to immunize people against the infection. Vaccine is available; it is not being used. In an era where resistant strains of bacteria are becoming even more widespread, I do not believe that it's right for us to detain people in this way when tried and tested methods of prevention are readily available.

Example 2: Methicillin-resistant *Staphylococcus aureus*

Vaccination is not the answer to everything. We cannot vaccinate against *Staphyloccocus aureus*, much to our chagrin, and resistant strains are now spreading widely. Methicillin-resistant *Staphylococcus aureus* (MRSA) first appeared as long ago as 1969. Although it was initially slow to spread, it gained momentum as it did so. In Canada the resistant strains were just 0.5 per cent of all *S. aureus* isolates in 1995; now they are approaching 10 percent. During the last twelve months, the proportion of *S. aureus* isolates resistant to methicillin has gone up by almost 40 percent.

In today's world this organism is now widespread throughout hospitals and is widely carried by healthy individuals. It has been described as a 'super bug' but it has no greater pathogenicity than ordinary strains of *S. aureus*. The truth of the matter is that the emergence of organisms that are resistant to antibiotics takes us back in time to an era when antibiotics had not been discovered.

Not everything was necessarily worse back in the 1930s. Because bacterial infections were mostly controlled by disinfectants and personal hygiene, standards of hospital hygiene were surprisingly high; and in many over-pressed present-day hospitals hygiene is more widely neglected. Personal hygiene features hardly at all in today's school curriculum; in earlier decades it featured much more prominently. We are suffering a detachment from microbiology - the subject should be taught at school, and taught from a very early age.

CHANGING ATTITUDES

Curiously, in the modern world we have become fastidious about personal cleanliness. Repeated showering is the norm, and sales of deodorant sprays and lotions have risen steadily. Perfumes for men have become popular in recent decades. The effect of this is to compromise the resident flora of the human skin, on many of which we rely for our health. In a leading article for *Nature* on December 11, 1975 (p 469) I described them as 'salugens' (= health promoters) and the term 'probiotics' is now loosely used to embrace these useful species. There is an argument that exposure to environmental microorganisms is important in childhood, as a way of challenging the immune system with antigens. This has much to commend it, but in the modern world we have to ask whether the existence of such challenges can be justified when new and invasive pathogens are spreading worldwide.

One example of the change would be *Cryptosporidium*, a protist spread by the excreta of farm animals. In earlier societies, this organism was habitually contracted during the first few years of life. It caused a trifling dysenteric illness with diarrhea. The disease conferred lifelong immunity to the parasite. In today's Western world we are much less likely to encounter the organism and, as a result, infections of *Cryptospodirium* are much more dangerous. In patients who are elderly or immunologically compromised this once-trivial disease has become a potential killer.

Our penchant for pre-wrapped foods causes additional problems. Food-poisoning organisms can proliferate under cling-film wrapping and within plastic sandwich containers. Levels of food-poisoning are growing worldwide, but we cannot rely on the published figures. We all have contact with victims of food-poisoning, but very rarely report them to the relevant health authorities. Whatever figures are released, we must realize that the true extent could easily be hundreds of times greater.

The Internet is compounding the problem; special meats can be ordered on-line and sent around the world by mail in plain wrappers. Monkeys, game animals, bears, and a whole range of illicit imports are now widespread all around the world. I have speculated that the recent outbreak of hoof and mouth disease in Britain stemmed from the illegal importation of exotic meats from the Far East, and there now seems to be some general agreement that this was indeed the likely source.

Globalization, in the sense of worldwide access to produce, creates new avenues for the international dissemination of infected produce. Mass air transportation imposes new risks of its own. Many Western people think little of casually traveling halfway round the world, and this is a disturbing trend from the viewpoint of the microbiologist. Susceptible people breathing recycled air inside an aircraft are inevitably at risk from a disease spread by one person in their midst. The airliner is a highly efficient means of transporting new infectious disease outbreaks across the world, and we are clearly at risk from new epidemics spread by air[1].

TARGETS FOR ATTENTION BY MICROBIOLOGISTS

For the microbiologist there are numerous organisms of current significance that warrant more detailed attention. We have briefly discussed the cases of TB and MRSA, and it would be instructive to refer to some of the others. In some cases we seem to be frightened of the wrong organisms. For example, *Bacillus anthracis*, the causative agent of anthrax that was recently used in mail-borne terrorism, is not infectious, person to person, and could not trigger an epidemic. Meanwhile, other bacteria are rapidly increasing yet the threat they pose is not widely discussed.

Bacillus cereus

This has long been a personal favorite. It is one of the first bacteria I ever cultured in my teens. It is a widespread gram-positive bacillus and is almost always found in non-sterile foodstuffs. Most of the strains are innocuous; some, however, secrete toxins that produce symptoms similar to those caused by *Staphylococcus aureus* and *Clostridium perfringens*. The organisms produce toxins within contaminated food, typically fish, meat and rice. Symptoms appear some 10 hours after eating. Toxins of high molecular weight produce diarrhea, while those of lower molecular weight typically cause nausea and vomiting. The symptoms usually subside within 24 hours. It is widely estimated that *B. cereus* is involved in 2 per cent of all outbreaks of food poisoning, but the short-term nature of the disease surely means that it is greatly under reported.

Bartonella

This organism produces a disease known during World War I as trench fever. The condition was caused by *Bartonella quintana* spread by lice and the symptoms include splenomegaly, pyrexia, rash and bone pain. Since the 1980s this disease, now more widely known as cat-fever, has re-emerged as an opportunistic infection in victims of HIV, notably in the USA and France. The tick *Ixodes pacificus* from California has since been shown to carry a reservoir of infection. Research in Sweden now suggests that the disease may be causally related to heart attacks in outdoor walkers and orienteers. Antibiotics to which the organism is sensitive include azithromycin, doxycycline, erythromycin and tetracycline.

Campylobacter

Since 1980 this new genus has been widely implicated as a leading cause of enteritis in the USA. There are three species: *Campylobacter jejuni*, which is implicated in ninety percent of outbreaks, with *C. coli* and *C. lari* which account for nine of the remaining ten percent. They are microaerophilic gram-negative organisms measuring 1.5-5 μm in length. The species mentioned here are generally non-invasive, though *C. fetus* is an invasive organism and strains of *C. jejuni* have occasionally been shown to be invasive. These strains cause pneumonia, meningitis, spontaneous abortion and severe Guillain-Barré syndrome. Most cases result from the consumption of fruit, vegetables, meat, poultry, shellfish, milk or water contaminated by animal waste. The bacterium is becoming increasingly widespread in supermarket food.

Chlamydiasis

Venerologists for decades used the term non-specific urethritis (NSU) for infections of the urethral tract. More recently the principal causative organism has been recognized as *Chlamydia pneumoniae*. In a book on sexual health in 1985 the disease was still a recent arrival on the scene, and I proposed that the term 'chlamydiasis' be adopted to identify the condition.

[1] Note that the outbreak of SARS began a year after this lecture. It caused more than 8,000 cases with over 800 deaths. I will examine this subject in the forthcoming *Encyclopædia Britannica Yearbook* for 2004

The era of liberal sexual mores has encouraged the spread of the organism, and during the following five years its incidence in the west increased 500 times. The symptoms are principally those of cystitis, but *C. pneumoniae* can cause a serious inflammation of the fallopian tubes with consequent sterilization of the patient. We are witnessing a virtual epidemic of this infection, and it will leave us a legacy that will be difficult to remedy.

Clostridium perfringens

Here we have a highly infectious organism; as few as 10 organisms per gram of food can cause food poisoning. There are several strains of *Clostridium perfringens* (also known by its earlier name of *C. Welchii*). Type A1 produces enteritis with marked colic. Type A2 produces an enterotoxin, while type C causes potentially serious necrotizing enteritis. Resistance has been reported to chloramphenicol, clindamycin, erythromycin, metronidazole, penicillin, and tetracycline. The spores can survive for prolonged periods, and viable bacteria can survive for a year in meat. The organism will not grow below 4.4°C, so refrigeration is a good means of control.

Helicobacter pylori

Bacteria were once believed to cause a host of diseases, including arthritis. Many people had all their teeth pulled out when the 'focal sepsis' theory was at its height, and infected teeth were seen as a trigger. More recently, bacteria have been casually discounted as a cause of diseases. Barry J. Marshall, an Australian microbiologist, believed that *Helicobacter pylori* were a cause of gastric ulcers. He drank a broth culture of the organism and immediately contracted gastritis. It has since been shown that 90 percent of patients with duodenal ulcers and 70 percent of those suffering gastric ulceration are positive for *H. pylori*. We now believe that there may be a connection with gastric carcinoma, such that the World Health Organization designated *H. pylori* as a 'Category 1' carcinogen in 1994. On the other hand, in Western areas where antibiotics have greatly reduced the incidence of the bacterium, levels of esophageal cancer have been increasing. Perhaps the organism is a familiar inhabitant of the human gastrointestinal tract, where it can help protect against cancer, but which can become pathogenic if its environment is disturbed.

Listeria

Listeria monocytogenes is a gram-positive flagellated bacterium. It has been known since the nineteenth century, and can be isolated from a wide range of animal hosts including about 40 species of mammals. In supermarkets, it has been isolated from soft cheeses, ice cream, raw vegetables, fish and meat, including uncooked sausages. Mild cases are like mild 'flu, sometimes with vomiting and diarrhea. In severe cases septicemia and meningitis can follow. *Listeria* can reproduce within leukocytes. It is also able to reproduce down to 3°C, so refrigeration does not stop its growth. Each year there are around 2,000 cases of *L. monocytogenes* currently reported in the US.

Lyme disease

Borrelia burgdorferi was first identified in 1984 and causes Lyme disease in the USA. Different species, *B. garinii* and *B. afzelii* cause the disease in Europe and Asia. Arthritis is typical of infection with *B. burgdorferi*, while cutaneous symptoms are typical of *B. afzelii* and neurological manifestations are more typical of *B. garinii* infections. The organism is spread by ticks that abound in areas frequented by walkers.

Salmonella

Disease caused by *Salmonella* infection is steadily increasing throughout the West. There are several species of gram-negative rod-shaped organisms, all of which (except *S. gallinarum* and *S. pullorum*) are actively motile. *Salmonella typhi* produces typhoid fever, and *S. paratyphi* causes a similar infection. The initial symptoms include diarrhea, cramping and headache, though severe arthritis may supervene after a month. The bacteria occur in shellfish, soil and water. In the retail environment they have been found in poultry and pork. *Salmonella enteritidis* is characteristic of poultry, and has given rise to advice against eating raw or soft-boiled eggs. There are as many as 4 million cases of salmonellosis in the US each year, representing a six-fold increase in the Northeastern US over the last decade. It is still on the increase.

Vibrio parahaemolyticus

This is the commonest cause of gastroenteritis in Japan. The bacteria are found in estuarine waters and are accumulated by filter-feeding mollusks. As a rule, these vibrios pass through the human gut without causing problems, but they sometimes attach themselves to the wall of the intestine where they secrete a toxin. The resulting disease causes diarrhea and vomiting, cramps, fever and headache. Most cases last for about three days, so it is rarely formally reported. There are about ten species of *Vibrio* that are pathogenic to humans, and many of them are on the increase.

Verotoxin-producing *Escherichia coli*

Verotoxin-producing *Escherichia coli* (VTEC) is also known as *E. coli* O157:H7. This strain seems to have arisen through the acquisition by a harmless *E. coli* of toxin-producing genes. An obscure organism in the 1990s, VTEC has since spread to huge numbers of cattle in the US, and it is increasingly widespread around the world. The bacterium produces a bloody diarrhea that can worsen and lead to widespread lytic damage to internal organs. Lavatory hygiene is important in preventing an outbreak, and so is the avoidance of raw or partly cooked beef. Some cases have been caught by children fondling farm animals at petting zoos. The bacteria have been spread through milk and fruit juice.

EMERGENT VIRUS DISEASES

The organisms we have so far considered, including *Campylobacter*, VTEC, MRSA, and drug-resistant *Mycobacterium* are among the bacterial pathogens that have emerged within the last generation. It is when we bring viruses into the picture that matters become potentially more worrying. There is an impressive armory of antimicrobials that are available for the treatment of bacterial diseases, but viruses pose problems of their own. We can look at a selection of recent arrivals to sense the urgency of the situation.

Dengue fever

Dengue fever is the most widespread of all hemorrhagic fevers across the world. Most cases do not progress to its final stage, but it remains the most rapidly spreading insect-borne disease known. The condition was first seen by Western medical science in 1780, though modern reports of epidemics date only from 1949. The causative agent is a Flavivirus and there are four serotypes (DEN-1, DEN-2, DEN-3, and DEN-4). Immunity to one strain does not confer immunity to the others. The vector of this virus disease is the mosquito *Aëdes aegypti*. More than two billion people live in at-risk areas, and tens of millions of new cases occur each year. Hemorrhagic fever occurs in a quarter of a million cases worldwide per year. Although no vaccine is available, an experimental attenuated candidate vaccine has been investigated in Thailand.

This infection is widespread across Africa, Asia and South America. The symptoms include pyrexia, myalgia, nausea and severe pain accompanied by bradycardia. Typically, the symptoms persist for a week (hence a common name, ‘seven-day fever’). But in others, the immune system collapses, with a further increase in temperature, convulsions, shock and a likely fatal outcome. Hemorrhagic dengue manifests itself as prostration and bleeding from the gastrointestinal tract and elsewhere, and has five percent mortality. In recent years the disease has been appearing in states in which it was previously undetected, including Venezuela (1990), Brazil (1991), Djibouti (1992), and Pakistan, Saudi Arabia and Nicaragua (1994).

Ebola and Marburg hemorrhagic fevers

The dangerous viruses of the Filoviridae were first recognized in 1967. Staff in Marburg, Germany, and Belgrade, Yugoslavia, became infected with a new virus from tissues of the African green monkey *Circopithecus aethiops*. Of the 25 primary cases, 7 had a fatal outcome. There have since been outbreaks in Kenya, South Africa and Zimbabwe.

The related Ebola virus gave rise to outbreaks in Zaire and Sudan in 1976, with over 500 reported cases. The mortality rate was 53 percent in Sudan and 88 percent in Zaire. A year ago there was an outbreak in Uganda of 280 cases of Ebola hemorrhagic fever that resulted in 89 deaths, a mortality rate of 24.9 percent.

Further discoveries of Filoviridae have been made in the cynomolgus monkey *Macaca fascicularis*, native to the Philippines. These are the Reston viruses which, though serologically similar to Marburg and apparently transmissible to humans, do not cause a disease in the human host. The symptoms and course of the diseases are profoundly unpleasant. After an incubation period of 4-16 days fever, headache and myalgia become manifest, soon followed by nausea, dehydration and diarrhea. Hemorrhage appears from all the bodily the orifices, lungs, abdomen and gastrointestinal tract. Vaccination of experimental animals with antigen, and with inactivated whole virus particles, has not revealed a prophylactic benefit following a challenge with live virus. A vivid portrayal of an epidemic in the California hills in the Hollywood film ‘Outbreak’ was drawn to the conclusion that a nuclear attack on the district was the only way to curtail it.

Hantavirus

During the war in Korea, a hemorrhagic fever caused by hantavirus was recognized by US scientists. This is a disease spread by rodents. However, cases have recently been reported from Argentina, Chile, and the US, notably California. The disease has a lengthy incubation period of about a month, followed by the development of severe respiratory disease with a probable fatal outcome. Over the last 15 years there have been 200 cases in Argentina, fewer than 30 in Chile, and a handful in Brazil and the US. A careful watch is being kept for future outbreaks.

Lassa fever

Although the effects of this disease were recorded in the 1950s, this Arenavirus was formally identified in 1969. Many patients act as symptomless carriers, but others develop an overwhelming disease. There is a gradual onset of headache, nausea, cough, vomiting and diarrhea. These progress to severe shock and hemorrhage with severe encephalopathy. It is now known that 15 percent of patients die, and those that survive may suffer deafness and a loss of coordination. The infection is found in Guinea, Liberia, Nigeria and Sierra Leone. There is a secondary host, the rat-like *Mastomys natelensis*. The disease has an incubation period of around 1-3 weeks. In one major outbreak in Sierra Leone in 1996-97, there were 823 cases with 153 deaths, a mortality rate approaching 19 percent.

Norwalk virus

This parvo-like virus has been known since 1972, and is responsible for outbreaks of short-lived gastroenteritis in closed communities such as schools and camps, etc. It is characterized as a mild to moderate illness that lasts only a few days. Since the mid-1970s the virus has been recorded as causing epidemics of enteritis among cruise ship passengers, several of which have had to curtail trips in order to bring home hundreds of complaining passengers.

The cruise companies issue statements about rigorous disinfection of ships over a period of a week or more, though it is actually the crew who need checking as much as the ship. The virus is spread by contact, and one can usually tell a ship that has suffered an outbreak because the staff offer to spray the hands of passengers as they enter the restaurant, or hand out sterilizing hand-wipes. The illness can best be controlled by the use of sensible sterilization by staff on features such as handrails and doorknobs, though few ships have introduced such measures. We will see further epidemics in the years ahead.

Nipah virus

Two years ago there was an outbreak of a new virus contracted from pigs in Malaysia and Singapore. Symptoms included acute encephalitis and respiratory distress that often resulted in death. The causative agent is a hitherto unrecognized Paramyxovirus that has been named Nipah virus, and was contracted from pigs.

By April 27 1999 there had been 257 cases of febrile encephalitis recorded by the Malaysian Ministry of Health, 100 of which died. Cases were then reported in Negeri Sembilan and Selangor. In Negeri Sembilan, almost 90 percent of the victims reported they had recently been close to pigs; two-thirds of the patients reported that the pigs with which they had been in contact had appeared unwell. The virus is probably not transmitted directly from person to person, and it was controlled by the slaughter of 900,000 pigs in the affected areas.

Paramyxovirus

A new equine morbillivirus caused an outbreak of a severe disease in horses and humans in 1994. The virus came from the fruit bat (or flying fox) *Pteropus*. Two outbreaks were reported: one at Brisbane, the other one a month later at Mackay. These towns are over 600 miles apart, and no connection has been found to link the outbreaks.

In the Mackay incident two horses became ill. They both died, and one person died of relapsing encephalitis. The first case in both outbreaks appears to have been a mare late in pregnancy which had been grazing on open pasture. Levels of mortality appear to be high: of 21 horses found to be infected at Brisbane, 14 succumbed to severe respiratory distress. There were two human contacts who suffered a similar disease, and one of them died. It is now known that roughly 10 percent of bats carry antibodies to the virus.

West Nile Virus

This disease has long afflicted the Balkans and Middle East. In 1997 there were over 500 cases in Romania, but the matter was not reported in America. On August 4 1999 the disease emerged in New York City, and an 80-year-old man died. This was the first time the virus had been detected in the Western Hemisphere, and it immediately hit the headlines. Some 20 species of birds, including the crow and the bald eagle, can carry the virus, which is spread by insects. The disease has 10 percent mortality: in 1999 there were 58 cases and seven deaths in the US, with much attendant publicity in the press and broadcast media across the western world. Further outbreaks are inevitable.

OTHER CAUSATIVE AGENTS

If the viruses are more disturbing than the bacteria, then how much more worried should we be by diseases in which there is no conventional pathogen? We are already afflicted by diseases like Alzheimer's, episodic leukemia, and crippling arthritis. In many cases there are suggestions that there are pathogens yet to be discovered. Let us look briefly at two diseases that have been recently documented. They serve to illustrate how much we have yet to learn.

Variant Creutzfeldt-Jacob Disease (vCJD)

There are several diseases caused by prions, unconventional agents that contain no RNA or DNA and thus contravene the most basic beliefs about the nature of infection. Those that affect humans include Creutzfeldt-Jacob Disease, Fatal Familial Insomnia, Gerstmann-Sträußler-Scheinker syndrome and Kuru. In animals we know of Chronic Wasting Disease of elk, Transmissible Mink Encephalopathy, plus Bovine and Feline Spongiform Encephalopathies (BSE). The spongiform disease of humans, believed caught from eating infected beef, has become known as variant CJD. In fact I have argued that the symptomatology is rather closer to Kuru, the brain disease found among the cannibals of Papua New Guinea. In that case, calling the disease 'variant CJD' would be no more logical than calling a Chihuahua a 'variant kitten'. CJD is something different; in my view, what we have really seen is a kind of Kuru in Western society.

During the BSE epidemic in Britain, the authorities in Brussels prevented Britain from exporting any beef, while allowing it to be consumed by the British people at home. I never understood this - it almost seemed as if Brussels was content to see the British as a more expendable people than the rest of Europe. There has been just one case in the US; a young woman named Charlene Singh, aged 23, developed the disease. It was believed she had contracted it in the UK. In Britain there has not been a year-on-year increase of cases, and I have said in many broadcast interviews that there remains no evidence of a vast epidemic. The teams working in the field keep warning us of the danger, however, doubtless with a view to securing tenure that will run well into the future.

There were many problems caused by the British government, and we were all assured that lessons had been learned. However, the subsequent epidemic of hoof and mouth disease in the UK suggests that the lessons were not really learnt.

Kawasaki disease

Kawasaki disease was first described in Japan in 1967. It is now the biggest cause of death from cardiac disease in the young. Most of the primary cases occur in children under five years old. They suffer pyrexia, reddening of the skin and eventual arthritis. In 20 per cent of victims, weakening of the coronary arteries subsequently develops, and the children collapse and die unexpectedly in their teens. Large doses of *gamma*-globulin, if administered within the first ten days of the illness, may curtail the course of the disease. This is a condition that has much in common with a reaction to a bacterial infection, but no causative agent has yet been identified. The cause remains a mystery; the effects are tragic and profound.

FACING THE FUTURE

The success of microbiology and medicine has been to eliminate many diseases. Some have been controlled by better hygiene and improved waste management. Others have been reduced through antibiotics or preventive medicine. Many scourges of comparatively recent memory have ceased to concern us - scarlet fever and poliomyelitis, for example - while episodic outbreaks of smallpox have been vanquished altogether.

Suddenly, matters seem very different. We are now facing new scourges, caused, in some cases, by entirely novel infective agents. Contact-lens wearers are threatened by *Acanthameba keratinoides*, for example, which damages the corneal surface. Where did it exist in nature before it came to infect humans? Nobody is sure. Sometimes new pathogens acquire their pathogenicity by accident. For example, *Legionella*, the causative agent of Legionnaire's Disease, exists within the human leukocyte population and is also a parasite of free-living amoebae. I dare say the protozoa mistake one host for another, and find the human white cell a suitable substitute for free-living amoebae when circumstances permit.

It is this essential opportunism of all pathogens that should forewarn us of difficulties ahead. We cannot introduce (for example) pre-packed chilled food without recognizing the avenues of infection that a temperature-resistant bacterium like *Listeria* will quickly exploit. The contact lens is a further example of a niche waiting for its pathogen. So is the fashionable exploitation of sexual liberation, which - exactly as predicted - has given us a silent epidemic of chlamydiasis. We note the incidence of sexually-trans-

Bugs in baguettes pose holiday hazard

From Adam Sage
in Paris

TRAFFIC jams and irresponsible drivers are not the only dangers facing holidaymakers on French motorways this summer. The sandwiches, too, are a risk, according to a new study.

A survey published yesterday by the car magazine, Auto Plus, said that half the sandwiches served in French motorway service stations were unsafe to eat.

Of 17 sandwiches tested for the weekly by the laboratory Clabo Conseil, nine contained levels of bacteria above the legal maximum in France. One in three salads was also unsafe.

Biologists from Clabo Conseil said that the sandwiches had been prepared by staff who had failed to wash their hands after going to the toilet. Other sandwiches had been left in warm temperatures for hours on end.

All those tested were ham and lettuce baguettes. One sandwich contained 51,000 times the legal maximum for bacteria.

6) Half the French sandwiches in service stations during 2001 have been reported to contain high levels of pathogens - one sample showed 51,000 times the legal limit for contaminants.

8) Recent outbreaks of Norwalk virus aboard cruise ships have led to the widespread introduction of hand-sprays like these for passengers as they enter restaurants. These precautions are destined to be more widely introduced.

Bin Laden link to 'mail order germs'

Osama bin Laden bought $10,000 (£7,000) worth of anthrax on the open market from private laboratories in Eastern Europe and Southeast Asia, according to a member of an Egyptian Islamic militant group (Katty Kay writes).

He obtained the anthrax, along with other deadly bacteria such as salmonella and e-coli, from factories that sold the germs by mail order. The revelation of just how easy and cheap it was to obtain biological weapons was made in a recent courtroom testimony by Ahmad Ibrahim al-Najjar, a member of the Egyptian Islamic Jihad

7) The illicit purchase of discarded nuclear weapons has attracted much media attention, but microbial weaponry is easier to develop and – as this report reminds us – the agents can be obtained on the open market.

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Doctor is killed by the superbug he discovered

By **Rachel Ellis**
MEDICAL CORRESPONDENT

THE doctor who first identified the killer pneumonia bug sweeping the world has died of the disease.

Italian medic Dr Carlo Urbani, 46, died yesterday in Thailand, where he had been receiving treatment for the mystery virus which he contracted while he was working in Vietnam.

Dr Urbani, an expert with the World Health Organisation (WHO), was the first to identify Severe Acute Respiratory Syndrome, or SARS, in an American businessman in a Hanoi hospital, where he later died.

Dr Urbani brings the superbug's death toll to 53, and 1,350 cases have now been identified worldwide.

9) Microbiologists have often suffered from the organisms they study. Dr Carlo Urbani of the World Health Organisation, who first identified SARS in an American businessman, died of the virus in Thailand.

Condemned meat was sold through supermarkets

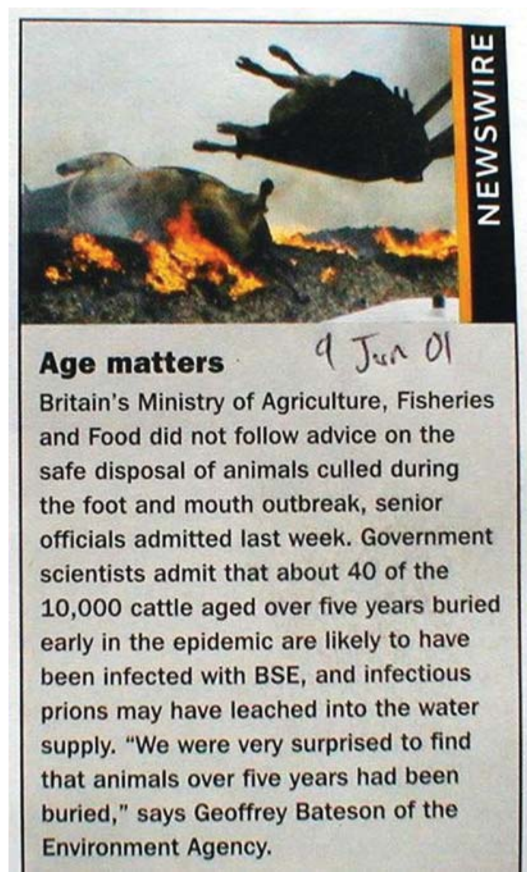
Rosie Waterhouse

10) New laws to control the safe handling of food are not enough to prevent abuse. According to this Sunday Times *report, large amounts of contaminated meat has been sent to British supermarkets.*

11) *During the hoof and mouth outbreak, hundreds of miles of footpaths were 'needlessly' closed, according to countryside campaigners. Hostels, country pubs and tourist centres were put out of business.*

13) *Hoof and mouth disease was controlled in the Polish ports by the use of obligatory hand-washing for all visitors. Here two American tourists are supervised on arrival at the Baltic port of Gdansk.*

12) *Signs in the arrivals halls of British airports and ports warned of the need for hygiene. Even in Canada, disinfectant footbaths were obligatory for all persons who had recently traveled in the UK.*


NEWSWIRE

Age matters 9 Jun 01

Britain's Ministry of Agriculture, Fisheries and Food did not follow advice on the safe disposal of animals culled during the foot and mouth outbreak, senior officials admitted last week. Government scientists admit that about 40 of the 10,000 cattle aged over five years buried early in the epidemic are likely to have been infected with BSE, and infectious prions may have leached into the water supply. "We were very surprised to find that animals over five years had been buried," says Geoffrey Bateson of the Environment Agency.

14) *In spite of assurances given during the BSE outbreak, medical advice on the safe handling of carcases has not been followed during the current hoof and mouth epidemic, according to* New Scientist.

mitted diseases in the category of 'sexually active' people, but this is a misnomer. Sexually active couples are everywhere, and are not at risk unless they are (as well as active) promiscuous. Unprotected promiscuous sex has become a life-threatening hazard. We already watch for hepatitis A in at-risk groups – drug users, promiscuous persons indulging in unprotected anal sex, recipients of blood factors by injection – and there are now plans to extend the routine vaccination of infants against hepatitis B. This points the way ahead; we will need to press for the widespread use of vaccination in the young if we are to control epidemics in future.

In the future we must be proactive on all levels. We need to watch for loopholes, and audit new processes in order to minimize the opportunities for pathogens to spread. We also need to be more familiar with the microbial world. No child should reach the age of 10 without having repeated Leeuwenhoek's observations of pond life. The majesty of the microbial universe is waiting for all to observe, and it is only through an understanding of our microbial confederates that we can begin to understand the minority that can do us harm. I want schools to start teaching medicine around the age of 6.

The fact that medical students first encounter the subject in medical school worries me a great deal. These topics remain unfamiliar to many; as a result, today's textbooks and newspapers are riddled with errors and mistakes on the subject. We cannot flourish in an era of biosciences when the public are disenfranchised from knowledge of what these organisms are like. Officialdom needs to pay heed, too. We need urgently to review our vaccination policies; this can be crucial and is particularly appropriate in conditions like the TB epidemic in the Eastern States. All too often public health services are being curtailed, and monitoring facilities are being wound down. This is unacceptable. Everyone needs to be aware of the realities.

Global warming, which officials in the US are still hesitant to accept, is already encouraging a spread of insect vectors. In the US, the Asian tiger mosquito *Aëdes albopictus* is now becoming widespread, and *A. albopictus* - which is somewhat hardier, and which first appeared in Texas in 1982 - has already spread to about 20 states in the US. This mosquito alone can spread dengue fever, yellow fever, Mayaro, Venezuelan and Eastern Equine Encephalomyelitis. The consequences for the health of the American people may cause much more concern than a need to drive large cars around overcrowded freeways.

Finally there is the question of personal responsibility. It is up to everyone to become instinctively familiar with the precautions that we need to take - precautions that are as positive and as instinctive as looking both ways before you cross the road. If there were to be a single innovation that I would advocate it would be a bowl of very dilute hypochlorite in every kitchen, ready for wiping down surfaces and cleansing hands. In the future we will all need to think about safety when it comes to transmissible disease.

The microscopists of the past gave us our insights, and we have neglected many of their pioneering visions in recent years. To the microscopists of today I say this: there has never been an age that needs you more. Only those who are familiar with microscopical revelations can understand the new problems that we face. More than any other instrument of science, the key to healthy and safe living in the new millennium is the microscope; the microscope and all it reveals.

[Note: this paper was revised and presented as: 'The Changing Face of Disease: Implications for Society' [at symposium entitled] Human Behavior and the Changing Pattern of Disease, 44th Symposium of the Society for the Study of Human Biology and the Human Biology Association, Cambridge University, UK, 1640-1720h, September 17, 2001.]