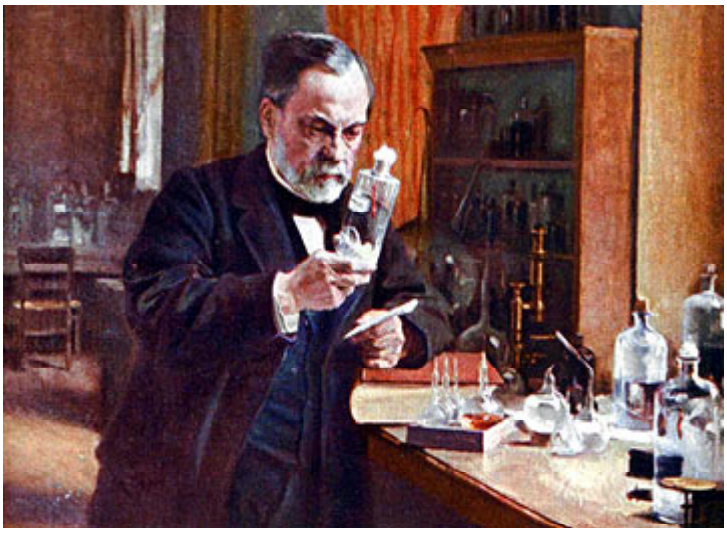
Genetics and infectious disease

The germ of an idea

Some people are more prone to infection than others. One answer could be to dose them with the molecules that their immune systems cannot make



LOUIS PASTEUR, the 19th-century French microbiologist and chemist, is credited with confirming that microbes cause disease. When studying ailing silkworms, he made two vital observations. The first was that la flacherie, as the worms' illness was called, was contagious. This led to the germ theory of disease and, ultimately, to the development of antibiotics to treat infectious illnesses in people. In all the excitement over germs, however, his second observation got overlooked: la flacherie was passed from parent to offspring. Almost 150 years later, the idea that susceptibility to infectious disease can be inherited is finally coming of age. A meeting held last week at the Pasteur Institute in Paris heard how the next generation of drugs will target not the microbial agents of infectious illness but their human hosts.

To this end, researchers are studying how different versions of certain genes could cause some people to succumb to infection whereas others are left relatively unscathed. They thus hope to explain not only why some people can

be infested with virulent microbes without contracting a disease (whereas others become ill even though they are less infected) but also why such patterns run in families and in ethnic groups.

Laurent Abel and Jean-Laurent Casanova of the Necker Medical School in Paris have found that a different version of a single gene out of the 25,000 or so in the human genome can make all the difference to whether or not a person suffers from many common diseases.

Nature not nurture

The Herpes simplex virus, for example, infects 80% of adults. The worst symptom in most of them is a cold sore but, in a few unlucky children, the virus causes a serious inflammation of the brain called H. simplex encephalitis (HSE), which can lead to brain damage resulting in epilepsy, mental retardation and even death. Dr Casanova has identified two genetic mutations in children who have survived HSE that result in the same deficiency—the lack of a molecule called type 1 interferon that plays a role in innate immunity.

Innate immunity is the defence against infection that babies are born with, as opposed to adaptive immunity which is acquired as people develop antibodies through their exposure to disease-causing agents. Whereas adaptive immunity is thought to be a response to specific bacteria, viruses, fungi and parasites, innate immunity has always been seen as the body's general response to all threats of disease. The children who survived HSE, however, were resistant to plenty of disease-causing agents other than the H. simplex virus, suggesting that innate immunity could be specific, too.

Dr Casanova thinks HSE is the first example of a disease that was thought to be purely infectious but which has turned out to be purely monogenic—that is, under the control of a single gene. He has found a half-dozen other diseases that behave similarly. Dr Abel, meanwhile, is trying to gauge how common these genetic effects are. Based on a study of nearly 200 Vietnamese families affected by another infectious illness, the bacterial disease leprosy, he and his colleagues have identified a single gene as a strong risk factor for leprosy in children under 16 years old.

The pair suspect that everyone will turn out to have narrow chinks in their immune armour that leave them vulnerable to certain infections, and that most life-threatening infectious diseases that strike before puberty will be monogenic—although they are far from proving this. Others believe that the

genetic control of susceptibility to infectious disease forms a spectrum, of which Dr Abel and Dr Casanova have only seen one extreme. At one end are diseases that are controlled by one or a few genes; at the other, diseases to which many genes contribute in small, cumulative ways.

Somewhere in the middle may be schistosomiasis, a debilitating disease caused by a parasitic flatworm carried by water snails, which affects 200m people worldwide. The worm causes liver damage that the body's natural mechanisms must repair. Those who are most susceptible to the disease have over-zealous repair mechanisms that replace too much liver with useless scar tissue.

Alain Dessein, of INSERM, a French medical research agency, who is based at the University of the Mediterranean in Marseille, has found that 70% of the susceptibility to schistosomiasis is under the control of one or two genes that regulate liver repair. He hopes that a pharmaceutical firm will now devise tests based on these genes to identify those in whom scarring progresses rapidly or slowly, as well as drugs that improve healing.

Malaria, which kills more than 1m people a year and contributes to the deaths of a further 1.7m, according to the World Health Organisation, probably falls at the multigenic end of the spectrum. In the 1950s Anthony Allison, a British biochemist, observed that Africans who carry a single copy of the genetic mutation that causes sickle-cell anaemia are protected against malaria. It is now known that genetic variability accounts for 25% of susceptibility to the disease, but that variations in the sickle-cell gene contribute to only a fraction of that. Other genes must therefore be involved.

Malarial mice

At McGill University in Montreal, Canada, Philippe Gros and his colleagues are looking for those genes in mice, by comparing the susceptibility of different types of mouse to one stage of the disease. Malaria is caused by parasites that are transmitted by mosquitoes. Once inside the body, the parasites multiply first within the liver and later within red blood cells. Dr Gros and his colleagues are examining the second part of this process because it is after this stage that infected blood cells can become trapped in small blood vessels in the brain, causing cerebral malaria and, potentially, death. They have found that, at least in mice, an enzyme called pantetheinase confers resistance to the multiplying of the malarial parasite within red blood cells.

It turns out that pantetheinase is needed for the synthesis of a small molecule called cysteamine and, by treating pantetheinase-deficient mice with cysteamine, Dr Gros claims to cure them of malaria. It remains to be seen whether cysteamine will have the same effect in people, but Dr Gros is planning clinical trials in which malaria patients will be treated with the molecule in combination with standard anti-malarial drugs.

The same principle—of replacing an immune molecule the body lacks, to increase its resistance to infection—underlies a treatment Dr Casanova is hoping to develop for HSE. On diagnosis with the condition, young patients who are found to have a type 1 interferon deficiency will be given both a standard anti-viral drug and the interferon they lack. Such a combined treatment could improve the chances for children who may otherwise die or suffer brain damage. Perhaps Pasteur's second observation will eventually have as great an impact on humanity as his first.

Drug-resistant infections

Riding piggyback

Farm animals are infecting people with a new strain of superbug

FILTHY surroundings that are home to a population fed on antibiotics provide the ideal breeding grounds for superbugs. But badly run hospitals are not the only such places. Farms where animals are reared intensively also provide an incubator for drug-resistant diseases. Recent research suggests that veterinary surgeons and farmers in Europe and Canada may be picking up potentially fatal infections from pigs and possibly cattle.

Superbugs evolve when common bacterial infections develop resistance to the drugs used to treat them. The most widespread cause of hospital infections, methicillin-resistant Staphylococcus aureus, or MRSA, is one such example. About a third of people carry some form of S. aureus on their skin, where the bacteria do no harm. However, if they enter the bloodstream, they can cause disease. And if the resulting illness cannot be treated because the bacteria are drug-resistant, the infection can prove fatal. MRSA killed some 19,000 people in America and 1,600 people in Britain in 2005, the latest year for which figures are available.

In the Netherlands such outbreaks are relatively rare. Yet a new strain called non-typable MRSA, or NT-MRSA, has recently emerged there. The strain first appeared in 2002 and now accounts for more than 20% of human infections. Unlike most other strains found in people, NT-MRSA strongly withstands a group of drugs called tetracyclines, which are antibiotics that are heavily used in livestock. It seems highly likely that the medication of farm animals led to the evolution of the strain that has since been passed to people. Indeed, last year Albert de Neeling and Xander Huijsdens of the Dutch National Institute for Public Health and the Environment, in Bilthoven, found NT-MRSA in 39% of pigs and at 81% of pig farms.

Now Dr Huijsdens and Inge van Loo of the St Elisabeth Hospital in Tilburg have found further evidence to support this theory. They compared 35 people with NT-MRSA with 76 people carrying other strains of the superbug. Those who carried NT-MRSA were 12 times more likely to have come into contact with

pigs and 20 times more likely to have come into contact with cattle. The pair plotted the infections on a map, and found that the distribution of NT-MRSA cases coincided with the locations of pig and cattle farms. The results will be published in a future issue of Emerging Infectious Diseases.

So far, it is not clear whether the strain is spreading beyond farms to cause infections elsewhere in the population. But Dr van Loo has detected MRSA, including the new strain, in meat samples from Dutch supermarkets and butchers. The bacteria were present only at low levels that are unlikely to cause disease if food is properly cooked. Certainly, no one is yet known to have caught NT-MRSA from eating infected meat. Yet keeping the bacteria out of the food chain would be a sensible idea. At least one outbreak of a different strain of MRSA has been traced to the eating of contaminated food by a hospital patient with a weakened immune system.

Because the pigs are exported, the problem is spreading to other countries. NT-MRSA has already been detected in Denmark, France and Singapore. In a paper to be published in Veterinary Microbiology, Scott Weese from the University of Guelph in Ontario, Canada, found the strain in 25% of local pigs and, more worryingly, in 20% of pig farmers. Human cases of NT-MRSA are extremely rare in Canada but could become more common if the infection spreads among the pig population.

Moreover, the United States is the biggest importer of Canadian bacon, ham and pork. It is already experiencing a large increase in the number of infections caused by new strains of MRSA that are emerging from places other than hospitals and nursing homes. Such infections appear to be more virulent and more easily spread between people than earlier strains. They have even afflicted the fit and the young — who were not previously thought to be susceptible to superbugs and the diseases they cause.

Planetary science

Barren land

Nov 29th 2007
From The Economist print edition

Why Venus is lifeless

FOR a planet named after the goddess of love, Venus is something of a misfit. Its clouds of sulphuric acid, crushing atmosphere of carbon dioxide and blast-furnace surface temperature of 457°C are anything but lovely. Yet in its youth it was, like its gentler sister Earth, swathed in oceans that provided a suitable breeding ground for life. What went wrong?

Since 1962 more than 30 spacecraft have made the trip to Venus, seeking to understand Earth's nearest neighbour and so-called twin planet. The most recent of these, Venus Express, was launched by the European Space Agency in 2005. In the current issue of Nature, nine papers report what it has found so far.

Hakan Svedhem, of the European Space Agency, and his colleagues say that Earth and Venus probably started out much the same. The Earth's oceans teemed with plants and animals that converted most of its atmospheric carbon dioxide into carbonates and sank to the bottom as they died, to become sedimentary rocks. By contrast, Venus lost most of its liquid water. That is because Venus, being closer to the sun, started to warm up. This generated more water vapour in its atmosphere, further increasing the temperature in a runaway greenhouse effect.

Planetary scientists have also long blamed Venus's sterility on the lack of an internal magnetic field. The sun zaps its planetary neighbours with the “solar wind”, a stream of highly energetic charged particles. Damaging cosmic rays also bombard the planets. The Earth is protected from much of this radiation because it has an internal magnetic field that generates a protective magnetosphere. But Venus has no such protection, possibly because it does not rotate much.

Yet according to Tielong Zhang, of the Space Research Institute at the Austrian Academy of Sciences, and his colleagues, Venus does still manage to avoid much of the bombardment. Dr Zhang says that the solar wind itself carries a

magnetic field all the way to Venus where it encounters the planet's electrically charged upper atmosphere, or ionosphere. Venus's ionosphere is highly conductive, and data taken by Venus Express suggest that the solar wind cannot penetrate it at any time. Like a boat trying to cut through the ocean waves, the induced magnetic fields pile up where the solar wind meets Venus's ionosphere. The solar wind fluctuates in strength, but is prevented from entering both when it is strong and when it is weak.

On the dark side of the planet things are much quieter. Shielded from the buffeting of the solar wind, ions quietly leak out of the atmosphere. Venus Express has detected oxygen, hydrogen and helium ions—remnants of early oceans—escaping into space. The two sisters may have started as twins but, as they have grown older, they have grown apart.

Vision and nutrition

A bird's eye view

Some creatures know how to identify and choose healthy food

ANTIOXIDANTS are the health freak's weapon of choice. They mop up molecules in the body that would otherwise damage cells and could cause cancer. They are found in many fruits and vegetables, and even in red wine. Without biochemistry, people would not know of their existence. But researchers now think that birds can see them and that they choose foods containing them.

In the wild, plants need to disperse their seeds to survive and colonise new areas. One way of doing this is to grow attractive fruits that animals eat, pips and all. The creatures then spread the seeds as nature takes its course. That is why plants produce fruit that is often brightly coloured and tasty. But do animals also choose to eat fruit because it is nutritious?

To find out, Martin Schaefer of the University of Freiburg, in Germany, and his colleagues set out to see whether creatures can sense antioxidants. They analysed how 60 different fruits appear to the birds that disperse their seeds.

Birds see colours in their own way, because they are sensitive to wavelengths, such as ultra-violet, that are invisible to people. The researchers found that birds could clearly perceive the strong ultra-violet coloration given to the fruit by the presence of a group of antioxidants called anthocyanins.

That does not necessarily mean that birds would chose anthocyanin-filled fruit. So Dr Schaefer conducted an experiment using 11 captive female blackcaps. For four days, the birds were given a choice between two cups of food that were identical except that the food in one was blue in colour because it contained anthocyanins. All the birds chose the food with the anthocyanins, which confirmed both that the birds could see the compound and had a preference for it. This suggests that, in evolutionary terms, having antioxidants present in fruit would make a plant more successful at attracting seed dispersers.

It also means that the birds may be able to medicate themselves. Dr Schaefer is now examining their choice of diet at stressful times, such as during migration. He wonders whether birds suffering oxidative stress increase their antioxidant consumption by choosing fruits with high anthocyanin content — rather like starting the day with a glass of orange juice when you feel a cold coming on.