Features

Evolution and disease

A recent meeting highlighted how much Darwinian thinking on natural selection illuminates the background to some major current human diseases and may offer insight into many more. **Nigel Williams** reports on a field seeking a place in mainstream medical education.

Evolution by natural selection is something most biologists freely talk and argue about but, perhaps surprisingly, it is not on the lips or curricula of most medical students. The teaching of medicine asks little of students to consider the implications of Darwin's work. However, while many people believe humans are now beyond the reach of natural selection, a growing group of researchers believe that in some populations and circumstances natural selection has exerted a powerful effect.

This link was explored in a meeting in London last month by the Academy of Medical Sciences on evolution and disease. The idea of taking a Darwinian perspective on disease first gained prominence with a book on the subject published by Randolph Nesse and George Williams ten years ago. Since then, many have been convinced that an evolutionary view can provide insights into many clinical conditions. But uptake by mainstream medical education has been limited, and many medical schools in the US still pay scant attention, according to research carried out by Nesse. So one of the aims of this meeting was to bolster the achievements within the field.

According to David Weatherall, former director of Weatherall Institute of Molecular Medicine in Oxford, and one of the conference speakers, the subject is an established one that produces solid knowledge with potential clinical use, but also one open to considerable speculation.

He dates the field to the late 1940s, when the British biologist J.B.S. Haldane pointed out the high frequency of genetic blood diseases – sickle-cell disease and thalassaemia – in some human populations. Haldane's suggestion that this may be linked to malaria resistance was a 'remarkable insight' says Weatherall. 'It took a long time to validate this but it turned out to be true. Sickle cell disease itself is very severe but people who are carriers of the disease, and do not have it actively, live normal lives and are far less likely to develop malaria,' he says. Two years ago, a case controlled study on children in Papua New Guinea showed that thalassaemia carriers were 60 per cent less likely than other children in the same villages to develop severe malaria.

It is not clear how long these adaptations have been at work, but Weatherall suggests that they date back about 5,000 years. And studies by Weatherall and his colleagues and other teams have shown that mutations protecting against the disease differ between different populations. 'It appears the mutations are local and are subject to local selection,' he says. However, studies by his group in the the Pacific island group of Vanuatu reveal that similar patterns of mutations are found on some neighbouring islands, including some where malaria is not found. But this puzzling pattern fits with current views on how and when humans colonised these islands.

Researchers have also found that the frequency of mutations in the populations exposed to malaria vary and are often highest in areas where the disease is most prevalent, again showing the importance of local factors.

Two species of malaria are dominant in causing human disease: *Plasmodium falciparum and P. vivax*. The two species co-exist in many parts of the world but *P. vivax* is notably absent from West Africa. This observation led to the classic discovery that the erythrocytes of the Duffy blood group negative individuals, who predominate in this region, are resistant to invasion by *P. vivax* but not by other species of malaria parasite.

Thalassaemia and sickle-cell disease are only the best-known adaptations to malaria. But the disease is such a danger across the tropical world that a wide range of countermeasures have emerged to fight it. Weatherall says there are millions of children with an enzyme defect that makes their red blood cells more likely to break up, which is doubtless malaria related.

Malaria is not the only such case, however. There are people whose genes make them more resistant to HIV/Aids. Over time this polymorphism might be expected to spread, as those against malaria have in the tropics, although, Weatherall says, nobody knows how this particular polymorphism came to be there in the first place. HIV has not been in contact with the human population long enough for resistance to it to convey a reproductive advantage, which would let it spread by natural selection. Instead, it may in the past have conveyed resistance to virus infections that are no longer problematic.

One of the issues addressed at the meeting was how fast evolution works. Weatherall's estimates suggest that the process can be very fast when the pressure is strong – it may take just decades for the proportion of people with innate resistance to increase in a case such as Aids, for example. This kind of rapid effect is also likely to be the cause of a large amount of human diversity, such as the existence of different blood groups. These involve different blood proteins

Deadly pressures: A mother comforts her child undergoing treatment for severe malaria in a children's ward at a hospital in Tanzania. It is estimated 1 million people die of the disease in Africa every year putting strong selection pressure on the affected populations. (Photograph: Andy Trump TDR/WHO, Science Photo Library.)

and different patterns of susceptibility to disease.

More examples of genetic variation in the face of disease are likely to emerge because the technology for analyzing genes and their variability is advancing fast. Knowing about the different forms of relative resistance to a disease might also lead to new ways of managing it. And if a new vaccine is being tested for its ability to attenuate malaria attacks, for example, it would help to know what percentage of the population is already immune before testing it.

Some of the human diseases that evolution may also provide an insight to include diabetes, breast cancer, obesity, hip fracture and depression. All of these are increasing in incidence in western societies. The gap between our ancient hunter-gather environments and present-day environments is thought by many to hold a clue to these problems. Pinning down answers is more difficult but many hope an evolutionary approach will help.

Evolutionary medicine is also contributing thought on the production and mutation of cancer cells. While childhood cancers exist, most cancers affect older people, and there has been speculation that they tend to appear when people have become old enough to have reproduced. At this stage the repair mechanisms that protect younger people run out. Mel Greaves, head of the Leukaemia Research Fund Centre at the Institute of Cancer Research in London, who has also written a recent book on the evolutionary legacy of cancer, highlighted the particular role of stem cells where there is a conflict between their role as a source of tissue replenishment throughout life but where such longevity renders them a major target for cancerous transformation.

Many in the field regard the evolutionary perspective as a counterbalance to the belief of some scientists who think that natural selection is no longer operating on human populations. 'In Africa, where malaria kills a million people every year and Aids even more, very rapid selection is still going on,' says Weatherall. And even in the developed world the evolutionary approach has something to offer. The connection between cancer and tobacco is clear. But work on diet and cancer has been less successful, while cancer risks from ionizing radiation and other hazards such as the oxidants that result from our own metabolism also need more work. 'In time our knowledge of the genetic make-up of the population is likely to be reflected in public health and treatment protocols,' says Weatherall. Medical students and their teachers may then need to sit up and listen.